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REVIEW ARTICLE

Safety and Tolerability of Antimicrobial Agents in the Older Patient

Luca Soraci[1] · Antonio Cherubini[2] · Luca Paoletti[2] · Gianfranco Filippelli[3] · Filippo Luciani[4] · Pasqualina Laganà[5] · Maria Elsa Gambuzza[6] · Elvira Filicetti[1] · Andrea Corsonello[1] · Fabrizia Lattanzio[7]

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Abstract

Older patients are at high risk of infections, which often present atypically and are associated with high morbidity and mortality. Antimicrobial treatment in older individuals with infectious diseases represents a clinical challenge, causing an increasing burden on worldwide healthcare systems; immunosenescence and the coexistence of multiple comorbidities determine complex polypharmacy regimens with an increase in drug–drug interactions and spread of multidrug-resistance infections. Aging-induced pharmacokinetic and pharmacodynamic changes can additionally increase the risk of inappropriate drug dosing, with underexposure that is associated with antimicrobial resistance and overexposure that may lead to adverse effects and poor adherence because of low tolerability. These issues need to be considered when starting antimicrobial prescriptions. National and international efforts have been made towards the implementation of antimicrobial stewardship (AMS) interventions to help clinicians improve the appropriateness and safety of antimicrobial prescriptions in both acute and long-term care settings. AMS programs were shown to decrease consumption of antimicrobials and to improve safety in hospitalized patients and older nursing home residents. With the abundance of antimicrobial prescriptions and the recent emergence of multidrug resistant pathogens, an in-depth review of antimicrobial prescriptions in geriatric clinical practice is needed. This review will discuss the special considerations for older individuals needing antimicrobials, including risk factors that shape risk profiles in geriatric populations as well as an evidence-based description of antimicrobial-induced adverse events in this patient population. It will highlight agents of concern for this age group and discuss interventions to mitigate the effects of inappropriate antimicrobial prescribing.

Key Points

Older patients are at high risk of infections and adverse events due to antimicrobial medications.

Inappropriate antimicrobial use contributes to complications, mainly due to drug underexposure that leads to antimicrobial resistance, and drug overexposure that leads to adverse effects and poor adherence because of low drug tolerability.

Antimicrobial stewardship interventions addressing adherence to guidelines, dosage adjustment in liver and kidney dysfunction, as well as formulary adaptations and therapeutic drug monitoring can be lifesaving and improve the safety and effectiveness of antimicrobial treatments.

✉ Andrea Corsonello
l.soraci@inrca.it

1 Unit of Geriatric Medicine, IRCCS INRCA, 87100 Cosenza, Italy

2 Geriatria, Accettazione geriatrica e Centro di ricerca per l'invecchiamento, IRCCS INRCA, Ancona, Italy

3 Oncology Department, Hospital of Paola, Cosenza, Italy

4 Infectious Diseases Unit of Annunziata Hospital, Cosenza, Italy

5 Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

6 Territorial Office of Messina, Ministry of Health, Messina, Italy

7 Scientific Direction, IRCCS INRCA, Ancona, Italy

1 Introduction

Infections are common in older and frail patients and are associated with a significantly higher risk of morbidity, mortality, and health care costs [1]. A diagnosis of infection in the elderly may be challenging because classic symptoms may lack or mimic those of a comorbid condition [2, 3]. Community-acquired pneumonia, for example, may present with confusion only and this will delay the diagnosis, especially in patients with underlying cognitive impairment or dementia. On the other hand, elderly patients may have fever without apparent infections, thus making a very difficult decision on how and when to start antibiotics [3, 4]. However, the choice of the class of antimicrobial agents in older patients is often a challenging issue. Indeed, the type of antibiotic should consider factors related to patient, culprit pathogen (if and whenever possible), pharmacokinetic (PK) and pharmacodynamic (PD) properties, and the presence of polypharmacy, which may significantly increase the risk of developing adverse drug reactions and interactions.

The aim of this review was to describe the PK and PD aspects that may affect the safety of antimicrobials in older patients, as well as their impact on polypharmacy and drug interactions involving antimicrobial agents. Potentially useful interventions for reducing the risk of drug interactions when prescribing antimicrobials to older patients are also reviewed.

1.1 Search Strategy

Identification of relevant articles to 1 September 2022 was performed on standard databases (MEDLINE and Cochrane Library) by combining the following keywords: 'Antimicrobial*'; 'older or elder* or over 65 or aging'; 'drug-related or medication-induced'. Search results were limited to studies written in the English language from 1990 to 2022. For the key studies, we reviewed the bibliographies and citations and performed an author search to identify any additional studies. Two independent reviewers (LS and AC) identified and summarized the study characteristics (design, sample size, demographics, and clinical data), thereby selecting studies deemed relevant for the aim of this review. 5291 articles were originally included; studies were initially screened based on title and abstract and 4890 articles were excluded. The full-text of the remaining 401 articles was screened and 213 were not found to fulfil the aim of the present review and were finally excluded, resulting in the inclusion of 188 articles.

2 Age-Related Changes in Pharmacokinetics/Pharmacodynamics and their Impact on Safety and Tolerability of Antimicrobial Agents

PK processes (absorption, distribution, metabolism, and excretion) undergo relevant modifications during aging (Table 1). The loss of functional capacity of several

Table 1 Age-related PK modifications potentially associated with antimicrobial adverse effects

PK phase	PK change → consequence
Absorption	1. ↓ Gastric acid production → ↓ drug dissolution and bioavailability (e.g. fluconazole, itraconazole) [8] 2. ↓ Gastric motility, small bowel surface area, and splanchnic blood flow → ↓ drug absorption [15, 18]
Distribution	1. ↑ Adipose tissue → ↑ half-life and toxicity of lipid-soluble antimicrobials (e.g. fluoroquinolones, macrolides, rifampin, tetracyclines, imidazole) [23, 24] 2. ↓ Lean body mass and total body water → ↓ distribution and ↑ plasma concentration and toxicity of hydrophilic antimicrobials (e.g. aminoglycosides, β-lactams, glycopeptides) [25, 26] 3. ↑ Interstitial fluid accumulation (e.g. edema, ascites) → ↓ concentration of hydrophilic antimicrobials with ↑ risk of AMR [25, 26] 4. Hypoalbuminemia (e.g. malnutrition/proteinuria, sarcopenia) → ↑ concentration and toxicity of highly protein bound antimicrobials (e.g. ceftriaxone, clindamycin, penicillins, sulfonamides [27, 30]
Metabolism	1. ↓ Hepatic blood flow and CYP enzyme activity → ↑ half-life and toxicity of antimicrobials undergoing liver metabolism (e.g. azoles, antiretrovirals, fluoroquinolones, macrolides) [34–36] 2. ↓ Availability of CYP hepatic metabolism (e.g. polypharmacy) → ↑ drug toxicity and risk of drug–drug interactions (e.g. azoles, antiretrovirals, fluoroquinolones, macrolides) [37–41]
Excretion	1. ↓ Renal blood flow and glomerular filtration rate → ↑ half-life, serum concentration, and toxicity of antimicrobials undergoing renal excretion (e.g. aminoglycosides, β-lactams, fluoroquinolones, trimethoprim/sulfamethoxazole) [62–71] 2. Renal replacement therapy → ↑ antimicrobial drug removal with ↓ serum concentration and ↑ risk of AMR

AMR antimicrobial resistance, *CYP* cytochrome P450, *PK* pharmacokinetics, ↓ indicates decreased, ↑ indicates increased

organs and reduced homeostasis plays a key role in the pathophysiology of these age-related changes. However, changes in PK may also result from the coadministration of selected drugs, as is the case for several antimicrobial agents. In this section, we summarize the most relevant modifications in PK occurring during aging, and PK interactions involving antimicrobial agents relevant to older patients. We will also review the peculiar PD processes involving antimicrobial agents and the impact of PK alterations on PD.

2.1 Absorption

Aging is characterized by a reduction in esophageal peristalsis, which contributes to the observed increase in the prevalence of reflux disease in advanced age [5]. The resulting increase in exposure of the esophageal mucosa to acid secretions [6] may lead to an increased risk of esophageal lesions caused by drugs [7]. Aging is also characterized by a reduction of gastric acid secretion [8], although such a reduction was not confirmed in subjects without *Helicobacter pylori* infection or gastric mucosal atrophy [9, 10]. In addition, no significant change in terms of atrophy or intestinal metaplasia was detected during long-term therapy with proton pump inhibitors [11], a very common and often inappropriate practice among older patients [12]. However, an increase in gastric pH, especially due to proton pump inhibitors or calcium carbonate use, can alter both the solubility and chemical stability of β-lactams, macrolides azoles, and atazanavir, thus reducing bioavailability [13]. Conversely, acidic drugs such as raltegravir have shown to become more available in less acidic environments, with potential increased bioavailability and toxicity [14]. Gastric emptying and peristalsis are also slowed during aging [15, 16], and splanchnic blood flow and bowel surface are reduced [17]; all these factors can contribute to decrease the bioavailability of amoxicillin and clavulanic acid when assumed after the meal [18]. The proper use of these agents in elders with altered gastrointestinal mobility needs to be addressed. Reduced active transport function may also lead to a significantly lower bioavailability of selected drugs [19, 20]. Drug interactions causing an inhibition of intestinal P-glycoprotein (P-gp) may affect either absorption or presystemic metabolism. For example, inhibition of P-gp by clarithromycin or levofloxacin may increase the serum concentration of sulfonylureas, such as glipizide, leading to refractory hypoglycemia [21–23]. Similarly, inhibition of intestinal P-gp by clarithromycin and erythromycin may increase digoxin concentration and toxicity [24]. Finally, specific antifungal agents, such as itraconazole and caspofungin can also inhibit P-gp [25].

2.2 Distribution

Several changes in physiology occur in body composition with aging and may significantly impact drug distribution (Table 1). Aging is associated with an increase in body fat mass by approximately 20–40% and a decrease in total body water and lean body mass by approximately 10–15% [26]. These changes result in a significant increase of the volume of distribution (Vd) for lipophilic drugs, such as macrolides, fluoroquinolones, rifampin, and tetracyclines, with consequent prolongation of their half-life [27]. Similarly, aging is associated with a significant reduction of the Vd for water-soluble drugs, including β-lactams, glycopeptides, aminoglycosides, and azoles, with a consequent more rapid increase in plasma concentrations [28] and the need to start with lower doses [29].

Aging-induced modifications of plasma protein binding have shown to be less relevant for drug therapy, as compensatory mechanisms of drug redistribution generally lead to stable steady-state unbound drug concentrations [25, 30]. Indeed, changes in protein binding may influence the area under the curve of the unbound fraction (f_u AUC) for few drugs highly extracted by the liver, extensively protein bound, and administered intravenously [31], such as haloperidol [32] and theophylline [33]. However, several diseases frequently observed in older patients may lead to more pronounced changes in protein binding capacity that cannot be ascribed to the aging process [31]. Furthermore, some antimicrobial medications may undergo protein binding drug interactions that increase the risk of drug toxicity. In this regard, cotrimoxazole may displace methotrexate and sulphonylureas from plasma protein binding sites, thus rising their concentrations and leading to increased risk of hypoglycemia and severe bone marrow depression [25], respectively.

Blood–brain barrier permeability undergoes significant modifications during aging, which may alter drug PK in the central nervous system (CNS). P-gp function declines during aging, which may cause an increased influx of toxic substances in the CNS, and a consequent increased risk of developing neurodegenerative diseases [34], as well as excessive cerebral levels of drugs and xenobiotics [35]. Until now, antibiotics seem to have a less prominent inhibitory effect on the blood–brain barrier P-gp activity: the rate of transfer of verapamil from plasma to brain was unaffected by the coadministration of clarithromycin, suggesting that a clinical dose of clarithromycin does not affect P-gp activity at the blood–brain barrier [36].

2.3 Metabolism

Relevant changes in metabolism occur during aging (Table 1). A 20–30% reduction in liver volume is observed with aging [37] and hepatic blood flow is reduced by

approximately 20–50% [38, 39]. These anatomical and functional changes lead to reduced hepatic first-pass effect, with relevant consequences for specific drugs [20, 40]. For example, drugs undergoing extensive first-pass metabolism may have their bioavailability increased [41, 42], while drugs that need to be activated in the liver may have their bioavailability reduced [43]. In older patients, a reduction up to 40% of the hepatic clearance of drugs undergoing flow-limited metabolism has been observed [39, 44]. Cytochrome P450 (CYP)-mediated phase I oxidization, reduction, and hydrolysis reactions are impaired to a greater extent with respect to phase II conjugation reactions, mainly due to the reduced hepatic blood flow and overall liver size [39, 44]. The effects of aging on CYP activities are still to be elucidated [45–47]. The aging process per se does not affect most CYP enzymatic activities and enzyme affinity for their substrates. Rather, the age-related reduced phase I hepatic clearance is largely to be ascribed to the above morphological and circulatory changes [37, 48]. Nevertheless, an age-related reduction by approximately 20% has been observed in the metabolism of CYP2D6 substrates [49, 50]. Such a finding was not confirmed for CYP3A subfamily substrates [51–53], and former evidence suggests that aging per se has no relevant impact on the activation of some important CYPs, including CYP3A4, CYP2D6 and CYP1A2 [54, 55].

Multiple antimicrobial medications, including fluoroquinolones, macrolides and antifungal azoles, undergo first-pass hepatic metabolism; after phase I oxidation and phase II conjugation processes, these drugs are transformed into hydrosoluble compounds that can be renally excreted [13, 56]. Among macrolides, erythromycin, clarithromycin, and telithromycin, but not azithromycin, are able to inhibit both intestinal and hepatic CYP3A4 [25, 57, 58]. Coadministration of these antimicrobials and other selected CYP3A4 substrates, including dihydropyridine calcium channel blockers, simvastatin, atorvastatin, lovastatin, cyclosporine, midazolam, and tacrolimus, may be harmful because of drug–drug interactions and increased risk of adverse effects. Careful evaluation of drug regimens is thus needed in order to limit the risk of confusion, sedation and falls from benzodiazepines [59, 60], hypoglycemia from sulfonylureas [61], rhabdomyolysis from statins [62], severe hypotension from calcium channel blockers [63], nephrotoxicity from immunosuppressive medications [25], and toxicity of phenytoin and theophylline [25, 57, 58, 64]. Furthermore, erythromycin, and to a smaller extent clarithromycin, and telithromycin may increase the risk of bleeding in older patients taking warfarin [25, 57, 58]. Additionally, macrolide-induced CYP3A4 inhibition may increase serum concentrations of cholinesterase inhibitors such as donepezil, thus enhancing vagal signaling and favoring dysregulation of sinus node cardiac conduction, with subsequent risk of sinus bradycardia, bradyarrhythmias, and neurocardiogenic syncope [65, 66]. Despite the fact that recent evidence did not show an increased risk of cardiac events in older patients taking donepezil or clarithromycin, the use of antimicrobial medications other than clarithromycin in this population should be preferred whenever possible [67]. Finally, prolongation of the QTc interval potentially leading to torsade de pointes and death may be caused by antimicrobial-induced CYP3A4 inhibition, with increased levels of some antiarrhythmics, tricyclic antidepressants, and antipsychotic agents [25, 68]. Of note, several antimicrobial medications have been associated with risk of QT prolongation: azoles, erythromycin, clarithromycin, chloroquine, moxifloxacin and to a lesser extent ciprofloxacin and levofloxacin. Among macrolides, azithromycin does not inhibit CYP3A4 and was originally considered of low cardiotoxic potential; however, recent evidence showed a small increase in the risk of cardiac death among older patients with pneumonia [69], while discordant results in other settings need further investigation [70, 71]. To date, the macrolide/ketolide solithromycin has shown no effects on cardiac repolarization and is considered well tolerated in patients with QT risk when a macrolide is indicated [68, 72].

Inhibition of CYP3A4 and CYP1A2 enzymes by ciprofloxacin, levofloxacin, and moxifloxacin may increase the toxicity of several drugs commonly used in the geriatric setting, such as benzodiazepines, fentanyl, carbamazepine, simvastatin, lovastatin, atorvastatin, theophylline, haloperidol, and warfarin [60, 73].

Conversely, rifampin induces CYP2C9, CYP2C19, and CYP3A4 enzymes, thereby decreasing the bioavailability of several drugs, including warfarin, phenytoin, valproic acid, caspofungin, azoles, digoxin, amiodarone, simvastatin, atorvastatin, lovastatin, β-blockers, and sulfonylureas [25, 73].

2.4 Excretion

Renal excretion of drugs undergoes relevant modifications during aging (Table 1). However, deterioration of kidney function with advancing age can be exacerbated by polypharmacy and multimorbidity, which are highly prevalent in older populations and are known to affect renal function independently of aging [74].

In general terms, a loss of renal mass up to 20–25% [75] and a decrease of kidney length by 15% characterizes kidney aging [76]. Histological changes in the aging human kidney include increased interstitial fibrosis, tubular atrophy, arteriosclerosis, and glomerulosclerosis [77–79]. Such morphological changes result in relevant functional modifications affecting the PK of either water-soluble drugs or water-soluble metabolites of lipophilic drugs, with a consequent increased risk of ADRs [80]. Indeed, the age-related reduction in the clearance of inulin ranges between 13% and 46% [74, 77, 81–83]. Aging is also associated with important

tubule-interstitial changes, including tubular diverticula, atrophy and fat degeneration, reduced sodium reabsorption, reduced potassium secretion, interstitial fibrosis, and medullar hypotonicity [84].

Many antimicrobial agents can undergo drug–drug interactions with renally excreted drugs. For instance, digoxin, methotrexate, and amantadine may affect renal tubular secretion of cotrimoxazole and increase its serum concentration and toxicity [25]. Similarly, ciprofloxacin can decrease tubular secretion and renal excretion of methotrexate, potentially leading to severe hepatic, renal, bone marrow, and dermatological adverse effects [25, 85]. Furthermore, use of probenecid, methotrexate, aspirin, and indomethacin can decrease tubular secretion of β-lactams, thus increasing their serum concentration. More specifically, probenecid was shown to double the AUCs of amoxicillin, ampicillin, ticarcillin and nafcillin, and increase the AUC of meropenem by 55% [25]. In this regard, administration of probenecid to boost β-lactam concentrations should be avoided in older patients as well as individuals with renal impairment or a history of seizure, as it may enhance the risk of antibiotic-induced convulsions [25, 86].

2.5 Pharmacokinetics/Pharmacodynamics

Several PD changes occur with aging [87]. In this context, PD processes involve the multiple relationships between antimicrobial serum concentration and binding capacity to microbial antigens, which in turn lead to cell growth inhibition or death, as measured by minimum inhibitory concentration (MIC) [88, 89]. Antimicrobial drugs can have either a concentration-dependent (e.g. aminoglycosides, metronidazole, fluoroquinolones, daptomycin, and tetracyclines) or time-dependent killing activity (e.g. β-lactams, clindamycin, and vancomycin). While PD activity of concentration-dependent antibiotics mainly depends on the maximum plasma concentration reached, the killing activity of time-dependent antibiotics depends on the amount of time during which the plasma concentration exceeds the MIC for the organism [88–90]. In particular, optimization of antibiotic treatment in patients with decreased renal function should take into consideration the type of bacterial killing. Indeed, the risk of overdosing of concentration-dependent antibiotics can be addressed by increasing the dosing intervals (e.g. changing from 6 to 8 h or 12 to 24 h) and maintaining the same dose, thereby maximizing the peak serum dose [91]. Conversely, reducing the dose of time-dependent antibiotics in older patients with impaired renal function may be performed by decreasing the dose and continuing with the same dose interval [91].

Given the tight interconnections between PK and PD, the two processes need to be considered when evaluating doses and times of antimicrobial administration.

Indeed, the PK/PD ratio is used to estimate the antimicrobial effectiveness by correlating free drug (f) exposure (area under the plasma concentration-time curve over 24 h of dosing [fAUC24]) to measures of drug potency (MIC). Other PK/PD parameters used in clinical practice are represented by fCmax/MIC, the $f\text{AUC}_{24}$/MIC (i.e. the area under the inhibitory plasma concentration-time curve [AUIC]), and the time above the MIC (T/MIC) [88]. In this regard, several studies have yet shown the benefits of an integrated approach combining PK and PD parameters in patients with infectious diseases. For instance, Preston et al. showed that among hospitalized patients with respiratory, skin, or complicated urinary tract infections, high $f\text{AUC}_{24}$/MIC values were associated with lower rates of clinical failure and low prevalence of adverse effects [92]. PK/PD parameters may also be used to monitor antimicrobial concentrations and clinical course of infections, thus assisting the clinician to intercept early antimicrobial resistance and the development of harmful adverse effects [93]. Furthermore, PK/PD modeling was adopted to tailor the dosing regimen of gentamycin to decreased renal function in patients with end-stage renal disease (ESRD) [94]. In other studies, PK/PD modeling was used to test the susceptibility of emerging strains of multidrug-resistant bacteria to traditional antibiotics, such as β-lactams and carbapenems [95, 96]. Integration of PK and PD can then be necessary to tailor antimicrobial treatments that may help achieve therapeutic goals, prevent selection of drug-resistant bacteria, and minimize toxic effects in the geriatric population [89, 93, 96].

3 Clinical Profile of Older Patients at Risk of Adverse Events and their Consequences

Older individuals are particularly prone to develop adverse drug events (ADEs) related to antimicrobial medications [60, 73]. Polypharmacy, comorbidities impacting renal and liver functioning, and reduced adherence to therapy due to cognitive and functional barriers (e.g. dysphagia), as well as age-related changes in PK and PD, contribute significantly to the higher incidence of antimicrobial ADEs in older patients [60, 73]. In this section, we describe the most important conditions whose early diagnosis and constant monitoring may intercept those segments of the elderly population at major risk of antimicrobial-associated ADEs.

3.1 Chronic Kidney Disease

Antimicrobial prescription in chronic kidney disease (CKD) represents a twofold clinical challenge, as inappropriately low or high doses are both deleterious. Underdosing is indeed associated with therapeutic failure and increased antimicrobial resistance, which is more common in CKD

[97, 98]. Conversely, overdosing may lead to toxicity and ADEs [99]. Inadequate estimation of renal function in older patients is one of the factors that complicate antimicrobial appropriateness [100]. Indeed, decreased serum creatinine levels secondary to muscle wasting, sarcopenia, and protein catabolism may lead to overestimation of estimated glomerular filtration rate (eGFR) calculated by creatinine-based Modification of Diet in Renal Disease (MDRD), Cockgroft–Gault, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [101], which are generally reported in product labels. Direct measurement of creatinine clearance or measured GFR (mGFR) should then be used to avoid overdosing of hydrophilic medications [102], especially in patients with mild–moderate CKD. Alternatively, recent guidelines have advocated the incorporation of innovative biomarkers such as serum cystatin C to improve the estimation of GFR among older patients in the 'creatinine-blind range' [103]. In these individuals with an eGFR between 45 and 70 mL/min/1.73 m^2 and urine albumin/creatinine < 30 mg/g, GFR estimation based on serum creatinine levels frequently leads to overestimation of renal function, potentially causing increased drug bioavailability and toxicity [103].

However, appropriate eGFR estimation is not always accompanied by correct antimicrobial dosing, despite the fact that dosage modifications of most renally cleared antimicrobials are implemented in most clinical guidelines. Indeed, non-adherence with dosing guidelines is common in patients with CKD, especially in critically ill patients in intensive care units where physicians often do not tailor antimicrobial dosing to eGFR in order to avoid underdosing and limit antimicrobial resistance, which is very common in these settings [104, 105]. Studies assessing the use of antibiotics at higher than recommended doses led to contrasting results, depending on the drug used and the dose reached. Indeed, a recent study evaluating the effects of overdosing of cephalosporins in advanced CKD did not find any association with increased adverse effects or treatment failure in older adults with eGFR <30 mL/min/1.73 m^2 [106]. In contrast, older patients treated with higher doses of fluoroquinolones reported to have increased 14-day hospitalization rates due to altered mental status [107]. However, the definition of appropriate dosing of antimicrobial medications in CKD is likely contrasted by the limited number of studies specifically conducted in patients aged 65 years or older, which mainly evaluated dosage adjustment of levofloxacin and meropenem [73]. However, the use of dosages tailored to renal function does not always limit the risk of over- and underexposure to antimicrobial treatments, as revealed by a recent study conducted in older hospitalized patients treated with appropriate doses of levofloxacin [108]. In this context, implementation of therapeutic drug monitoring (TDM) in an acute care setting when dealing with older patients with CKD may be useful to approach antimicrobial dosage adjustment and prevent antimicrobial adverse effects and toxicity [109].

3.2 Liver Disease

Antimicrobial treatment in patients with liver diseases is a clinical challenge, as these patients are often characterized by a high risk of serious infections and a less favorable risk/benefit profile [110, 111]. Infections represent the most common and life-threatening complication of liver cirrhosis, with an overall incidence ranging from 25 to 40% in patients with decompensated cirrhosis [112]. The most frequent type of infections in patients with liver cirrhosis are represented by spontaneous bacterial peritonitis, followed by urinary tract infections, pneumonia, and soft tissue infections [113]. According to recent evidence, even mild impairment of liver function may increase the susceptibility to infections. Indeed, patients with non-alcoholic fatty liver disease, whose prevalence increases with advancing age, are more vulnerable to infections [114]. Treatment of patients with liver dysfunction is also challenging as many factors concur to impair antimicrobial metabolism. Liver dysfunction directly affects clearance of several antibiotics that undergo phase I metabolism, have a high protein binding, or are associated with a high prevalence of hepatotoxicity [115, 116]. In the presence of hypoalbuminemia related to impaired protein synthesis, highly bound antimicrobials undergo an increase in their free fraction with a high potential of adverse side effects and drug-related toxicity. Furthermore, their serum concentration tends to decrease more easily over time, thus potentially leading to antimicrobial resistance when facing bacterial infection from organisms with a high minimal inhibitory concentration (MIC) [117]. Prescription of ceftriaxone, vancomycin, ertapenem, and aztreonam, which are commonly used in acute care settings, should be carefully considered because of the high affinity with serum albumin [118]. Furthermore, most β-lactams that are not metabolized by the liver can undergo indirect fluctuations in their serum concentration related to increased Vd in patients with third-space retention and those with renal dysfunction, which is commonly associated with liver cirrhosis [115]. On the other hand, many lipophilic antibiotics, including fluoroquinolones, macrolides, tetracyclines, oxazolidinones, and metronidazole, are less affected by Vd but can shift from cells to plasma in patients with hypoalbuminemia [101]. Current evidence suggests antibiotics that can be safely prescribed in cirrhotic patients of all ages, with the Child–Pugh score guiding dosage [115, 119]; however, despite the fact that TDM would help achieve the optimal concentrations in this population, to date no study has been specifically conducted in patients older than 65 years of age.

3.3 Polypharmacy

The high prevalence of multimorbidity and polypharmacy among older adults contributes to the relatively high risk of interactions between antimicrobials and other drugs [60, 73]. Drug–drug interactions put the patients at risk of ADEs and negative health outcomes [60, 73] but are not easily predictable. As such, prescription of antimicrobials should always be preceded by a review of a patient's medication list for sources of potential drug–drug interactions (Table 2) [120–142]. Some interactions are particularly bothersome and deserve special attention.

Prescription of trimethoprim and sulfamethoxazole inhibits resorption of potassium in the distal renal tubule, resulting in increased risk of hyperkalemia and hospitalization [143]; caution is needed when used along with angiotensin-converting enzyme inhibitors (ACEi) and potassium-sparing diuretics. Additionally, trimethoprim/sulfamethoxazole increases the toxicity of phenytoin [144] and sulfonylureas [145], leading to neurological symptoms (confusion, vomiting and coma) and increasing the risk of hypoglycemia, respectively. Another important interaction involves antibiotics able to suppress bacterial growth and production of vitamin K in the gastrointestinal tract, thereby potentiating the effect of warfarin. Indeed, prescription of warfarin with some medications, including quinolones, fluconazole, trimethoprim-sulfamethoxazole, and amoxicillin, may increase the international normalized ratio (INR) and the risk of bleeding [146]. Similarly, some antimicrobials interfere with the activity of the P-gp transporter and CYP3A4 enzyme, thus leading to potential interactions with direct oral anticoagulants (DOACs) [147, 148]. Rifampin

Table 2 Drug–drug interactions

Antimicrobial agent	Interacting drugs ➞ adverse side effect
Aminoglycosides [120]	Amphotericin B, cyclosporin, cisplatin, loop diuretics, tacrolimus, vancomycin ➞ ↑ nephrotoxicity
Amoxicillin, ampicillin [121, 122]	Allopurinol ➞ rash
Fluoroquinolones [123–126]	Medications containing aluminum, iron, magnesium, or zinc; antacids; sucralfate ➞ ↓ absorption of fluoroquinolones
Ciprofloxacin	Antiarrhythmics ➞ ventricular arrhythmias
	Calcium-containing supplements ↓ absorption of ciprofloxacin
	Theophylline ➞ ↑ theophylline concentration
	Warfarin ➞ ↑ bleeding risk
Linezolid [127]	Serotoninergic drugs (MAOIs, TCAs, SSRIs) ➞ serotonin syndrome
Azithromycin [128]	Drugs containing aluminum or magnesium ➞ ↓ azithromycin absorption
Clarithromycin and erythromycin [129–131]	Calcium channel blockers, HMG-Co-A reductase inhibitors, cyclosporine, digoxin, theophylline, and warfarin; DOACs ➞ ↑ concentration of interacting drugs; ↑ concentration of the antibiotic (calcium channel blockers).
Metronidazole [132]	Warfarin ➞ ↑ bleeding risk
	Alcohol ➞ disulfiram-like reaction
Rifampin [133]	Antacids ➞ ↓ rifampin concentration Antiarrhythmics, benzodiazepines, calcium channel blockers, corticosteroids, digoxin, enalapril, estrogens and/or progestins, methadone, phenytoin, tamoxifen, theophylline, valproate, voriconazole, warfarin, DOACs ➞ ↓ concentration of the interacting drugs
Tetracyclines [134–138]	Drugs containing aluminum, calcium, iron or magnesium; bismuth subsalicylate ➞ ↓ tetracycline absorption
	Digoxin ➞ ↑ digoxin toxicity
Triazole antifungals [139–141]	Carbamazepine, phenobarbital, phenytoin and rifampin ➞ ↓ concentration of antifungals
	Antiarrhythmics, benzodiazepines, calcium channel blockers, corticosteroids, digoxin, HMG-CoA reductase inhibitors, sulfonylureas, warfarin, DOACs ➞ ↑ concentration of interacting drugs
Itraconazole, ketoconazole	Antacids, H2-receptor antagonists, PPIs ➞ ↓ antifungal absorption
Voriconazole	Phenytoin, PPIs ➞ ↑ concentration of interacting drugs
Trimethoprim-sulfamethoxazole [142]	Phenytoin ➞ ↑ phenytoin concentration Sulfonylureas ➞ hypoglycemia Warfarin ➞ ↑ bleeding risk ACE inhibitors, potassium-sparing diuretics ➞ hyperkalemia

ACE angiotensin-converting enzyme, *DOACs* direct oral anticoagulants, *HMG-CoA* 3-hydroxy-3-methylglutaryl coenzyme A, *MAOIs* monoamine oxidase inhibitors, *PPIs* proton pump inhibitor, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

is both a cytochrome inducer and a P-gp inducer. Indeed, its coadministration with DOACs will accelerate their metabolism, thus causing a reduction of bioavailability of anticoagulants, with subsequent increased thrombotic risk. Conversely, administration of DOACs with inhibitors of CYP or P-Gp will slow the metabolism of DOACs, thus increasing their serum concentration and, consequently, the risk of bleeding. Antimicrobial CYP inhibitors include itraconazole, fluconazole, ketoconazole, clarithromycin, and erythromycin, while antimicrobial P-gp transporter inhibitors include azithromycin, clarithromycin, erythromycin, itraconazole, and ketoconazole [147, 148].

3.4 Cognitive Impairment

Cognitive impairment represents a risk factor for poor antimicrobial medication adherence and development of several infectious diseases, including respiratory and urinary tract infections, skin and soft tissue infections, and sepsis [149, 150], which are both associated with increased mortality in this setting [151, 152].

The diagnosis of infections in patients with cognitive impairment of varying degree and severity still represents a clinical challenge because of several factors. First, a diagnosis of infection is often delayed as cognitive dysfunction affects patients' ability to communicate their symptoms and physicians' capacity to clinically monitor the course of the disease [149]. Furthermore, typical symptoms of infections such as fever, chills, and urinary complaints, are often lacking in patients with low cognitive reserve, while atypical symptoms often include neurological symptoms that may contribute to worsen cognitive function, as well as to delay diagnosis and appropriate management. In this regard, both urinary tract and respiratory tract infections often manifest with confusion, dizziness, memory complaints, and coma [153–155]. In outpatient settings, appropriate diagnosis is also complicated by difficulties in obtaining high-quality clinical specimens from patients unable to collect these samples because of poor cognitive function [149].

Even when infections are promptly recognized and diagnosed, their appropriate management can be difficult because of decreased adherence to therapeutic regimens and potential drug–drug and drug–disease interactions [156–158]. Memory impairments and forgetfulness may affect both timing and taking adherence, which have distinct impacts on clinical outcomes depending on the pharmacologic properties of the administered drugs [159]. Indeed, for time-dependent antibiotics, administering multiple doses over the course of the day is necessary to reach the clinical effectiveness, especially for short half-life molecules such as β-lactams. As a consequence, both timing and taking adherence are equally important. Conversely, for concentration-dependent antibiotics, taking adherence is more important than timing adherence, especially for long half-life antibiotics, as reaching the peak serum concentration is necessary to ensure clinical success [159]. In any case, simplification of complex drug regimens and communications between clinicians, patients, and caregivers may help increase adherence and improve clinical outcomes to antimicrobial regimens.

Another factor of concern is represented by the increased vulnerability of cognitively impaired individuals to the neurotoxic effects of antimicrobials [160]. Indeed, several antibiotics, including penicillins, levofloxacin, macrolides, metronidazole, and antimycobacterial agents, as well as antivirals and antimalarials, may cause cognitive adverse effects ranging from mild cognitive problems to encephalopathy and coma [149]. Many neurological disorders such as epilepsy and stroke can increase the permeability of the blood–brain barrier and further enhance β-lactam neurotoxicity [161]. Furthermore, prolonged administration of some antimicrobial medications, such as vancomycin, ampicillin, and streptozocin, may induce profound changes in the gut microbiota composition, altering the gut–brain axis involved in the pathogenesis of several neurodegenerative disorders [162–165]. A cumulative duration-dependent relationship between dementia incidence and days of antibiotic exposure recently emerged in a retrospective cohort study [166]. The association was significant after adjustment for several confounding factors potentially related to cognitive decline, including infectious diseases and dysphagia [166]. Furthermore, exposure to long-term antibiotic use during mid-life was recently associated with decline in cognitive performance [167]. In a study conducted among patients with Alzheimer's disease, a 12-month treatment with doxycycline and rifampin compared with placebo caused a decline in cognitive function [168]. However, to date the evidence supporting these associations is still limited and needs further studies to be confirmed.

4 Adverse Events from Antimicrobial Agents among Older Patients

All classes of antimicrobials, such as antibiotics, antifungals, antimycobacterial agents, and antivirals, may cause adverse reactions that can involve one or more organ systems (Tables 3, 4). Older patients using antimicrobials have a higher risk of ADRs due to age-related changes in PK and PD, multimorbidity, and polypharmacy. Although the use of antimicrobials is widespread among older adults, high-quality data on ADRs in the older population are often lacking and only limited information is available on specific ADRs and their prevalence.

Table 3 Adverse drug reactions to antibiotics

Antimicrobial agents	Common adverse reactions	Adverse reactions at increased risk in older adults
Aminoglycosides [170–174]	Nephrotoxicity, ototoxicity	Nephrotoxicity, ototoxicity
Tetracyclines [176, 177]	Photosensitivity, cutaneous infections, esophagitis, hepatotoxicity, pancreatitis	–
Sulfonamides and trimethoprim [171–173]	Nephrotoxicity, gastrointestinal intolerance, hypersensitive reactions, dermatologic reactions	Nephrotoxicity, neurotoxicity
Polymyxins [101, 169]	Nephrotoxicity and neurotoxicity	Nephrotoxicity
Oxazolidinones [101, 172]	Thrombocytopenia, neurotoxicity	–
Macrolides [102, 175, 176]	Gastrointestinal intolerance, hepatotoxicity, cardiotoxicity, ototoxicity	Ototoxicity, neurotoxicity
Glycopeptide [171, 175]	Nephrotoxicity, ototoxicity, red man syndrome	Nephrotoxicity
Lipopeptides [179]	Nausea, muscle toxicity, eosinophilic pneumonia	–
β-Lactams [171, 173, 180–188]	Hypersensitive reactions, gastrointestinal intolerance	Nephrotoxicity, neurotoxicity *Clostridioides difficile* infection (broad-spectrum penicillins and combinations, third/fourth-generation cephalosporins, carbapenems)
Fluoroquinolones [189–191]	Tendinopathy, *Clostridioides difficile* infection, cardiotoxicity	Tendinopathy, neurotoxicity, *Clostridioides difficile* infection
Nitroimidazoles [172]	Neurotoxicity, cardiotoxicity	–
Nitrofurans [101, 172]	Neurotoxicity	Neurotoxicity
Lincosamides [175, 183]	*Clostridioides difficile* infection	*Clostridioides difficile* infection

Table 4 Adverse drug reactions to antifungals, antimycobacterial agents, and antivirals

Antimicrobial class/agent	Common adverse reactions	Adverse reactions at increased risk in older adults
Echinocandins [139–141]	Nausea, hepatotoxicity, skin rash, phlebitis	–
Triazoles [139–141]	Gastrointestinal intolerance, skin rash, hepatotoxicity	Hepatotoxicity, neurotoxicity
Amphotericin B [141, 192, 194]	Infusion-related reactions, hepatotoxicity, hematological effects, nephrotoxicity	Nephrotoxicity
Flucytosine [141]	Inhibition of the bone marrow, hepatotoxicity	–
Isoniazid [175, 184, 195, 196]	Hepatotoxicity	Hepatotoxicity, neurotoxicity
Rifampin [171, 175, 184]	Red-orange discoloration of urine, tears, and sweat	Nephrotoxicity, hepatotoxicity (association with isoniazid)
Nucleosides/nucleotides excluded reverse transcriptase inhibitors [198–203]	Nephrotoxicity, gastrointestinal intolerance	Neurotoxicity
Derivatives of phosphonic acid [171, 204]	Nephrotoxicity	Nephrotoxicity
Neuraminidase inhibitors [205, 206]	Gastrointestinal intolerance	–
Interferon-α [207, 208]	Influenza-like symptoms, nausea, headache, depression, alopecia	–
Nucleoside/nucleotide reverse transcriptase inhibitors [209, 210]	Mitochondrial toxicity	Nephrotoxicity, bone toxicity
Non-nucleoside reverse transcriptase inhibitors [211, 212]	Dermatologic reactions, hepatotoxicity	–
Protease inhibitors [213, 214]	Hyperlipidemia, lipodystrophy, hyperglycemia, insulin resistance	–

4.1 Adverse Drug Reactions to Antibiotics

4.1.1 Aminoglycosides

Aminoglycosides can potentially cause ototoxicity and nephrotoxicity [169, 170]. Older patients are more vulnerable and have a greater risk of toxicity with prolonged length of therapy (≥ 3 days) and concomitant use of ototoxic or nephrotoxic agents [101, 171]. Ototoxicity occurs as both vestibular (e.g., dizziness, ataxia, nystagmus) and cochlear (e.g., hearing loss) dysfunction in up to 15% and 2–25% of patients, respectively [172]. Nephrotoxicity is more common than ototoxicity, affecting between 10 and 30% of patients and presenting as acute tubular necrosis [171, 173]. Chinzowu et al. analyzed the absolute risk of acute kidney injury among older adults due to aminoglycoside exposure. Among 1853 patients across eight studies, 15.8% developed acute kidney injury after treatment with aminoglycosides. The absolute risk was 15.1% (95% confidence interval [CI] 12.8–17.3%) and was significantly higher than the average risk among younger patients (10.5%, 95% CI 10.1–10.8%) [174].

4.1.2 Tetracyclines

All tetracyclines such as doxycycline, minocycline, and tigecycline can potentially cause adverse reactions, including photosensitivity, cutaneous infections, esophagitis, and hepatotoxicity [175, 176], but the prevalence among older adults has not been specifically investigated.

4.1.3 Sulfonamides and Trimethoprim

Sulfonamides are among the most common drugs associated with nephrotoxicity, presenting as acute interstitial nephritis and crystal nephropathy [171, 173]. Other common toxicities induced by trimethoprim-sulfamethoxazole are gastrointestinal, hypersensitivity, and dermatologic reactions [172]. Although rare, the risk of neurotoxicity induced by sulfonamides is higher among older adults. Symptoms of neurotoxicity include delirium and psychosis, and more commonly, headache and drowsiness. The mechanisms are unknown but seem to be related to glutathione deficiency that is often present in geriatric patients [101, 169, 172].

4.1.4 Polymyxins

Polymyxins are frequently associated with nephrotoxicity and neurotoxicity. Colistin induces nephrotoxicity, and particular attention is required among older patients [101]. Among neurotoxic symptoms, headache, dizziness, and lower limb weakness are the most common [169].

4.1.5 Oxazolidinones

Thrombocytopenia is the major adverse effect after linezolid treatment. Duration of treatment and low baseline platelet count are associated with a higher risk of this ADR [101]. Symptoms of neurotoxicity have also been documented. Among these symptoms, headaches and peripheral neuropathy seem to be the most common but the incidence in older patients is unknown. The concomitant use of linezolid and agents that stimulate the CNS should be avoided due to the higher risk of neuropsychiatric events [172].

4.1.6 Macrolides

It is well-known that this class of drugs might cause gastrointestinal intolerance, hepatotoxicity, cardiotoxicity, and ototoxicity [172, 175, 176]. Ototoxicity presents as hearing decrements and tinnitus. For these reasons, macrolides should be avoided in older patients with baseline hearing problems [176]. Several studies reported a high risk of QT prolongation leading to cardiac arrhythmias, underlying that this ADR is limited to patients with higher-risk baseline such as pre-existing cardiovascular conditions and concomitant use of drugs, leading to arrhythmias [73, 176, 177]. However, other studies did not confirm the risk of arrhythmias [101]. Neurotoxicities such as delirium and psychosis are rare, but although the association is still not clear, neurotoxic events may occur more easily in older patients [172]. A recent systematic review by Chinzowu et al. highlighted an overall risk of acute kidney injury among older patients of 0.3% (95% CI 0.3–0.3%) [174].

4.1.7 Glycopeptides

Nephrotoxicity, ototoxicity, and, more rarely, red man syndrome (hypersensitivity reaction with signs of flushing and/or erythematous rash on the upper torso, neck, and face) are typically associated with glycopeptides [171]. Nephrotoxic events are the most feared of these adverse events because they occur with a high risk in older patients [101]. A recent meta-analysis by Hirai et al. highlighted that among 634 patients across eight studies treated with teicoplanin, the overall incidence was 11.0% (95% CI 8.0–13.0), with a higher risk in patients aged > 65 years [178]. Chinzowu et al. analyzed the risk of acute kidney injury among older adults in treatment with glycopeptides across eight studies (total of 23,431 participants), finding an overall absolute risk of 19.1% (95% CI 15.4–22.7%) [174]. The nephrotoxicity occurs as acute tubular necrosis but the mechanism of ADR

is unknown [171, 173]. Ototoxicity occurs as hearing loss and/or tinnitus and is generally reversible [169, 175].

4.1.8 Lipopeptides

Common mild ADRs are constipation, nausea, and vomiting, while other less frequently reported but severe ADRs include myopathy and rhabdomyolysis, eosinophilic pneumonia, drug reaction with eosinophilia and systemic symptoms (DRESS), tubulointerstitial nephritis, peripheral neuropathy, and neutropenia [179]. Unfortunately, no data are available referring to the older population.

4.1.9 β-Lactams

β-Lactam antibiotics are among the most prescribed drugs in both community and hospital settings [180]. These antibiotics are grouped together based on the β-lactam ring in their chemical structure, and subdivided into four families: penicillins, cephalosporins, carbapenems, and monobactams. Hypersensitive reactions are common and frequent ADRs associated with the use of penicillins, involving approximately 10% of the population, and with higher rates reported among older and hospitalized patients [180]. Patients who are allergic to penicillins may show cross-reactivity towards the other class. Nevertheless, the cross-reactivity seems to be overestimated [180, 181]. β-lactam antibiotics are commonly associated with nephrotoxicity (acute interstitial nephritis), especially in older patients [73, 171, 173]. Gastrointestinal reactions such as nausea, vomiting, and diarrhea are frequently associated with β-lactams, more often in older patients than in adults [182]. Penicillins (broad spectrum), cephalosporins (third/fourth-generation) and carbapenems may induce *Clostridioides difficile* diarrhea and colitis with a higher risk in patients ≥ 65 years of age [183]. Hepatotoxicity presenting as cholestasis and jaundice is commonly associated with the use of amoxicillin-clavulanic acid and flucloxacillin, with older age and longer duration of treatment as risk factors [181, 184]. Piperacillin/tazobactam may exacerbate heart failure, delivering a high sodium load [185]. Although rare, serious neurotoxicity related to β-lactam antibiotics are described in the literature [186–188], with a high risk in older patients using piperacillin/tazobactam, cephalosporins (particularly cefepime), and carbapenems [101, 172, 181]. Neurotoxic symptoms include seizures, encephalopathy, myoclonus, tremors, hyperexcitability, and hyperactivity [101, 172, 181, 186–188]. The ability of β-lactam antibiotics to induce neurotoxicity seems to be linked to the β-lactam ring [169, 186]. Although this adverse reaction may be difficult to recognize in critically ill patients, Payne et al. analyzed the neurotoxicity of cefepime (median age of 69 years), finding that 26% of patients experienced neurotoxicity despite appropriate dosing [188].

4.1.10 Fluoroquinolones

In general, fluoroquinolones are well tolerated; however, it is well-known that tendinopathy such as Achilles tendon rupture and Achilles tendinitis are correlated with their use [189]. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulatory authorities recommended special caution in older adults because these patients are at higher risk of tendon injury and it is suggested they avoid concomitant treatment with a fluoroquinolone and a corticosteroid [190, 191]. CNS effects such as dizziness, hallucinations, and seizures are not frequent but seem related to older age [172, 189], particularly in patients aged > 80 years [175]. Fluoroquinolones can rarely cause cardiotoxicity, inducing prolongation of the QT interval and increasing the risk of arrythmia [101, 189]. Furthermore, an increased risk of *Clostridioides difficile* infection is well-documented among older patients in treatment with fluoroquinolones [176, 183].

4.1.11 Nitrofurans

Common adverse reactions of nitrofurantoin include neurotoxicity, such as headache, dizziness, and drowsiness. The risk is higher in older adults [101, 172].

4.1.12 Nitroimidazole

Metronidazole can cause neurotoxicity and cardiotoxicity with prolonged use but the ADRs occur across all ages and are not specific for older adults [73, 172].

4.1.13 Lincosamide

The most well-known ADR of clindamycin is its disruptive effect on gut flora and the resultant diarrhea and colitis due to the overgrowth of *Clostridium difficile* [175, 183].

4.2 Adverse Drug Reactions to Antifungals

4.2.1 Echinocandins

Echinocandins are reportedly well tolerated [141]. The most common ADRs of echinocandins are mild and reversible, such as nausea, elevated hepatic enzymes, rash, and phlebitis [139–141]. Caution should be advised in older patients with liver dysfunction.

4.2.2 Triazoles

ADRs of triazoles include abdominal pain, nausea, vomiting, diarrhea, skin rash, and sometimes hepatotoxicity ranging from elevation of serum aminotransferases to fatal

hepatic failure, especially in patients with pre-existing hepatic dysfunction [139–141]. Itraconazole and fluconazole can potentially cause cardiotoxicity for prolongation of the QT interval [73] and itraconazole can occasionally cause worse heart failure. Voriconazole can cause neurotoxicity, including visual and auditory hallucinations. The safety of voriconazole is similar in older patients compared with adults, but in clinical trials, voriconazole plasma concentrations were 80–90% higher in the former group [141].

4.2.3 Amphotericin B

Infusion-related reactions, hepatotoxicity, hematological effects, and nephrotoxicity are typically associated with the use of amphotericin B [141, 192]. Nephrotoxicity is the most feared of these because it can occur in most older patients, presenting with an increased creatinine level, hypokalemia, and/or hypomagnesemia [139–141, 192]. Although the lipid formulations have been shown to be substantially less toxic than conventional amphotericin B, particularly with respect to nephrotoxicity [193], concomitant use of other nephrotoxic drugs should be avoided [141, 192]. Furthermore, amphotericin B may cause heart failure but symptoms normalize with discontinuation of therapy [194].

4.2.4 Flucytosine

High plasma levels of flucytosine, maintained for a long time, cause reversible inhibition of the bone marrow and hepatic dysfunction. The concurrent use of flucytosine and nephrotoxic drugs should be avoided due to the risk of accumulation of flucytosine [141].

4.3 Adverse Drug Reactions to Antimycobacterial Agents

4.3.1 Isoniazid

It is well-known that isoniazid is hepatotoxic and the risk of hepatotoxicity increase with the age [175, 184, 195, 196]. Among antituberculosis drugs, isoniazid is the most hepatotoxic and patients aged ≥ 60 years are 3.5 times more likely to have liver injuries [184]. The risk increases with the association of rifampin [184]. Neurotoxic effects are common and include peripheral neuropathy [175], ataxia, restlessness, and insomnia [197].

4.3.2 Rifampin

Rifampin frequently causes red-orange discoloration of urine, tears, and sweat [175]. Nephrotoxicity is common in older adults [73] and the incidence varies from 1.8 to 16%, but the discontinuation of therapy leads to recovery in about 3 weeks [171]. As explained above, the combination of rifampin with isoniazid increases the risk of hepatotoxicity [184].

4.4 Adverse Drug Reactions to Antivirals

4.4.1 Nucleosides/Nucleotides Excluded Reverse Transcriptase Inhibitors

Acyclovir and ganciclovir are antiviral drugs used in the treatment of infections against herpes simplex virus and varicella zoster and against cytomegalovirus, respectively [198]. These drugs may be associated with nephrotoxicity by crystallization, precipitation, and obstruction of the renal tubule. In particular, the nephrotoxicity indication of acyclovir ranges from 12 to 48% [171]. Acyclovir is well tolerated but can cause gastrointestinal upset and headache [199]. Neurotoxicity (signs of confusion, hallucinations, and agitation) is a rarer ADR and occurs mainly in older patients or patients with renal dysfunction [200]. Given the high risk of neurological ADRs, older patients should be carefully monitored for these effects, which are generally reversible once treatment is discontinued [199]. The ADRs of ganciclovir are neutropenia, thrombocytopenia, mucositis, and hepatic dysfunction, and should be administered in older patients under close renal supervision to avoid toxicity [201]. Remdesivir and molnupiravir are antivirals for the treatment of coronovairus disease 2019 (COVID-19). The most commonly encountered ADRs with the use of remdesivir are nausea, vomiting, and transaminase elevations [202]. Molnupiravir can frequently cause headaches, diarrhea, and nausea [203]. Unfortunately, the prevalence of ADRs of remdesivir and molnupiravir in older patients is unknown.

4.4.2 Derivatives of Phosphonic Acid

Foscarnet is a direct-acting antiviral derived from phosphonic acid. When present, ADRs are severe and include nephrotoxicity due to renal tubule obstruction [171] and neurotoxicity. Therefore, foscarnet should be used with caution in older patients with impaired renal function [204].

4.4.3 Neuraminidase Inhibitors

Oseltamivir and zanamivir are neuraminidase inhibitors of influenza A and B viruses. Gastrointestinal disturbances can occur with oseltamivir. Zanamivir can cause cough, sore throat, and, in asthmatic patients, bronchospasm [205, 206].

4.4.4 Interferon-α

Interferon-α could be used in older patients for the treatment of hepatitis B and C. Common ADRs include fever,

influenza-like symptoms, nausea, headache, depression, and alopecia that may be more severe in older adults [207, 208].

4.4.5 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

Although rarely reported, the risk of causing mitochondrial toxicity is a hallmark of this class of drugs. Toxicity is manifested by symptoms of myopathy, neuropathy, and lactic acidosis with fatty liver, particularly with lamivudine. Even at low doses, the use of adefovir-dipivoxil can cause nephrotoxicity. Tenofovir can cause renal and bone toxicity in HIV-infected patients. Particular caution should be exercised in older patients at risk of renal dysfunction and osteoporosis [209, 210].

4.4.6 Non-nucleoside Reverse Transcriptase Inhibitors

First-generation non-nucleoside reverse transcriptase inhibitors such as nevirapine and efavirenz have been associated with skin erythema and hepatotoxicity [211]. Efavirenz can cause neurotoxicity and cardiotoxicity, but unfortunately the prevalence among older adults has not been specifically investigated [212].

4.4.7 Protease Inhibitors

Typical ADRs of this class of drugs are the risk of hyperlipidemia, lipodystrophy, hyperglycemia, and insulin resistance, but limited information is available on their prevalence among older adults [213]. Nirmatrelvir is a protease inhibitor antiviral used in combination with ritonavir for the treatment of COVID-19. The most common ADRs reported with this treatment are dysgeusia, headache, and gastrointestinal disturbances, but no studies have been performed in older patients [214].

5 Interventions to Improve Safety and Tolerability

Appropriate use of antimicrobials in the elderly can be lifesaving given the high prognostic impact of infections in this population. Inappropriate antimicrobial prescriptions in older patients are instead associated with increased risk of antimicrobial resistance, adverse side effects, morbidity, and mortality [215]. A barrier for the diagnosis and prevention of antimicrobial inappropriate prescriptions in clinical practice is currently represented by the lack of a gold-standard tool to evaluate antimicrobial inappropriateness. This is partly related to the different definitions of inappropriate antimicrobial treatment found in the literature and to the paucity of studies specifically conducted in elderly patients (Table 5) [216–226]. Some studies have defined inappropriateness based on clinical variables (presence of signs and/or symptoms of infection despite antimicrobial treatment [217, 219], while others have considered the appropriateness of diagnosis, dosage, route of administration, or duration of antimicrobial treatment [222, 224–227]. More objective methods to evaluate appropriateness are based on positivity of microbiological testing results but they are time-consuming and are not always available [218]. Finally, some studies used multiple criteria to evaluate appropriateness, based on clinical examination, laboratory evaluations, and adherence to guideline-based recommendations [220, 221, 223]. Recent studies comparing distinct criteria for inappropriate antimicrobial prescriptions have shown limited agreement among them [228, 229]. The proportion of inappropriate antimicrobial treatment varied widely across studies and care settings, as a likely result of heterogeneity of criteria used to evaluate appropriateness and inappropriateness of antimicrobial prescriptions; however, despite the fact that the definition of a gold-standard measure for inappropriate antimicrobial use has not yet been provided, inappropriate antimicrobial prescribing deserves to be addressed because it is associated with poor outcomes among older individuals [230]. In order to improve the appropriateness of antibiotic prescriptions in acute and long-term care settings, several antimicrobial stewardship (AMS) strategies have been implemented and taken into consideration (Table 6) [166, 230–238]. AMS is defined as the careful and responsible management of antimicrobial medications used to treat or prevent infections, in order to provide a prescription of the right drug, at the right time, at the correct dose, and for the appropriate duration [239]. The objectives of AMS include the containment of infectious diseases, appropriate antimicrobial use, and reduction of the emergence and spread of multidrug-resistant microorganisms. Despite these goals being universally recognized, standardized methods for their implementation and monitoring across different settings are still undefined. Distinct interventions are included in AMS programs; formulary modifications, including the choice of monotherapy targeting the more likely microorganism at the site of infection should be preferred over combination therapy whenever possible [240]. Combination therapy using narrow-spectrum antibiotics enhances the synergism of distinct antimicrobial compounds and is particularly active against Gram-negative bacteria [241]. Use of antibiotic resistance breakers, such as β-lactamase inhibitors, can be used to improve the efficacy of antimicrobials against multidrug resistance microorganisms. Another two AMS interventions used to contrast antimicrobial resistance are antimicrobial cycling and de-escalation; antimicrobial cycling consists of antimicrobial rotation aimed at decreasing the selective pressure on a particular drug in order to limit antimicrobial resistance [242], and antimicrobial de-escalation consists of antimicrobial switch

Table 5 Criteria used to evaluate drug inappropriateness

Study	Appropriateness criteria	Prevalence of drug inappropriateness
Cantudo-Cuenca et al.; hospitalized older patients ($N = 184$) [217]	Pharmacist-guided diagnosis based on Loeb's consensus criteria	Emergency department: 85% Hospital or primary care: 46% Long-term care facilities: 42%
Chandrasekhar et al.; hospitalized adults in India ($N = 90$) [216]	Adherence to national guidelines and Gyssens' criteria	70%
Kadri et al.; older patients with HIV ($N = 175$) [218]	Concordance between prescription and blood cultures	67%
Loeb et al.; older patients in long-term care facilities ($N = 646$) [219]	Assessment of prescriptions based on clinical symptoms and signs	42%
Magill et al; hospitalized adults in the US ($N = 1566$) [220]	Antimicrobial use defined as supported if: 1. there was a clinical indication; 2. antimicrobial selection was consistent with international guidelines and/or microbiological data; 3. duration was consistent with international guidelines recommendations	46% for fluoroquinolones 27% for vancomycin
Nguyen-Hoang et al.; hospitalized older patients with sepsis ($N = 134$) [226]	Adherence to recommendations about dosage and route of administration	43%
Núñez-Núñez et al.; hospitalized older patients with antibiotic prescriptions ($N = 1600$) [227]	Adherence to recommendations about dosage and route of administration	49%
Rutten et al.; nursing home residents with suspected UTIs ($N = 114$) [221]	Integrated electronic tool for antibiotic prescribing in urinary tract infections: 1. symptoms and signs; 2. urinalysis; 3. antibiotic treatment; 4. comorbidities	38%
Saatchi et al; community-dwelling older individuals ($N = 5{,}460{,}270$) [222]	Prescription of antimicrobials associated with indication	50%
Tobia et al.; older outpatients ($N = 153$) [223]	Medication Appropriateness Index (MAI): presence of symptoms; drug effectiveness, dosage, route of administration, adherence; drug–drug and drug–disease interactions	35%
van Buul et al; older patients in long-term care facilities ($N = 208$) [224]	Clinical algorithm for appropriateness in respiratory tract infections	14%
Vergidis et al.; older patients in long term care facilities ($N = 752$) [225]	Indication-based	21%

UTIs urinary tract infections

from broad- to narrow-spectrum molecules, when laboratory findings of culture and sensitivity are available [243]; however, despite these opportunities, antimicrobial rotation and de-escalation are poorly studied in older patients. On the other hand, promotion of education and the importance of timely and appropriate microbiology sampling, as well as TDM with feedback, have been shown to be effective in decreasing antibiotic consumption and inappropriate use in long-term care settings [244, 245]. Dose optimization using PK and PD properties is also important. Several antibiotics need dosing modification according to renal and hepatic function to increase the benefits and limit the risk of toxicity and ADEs (Table 7) [121–138, 142, 246–268]; however, despite the importance of dosage adjustments in patients with renal and liver function impairment, these adjustments are rarely made and non-compliance with dosing guidelines is common [60]. In these cases, TDM-guided dosing is the most effective way to ensure optimal drug exposure for several antibiotics [269]. Despite the absence of studies specifically conducted in older patients, current literature has shown benefits of TDM in preventing hematologic toxicity of linezolid, nephrotoxicity of aminoglycosides and vancomycin, and neurotoxicity of β-lactams [269]. However, while there are many barriers to be overcome, AMS interventions have been shown to significantly improve different phases of the prescribing process and mitigate the effects of inappropriate antimicrobial prescribing in both long-term care and acute care older patients [226, 244, 270, 271]. There is then an urgent need to deliver effective and standardized AMS interventions and to find the best way to implement AMS programs in order to maintain their benefit over time.

Table 6 Potential changes required to address antimicrobial misuse in elderly individuals

Area of potential antimicrobial misuse	Evidence-based risks in geriatric populations	Potential actions to improve safety and tolerability
Inappropriate empirical antimicrobial prescribing (prescription of antimicrobials without previous microbiological investigations) [230, 231]	Associated with poorer outcomes	1. In stable and asymptomatic patients, the 'wait and see' approach (wait 2–3 days to have culture results before starting treatment) has to be preferred 2. In unstable or symptomatic patients, or when delaying treatment for the first 2–3 days is not appropriate, the empirical antimicrobial therapy should be started with drugs targeting the likely causative microorganisms (e.g. symptomatic UTIs) 3. In patients with previous hospitalizations and infections, review of recent antimicrobial resistance results is important to guide empirical antimicrobial prescribing
Excessive duration of antimicrobial treatment [232]	Associated with increased antimicrobial-induced adverse effects and antimicrobial resistance outbreaks	1. Duration of antimicrobial treatment should adhere to evidence-based guidelines: antimicrobial courses ≤7 days are as effective as longer courses for most bacterial infections; a course ≤5 days is sufficient for uncomplicated UTIs and respiratory tract infections; topical antifungals for ≤15 days are as effective as longer treatment for most skin conditions 2. Prescribed antimicrobials should be reviewed after 2–3 days of treatment to evaluate clinical response, adverse effects and, eventually, microbiological results 3. Chronic use of renally excreted antimicrobials should be avoided 4. A rapid but timely de-escalation is recommended to reduce the duration of empirical antibiotic treatments [233]
Use of outpatient broad-spectrum or parenteral antimicrobials for older people with end-stage illness or advanced dementia [166]	Broad-spectrum use of antibiotics in end-stage patients have shown contrasting results [235] Caution is needed when administering antibiotics to patients with dementia because of the potential of antibiotic-induced cognitive decline. Treatment of infection in advanced dementia has led to contrasting results	1. Specialized teams aimed at monitoring patients taking outpatient parenteral antimicrobial treatment could prevent rehospitalizations and adverse effects 2. Optimizing the management of antimicrobial use in patients with advanced dementia needs a multidisciplinary approach involving geriatrics and infectious disease specialists, and, in more advanced stages of the disease, palliative care specialists
Use of prophylactic antimicrobial treatment in patients with asymptomatic bacteriuria or minimally symptomatic urinary tract infections [236]	Asymptomatic bacteriuria is widespread in hospitalized older patients and nursing home older residents, especially those with chronic indwelling urinary catheters Evidence from randomized controlled trials does not support prophylactic use of antimicrobials in patients with asymptomatic bacteriuria as it does not prevent recurrent bacteriuria or asymptomatic infection	1. Urinalysis and/or urine cultures should not be routinely performed in asymptomatic patients 2. In patients with minimal symptoms, a watch-and-wait approach is preferred over prompt antimicrobial use In chronically catheterized older patients, the indwelling catheter should be changed before starting the antimicrobial treatment; the urine specimen should be collected from the newly introduced catheter; discontinuation of catheter use whenever possible is key to preventing urinary tract infections

Table 6 (continued)

Area of potential antimicrobial misuse	Evidence-based risks in geriatric populations	Potential actions to improve safety and tolerability
Use of quinolones as empirical treatment for urinary tract infections [236]	Their use is common in community-dwelling and nursing home older patients; quinolones share excellent bioavailability, long half-life, and broad-spectrum activity. However, their adverse effects are particularly common in older individuals. Furthermore, their widespread use concurred to select quinolone-resistant gram-negative bacteria, such as *Escherichia coli*, which may drive multidrug-resistant urinary infections. Additionally, they increase the risk of *C. difficile* gastrointestinal infections	Quinolones should be avoided as first-line empirical therapy unless the patient is known to have a urinary multidrug-resistant organism with a sensibility to quinolones and if no alternative options are available
Antimicrobial treatment for upper respiratory tract infections or acute bronchitis without confirmed bacterial infections [237]	Many non-infectious conditions may cause cough in older patients: chronic obstructive pulmonary disease, chronic bronchitis, adverse drug events, etc. Upper respiratory tract infections are commonly caused by viruses, and empirical antibiotic treatment is often unnecessary (unless for patients with prolonged symptoms and/or underlying lung disease) [237]	Differential diagnosis between bacterial and viral respiratory tract infections is necessary to reduce inappropriate antimicrobial use
Routine antimicrobial treatment for gastroenteritis [234]	Antimicrobials are not routinely recommended for treating gastroenteritis because most cases are caused by viruses rather than bacteria Consider *C. difficile* infection especially in older patients with recent hospitalizations and previous or current antibiotic exposure	Enhance infection prevention and control measures Microbiology testing is always necessary to identify pathogens (e.g. viral testing, stool *C. difficile*) Antimicrobials are recommended in selected cases: 1. Empirical treatment for severe gastroenteritis. Presence of a specific pathogen in a stool specimen in patients with no clinical improvement
Targeted treatment against organisms isolated from skin lesions or chronic ulcers [238]	Diagnosis of infection should be clinical; swabs should be used to identify pathogens where there is a clinical suspicion of infection requiring antimicrobials. Indeed, false positive swabs are common as all wounds and ulcers will contain bacteria If the ulcer or skin lesion does not appear infected, antimicrobials are not indicated (nor systemic or topical) as they do not improve wound healing while increasing the risk of antimicrobial adverse effects and colonization with multidrug-resistant organisms	For non-infected ulcers or skin lesions, active ulcer dressing is the first-line management strategy. Other strategies include the assessment and treatment of pain and underlying causes (e.g. nutritional deficits, pressure injury, diabetes mellitus, vasculopathies, edema) For infected ulcers or skin lesions, systemic antimicrobial therapy is indicated in the case of cellulitis, deep soft tissue, or bone infection

C. difficile Clostridioides difficile, *UTIs* urinary tract infections

Table 7 Recommended dose adjustments of antibiotics according to various degrees of creatinine clearance

Antibiotic	Route of administration	CrCl (mL/min/1.73 m^2) and recommended dosage
β-Lactams		
Amoxicillin [121]	PO	> 30: 250–1000 mg q8h 10–30: 250–500 mg q12h < 10: 250–500 mg q24h
Amoxicillin/clavulanate [246]		> 30: 875/125 mg q12h 10–30: 250–500/125 mg q12h < 10: 250–500/125 mg q24h
Ampicillin/sulbactam [122]	IV	≥ 30: 1.5–3 g q6–8h 15–29: 1.5–3 g q12h < 15: 1.5–3 g q24h
Cefazolin [247]	IV	> 54: 1–2 g q8h 35–54: 1–2 g q12 h 11–34: 0.5–1 g q12 h ≤ 10: 0.5–1 g q18–24h
Cefepime [248]	IV	> 60: 0.5–2 g q8–12h 30–60: 0.5–2 g q12–24h 11–29: 0.5–2 g q24h ≤10: 0.25–1 g q24h
Cefotaxime [249]	IV	≥ 20: 1–3 g q6–12h < 20: Change maintenance dose to 1–2 g q24h
Cefoxitin [250]	IV	> 50: 1–2 g q8–12h 30–50: Change maintenance dose to 1–2 g q12–24h 10–29: Change maintenance dose to 0.5–1 g q12–24h < 10: Change maintenance dose to 0.5–1 g q24–48h
Ceftazidime [251]	IV	> 50: 1–2 g q8h 31–50: 1 g q12h 16–30: 1 g q24h 6–15: 500 mg q24h < 6: 500 mg q48h
Ceftriaxone [252]	IV	No adjustment needed 1–2 g q12–24h
Cefuroxime [253, 254]	PO	250–500 mg q12h. No adjustment needed
	IV	> 20: 0.75–1.5 g q8h 10–20: 750 mg q12h < 10: 750 mg q24h
Cephalexin [255]	PO	≥ 30: 0.25–1 g q6h 15–29: 250 mg q8–12h 6–14: 250 mg q24h < 6: 250 mg q48–60h
Ertapenem [259]	IV	≥ 30: 1 g q24h < 30: 500 mg q24h
Imipenem and cilastatin [260]	IV	≥ 90: 500–1000 mg q6–8h 60–89: 400–750 mg q6–8h 30–59: 300–500 mg q6–8h 15–29: 200–500 mg q6–12h < 15: Contraindicated unless dialysis is instituted within 48 h
Meropenem [262]	IV	> 50: 500–1000 mg q6–8h 26–50: 500–1000 mg q12h 10–25: 250–500 mg q12h < 10: 250–500 mg q24h
Oxacillin [265]	IV	No adjustment needed 250–1000 mg q4–6h

Table 7 (continued)

Antibiotic	Route of administration	CrCl (mL/min/1.73 m^2) and recommended dosage
Piperacillin/tazobactam [263]	IV	*Traditional infusion* > 40: 3.375 q6h or 4.5 g q8h 20–40: 2.25 g q6h < 20: 2.25 g q8h *Extended 4-h infusion* ≥ 20: 4.5 g q8h < 20: 4.5 g q12h *Antipseudomonal infusion* > 40: 4.5 g q6h 20–40: 3.375 g q6h < 20: 2.25 g q6h
Ticarcillin [266]	IV	> 60: 3 g q24h 30–60: 2 g q4h 10–30: 2 g q8h < 10: 2 g q12h < 10 and hepatic dysfunction: 2 g q24h
Quinolones		
Ciprofloxacin [123, 124]	PO	> 50: 250–750 mg q8–12h 30–50: 250–500 mg q12h 5–29: 250–500 mg q18h < 5: 250–500 mg q24h
	IV	> 30: 200–400 mg q8–12h 5–29: 200–400 mg q18–24h
Levofloxacin [125]	PO/IV	≥ 50: 250–750 mg q24h 20–49: 250–750 mg q24–48h < 20: 250–500 mg q48h
Moxifloxacin [126]	PO/IV	No adjustment needed 400 mg q24h
Macrolides		
Azithromycin [128]	PO/IV	No adjustment needed 250–500 mg q24h
Clarithromycin [129]	PO	≥ 30: 0.5–1 g q12h < 30: 0.25–0.5 g q12h
Erythromycin [130, 131]	PO	≥ 10: 250–800 mg q6–12h < 10: 125–400 mg q6–12h
	IV	≥ 10: 15–20 mg/kg divided q6–8h < 10: 50% total dose at the same interval
Tetracyclines		
Doxycycline [135, 136]	PO/IV	No adjustment needed 50–100 mg q12h
Minocycline [137]	PO	No adjustment needed Loading dose of 200 mg q24h followed by 100 mg q12h
Tetracycline [134]	PO	> 50: 250–500 mg q6–12h 10–50: 250–500 mg q12–24h < 10: 250–500 mg q24h
Tigecycline [138]	IV	No adjustment needed 100 mg followed by 50 mg q12h (decrease maintenance dose to 25 mg in hepatic dysfunction, Child–Pugh C)
Others		
Clindamycin [256, 257]	PO	No adjustment needed 150–450 mg q6–8h
	IV	No adjustment needed 600–1200 mg q6–12h
Daptomycin [258]	IV	≥ 30: 4–6 mg/kg q24h < 30: 4–6 mg/kg q48h

Table 7 (continued)

Antibiotic	Route of administration	CrCl (mL/min/1.73 m^2) and recommended dosage
Isoniazid [261]	PO	No adjustment needed 5 mg/kg up to 300 mg q24h
Linezolid [127]	PO/IV	No adjustment needed 400–600 mg q12h
Metronidazole [132]	PO/IV	≥ 10: 500 mg q8h < 10, or severe hepatic impairment: consider 250 mg q8h if duration > 14 days
Nitrofurantoin [264]	PO	≥ 60: 100 mg q12h < 60: Not recommended (poor effect and increased toxicity)
Rifampin [133]	PO/IV	No adjustment needed 10 mg/kg up to 600 mg q24h
Trimethoprim/sulfamethoxazole [142]	PO	> 30: 800/160 mg q12h 15–30: 400/80 mg q12h < 15: Not recommended
	IV	> 30: 8–20 mg/kg (based on trimethoprim component) administered in 2–4 doses q6–8h 15–30: Half the usual regimen < 15: Not recommended
Vancomycin [267, 268]	PO	No adjustment needed 125 mg q6h
	IV	≥ 90: 15–20 mg/kg q12h 70–89: 15–20 mg/kg q8h 46–69: 15–20 mg/kg q12h 30–45: 15–20 mg/kg q18h 15–29: 15–20 mg/kg q24h < 15: Monitor levels to determine when to dose

CrCl creatinine clearance, *IV* intravenously, *PO* orally, *qxh* every *x* hours

6 Conclusions

Inappropriate prescription of antimicrobials to older patients represents a clinical challenge and a global issue that contributes to the spread of multidrug resistant microorganisms. Age-related changes in PK and PD processes increase the risk of drug underexposure that predisposes to the emergence of resistance, as well as of drug overexposure with potential adverse effects and drug discontinuation for poor tolerability. Multiple chronic diseases and polypharmacy complicate the choice of proper antimicrobial treatment and further increase the risk of adverse effects. Selected AMS interventions addressing adherence to guidelines, dosage adjustment in liver and kidney dysfunction, as well as formulary adaptations and TDM can be life-saving and can improve the safety and effectiveness of antimicrobial treatments. However, standardization of AMS strategies is necessary for their implementation in clinical practice across distinct settings of care. Prospective clinical trials involving older patients are required, ideally focusing on the population older than 80 years of age, which is often neglected and poorly represented. In the meanwhile, clinicians are advised to prescribe judiciously to prevent unnecessary treatment and decrease the risk of inappropriate prescriptions in older patients with infectious diseases.

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