**Considerations on antibiotic therapy in elderly patients: a brief review**

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**Abstract**

With the increasing number of elderly people, more and more attention has been paid to prescriptions of these population, especially to the antimicrobial drugs. Due to physiological changes, comorbidity, immunosuppression and other factors, antibacterial drugs are significantly affected by those in the elderly. It is important to balance the efficacy and safety of antibiotics for the elderly and minimize the toxicity meanwhile maximize the efficacy. This brief review discusses pharmacokinetics and pharmacodynamics, drug-resistant bacteria, adverse drug reactions and drug-drug interactions that should be considered when prescribing antibacterial drugs for the elderly.

**Key words:** the elderly; antibiotics; PK/PD; adverse drug reactions; drug-drug interactions

**1.Introduction**

According to World Health Organization (WHO), the number of people aged over 60 years, will have a sharp rise from 900 million to 2 billion between 2015 and 2050 (moving from 12% to 22% of the total global population) [1]. Antibiotics are commonly prescribed in the geriatric population, and antibiotic overuse in elderly are more around 50% per capita than young adults [2]. Different characters in pharmacokinetics (PK) and pharmacodynamics (PD) from general population, comorbidities such as cardiovascular, cerebrovascular diseases and cancer, much more potential drug-drug interactions (DDIs) and adverse drug reactions (ADRs), which pose a major challenge of optimizing antibiotics therapy in the elderly [3]. Therefore, making prescriptions in the elderly are tough, particularly in balancing the efficacy, safety of drugs, and tolerance and compliance of patients. Currently, multi-drug-resistant (MDR) bacteria has become a commonplace and caused an increasing burden in the elderly. In this review, we outline the changes of PK/PD in the elderly, and discuss the importance of DDIs and ADRs in antibiotic treatment.

**2.Pharmacokinetic Considerations**

The physiological changes related to drug absorption in elderly patients are mainly as follows

(1) Decreased blood flow in the gastrointestinal tract may lead to the prolonged peak time;

(2) Small intestinal mucosa atrophy lead to decreased absorption;

(3) Delayed gastric emptying and slowed intestinal peristalsis.

These physiological changes may affect the pharmacokinetic parameters of oral antimicrobials, such as bioavailability [4]. For example, cefpodoxime esters absorption may be 30 percent lessened in the elderly than that in the young, as well as extended half-life. In addition, bioavailability of azithromycin and erythromycin is decreased in the stomach due to the increased pH [5-7]. Proton pump inhibitors significantly increases the pH in stomach, which exerts strong impact on the bioavailability of drugs depends on dissolution or absorption in an acidic environment. For instance, itraconazole capsule is usually taken combined with cola to increase the bioavailability [8].

In further, malnutrition and physiological changes affect the drug distribution in the elderly patients. Increased fat, reduced lean body weight and redistributed body fluids contribute to the different effect on hydrophilic and lipotropic antimicrobial agents, leading to a higher blood concentration of hydrophilic antibiotics and lower blood concentration of lipotropic antibiotics. Lipotropic antibiotics, such as rifampicin, quinolones, tetracyclines, and voriconazole, are widely distributed in adipose tissue and have long half-life [9]. Malnutrition or chronic diseases result in reduced activation of partial hepatic cytochromes, and drug metabolism is reduced in patients with cachexia [10]. However, changes in plasma protein binding do not obviously affect the drug exposure in these patients and most patients do not need an adjustive regimen [11]. Moreover, the fact of lower drug exposure due to edema triggered by heart failure and liver cirrhosis, leading to dilution of hydrophilic antimicrobial agent concentrations. Therefore, higher dose or continuous intravenous infusion maybe more prevalent for those patients [12,13]. Due to aging or liver disease, hepatic function has a distinct effect on metabolism. Voriconazole, linezolid and tigecycline have a long half-life because of reduced metabolism by decreased hepatic blood flow or liver function [9,14]. Comorbidities are usually accompanied by multiple drug treatment in elderly patients, which leads to DDIs and is important for liver enzyme substrates such as azoles, quinolones, antiviral drugs and macrolides [15]. For patients with impaired liver function, it is necessary to assess the patient's liver function and adjust the dose of the drug according to the latest pk-pd research results [16].

It is critical for elderly patients considering the impact of drug clearance on antimicrobial exposure. Renal dysfunction is common in the elderly which results in drugs accumulation, higher serum concentration, even toxicity [17]. By the renal elimination, drugs have more pronounced accumulation due to impaired kidney function [18]. Therefore, it is essential to monitor renal function when evaluating the pharmacokinetics of antibiotics in elderly patients. The renal function is crucial for clearance of most antimicrobials, including β-lactams, glycopeptides, aminoglycosides, daptomycin, ciprofloxacin, levofloxacin, trimethoprim/sulfamethoxazole (TMP/SMX), etc [19]. The Cockcroft-Gault formula is one of widely applied and reliable methods to assess renal function [20].

**3. Drug-resistant bacteria considerations**

Drug-resistant bacteria is an extremely serious problem in the treatment of infectious disease. [21]. Once multi-drug resistant bacteria emerged, the choice of antibiotics for the elderly is limited. Actually, the infectious risk of resistant bacteria has mounted up [22]. In terms of risks of MDR bacterial infections, it is acknowledged that chronic disease, hospitalization, impaired immune function, invasive medical devices are of importance [23-25].The infections of ESBs, MRSA, and enterococcus in care settings are pervasive, which leads to higher mortality, longer hospital stays and more heavier financial burden [26]. The previous study showed that drug-resistant bacterial infections are not attributable to "old age" itself as a direct risk factor [27]. In conclusion, we must take into account this problem rationally and place more emphases on the rational choice of antibiotics. Any inappropriate use of broad-spectrum antibiotics will pay a heavy price because of "old age".

**4.****Adverse drug reaction (ADR) considerations**

In general, multiple drugs and comorbidity is the major cause of morbidity and mortality and is associated with high ADRs [28]. CLARICOR study showed that the 65-year-old patients in clarithromycin group was related to a higher risk rates of cardiovascular death than the placebo group [29]. Similarly, when it comes to arrhythmias and longer QT intervals, it is calling for more attention to the risk of heart-related adverse events caused by quinolones. There has been an increasing awareness that prolonged QT intervals is associated with moxifloxacin. [30]. Quinolones are at risk of developing arrhythmias in elderly patients [31].

There is no denying the fact that thrombocytopenia is a noteworthy ADR. Bi et al. reported that 24% of the elderly patients developed linezolid-related thrombocytopenia, and the lower thrombocyte baseline is accompanied with the higher adverse reaction risk [32]. Therefore, it is wise to address the skeletal and musculoskeletal problems triggered by some antibiotics. For example, daptomycin and quinolones can lead to creatine kinase elevations [33-34].

Usually, metabolism-related side-effects are easier to ignore. The risk of fluctuation of blood glucose was obvious in the case that levofloxacin combined with hypoglycemic agents in elderly diabetic patients [35,36]. Clinicians always pay attention to renal impairment caused by vancomycin and aminoglycosides. However, renal function impairment caused by beta-lactams also should not be ignored [37,38].

There has been an increasing awareness that psychiatric side effects caused by antibiotics, such as epilepsy, hyperactivity, and insomnia. We must consider this issue rationally in patients with central nervous system disease in order to avoid the rare life-threatening ADRs [39-41].

**5.Drug interaction considerations**

A retrospective cohort study of 22272 US veterans showed that DDIs is another potential risk: warfarin combined with TMP/SMX, metronidazole, fluconazole, ciprofloxacin, levofloxacin, clarithromycin and azithromycin, which resulted in higher risk of hemorrhage [42]. Low-risk antibiotics included clindamycin and cephalexin, besides, patients with low basal international normalized ration（INR）value have a relatively low risk of bleeding [42]. In fact, closely monitored INR during warfarin prescription is important to avoid bleeding in geriatric population.

Is there a similar risk of hemorrhage when combing new oral anticoagulants (NOACs) with antibiotics? Some DDIs associated with permeable glycoprotein (P-gp) and cytochrome 3A4 (CYP3A4) can increase the bleeding risk. [43]. It was reported that the exposure of dabigatran was sharply reduced by rifampicin, a pronounced inducer of both cytochrome P450 (CYP 450) and P-gp. Conversely, inhibitors including itraconazole, voriconazole and ketoconazole, significantly improved the bioavailability of dabigatran, apixaban and rivaroxaban. It has the same effect on NOACs combined with clarithromycin, erythromycin as well as fluconazole, inhibited the metabolism of CYP 450. When it comes to outpatients, avoiding such combination therapy and regular monitoring INR can lower the risks of DDIs of bleeding [44].

Many experts point out that carbapenems directly contribute to insufficient serum concentration of valproic acid (VPA) and epileptic seizure [45]. Actually, VPA blood concentration within 24 hours reduced about approximately 60% caused by carbapenems. Ertapenem and meropenem had a greater effect on VPA than imipenem/cilastatin [46].

In terms of DDIs risks of antifungal drug, it is acknowledged that azoles such as voriconazole and isavuconazole, increase the concentration of tacrolimus, cyclosporine and sirolimus as well as nephrotoxicity; amphotericin B co-administrated with diuretics, invited extremely serious electrolyte disturbance and nephrotoxicity, especially life-threaten and irreversible hypokalemia.

There are many commonly held beliefs about severe DDIs that is paid attention to

blood concentration monitoring of immunosuppressive agents for azoles [47,48] or monitoring electrolytes and renal function for amphotericin B [49].

**6.Conclusion**

In summary, the rational use of antimicrobials is an extremely complex problem in elderly patients. A series of physiological changes occurred in the elderly patients, and the PK and PD of the drug also altered accordingly. Some key changes may be overlooked, but some do have significant clinical implications. At the same time, multiple comorbidities and multi-drug treatments increase the risk of ADRs and DDIs. Elderly patients usually live in care facilities and are at risk of infection. Therefore, it is necessary to form a multidisciplinary team, including geriatricians, clinical pharmacists, microbiologists and infectious disease specialists, to optimize the use of antibiotics.

We point out that for the aged patients, if possible, therapeutic antibiotics monitoring contributes directly to efficacy and safety. In view of the seriousness of the problem of unreasonable use of antibiotics in the elderly, effective measures should be taken before things get worse. The comprehensive and effective monitoring programs also have benefits among outpatient settings. In the future, clinical trials of both novel and combined antibiotic treatment should put a premium on the geriatric population, so as to provide stronger evidence for the optimization of antibiotics therapies.

**Reference**

[1] 10 facts on ageing and the life course. <https://www.who.int/features/factfiles/ageing/ageing_facts/en/>

[2] Cruz SP, Cebrino J. Prevalence and Determinants of Antibiotic Consumption in the Elderly during 2006-2017. *Int J Environ Res Public Health*. 2020;17(9):E3243. Published 2020 May 6. doi:10.3390/ijerph17093243

[3] Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. *Eur J Clin Pharmacol*. 2013;69(3):319‐326. doi:10.1007/s00228-012-1387-2

[4] Bai JPF, Burckart GJ, Mulberg AE. Literature Review of Gastrointestinal Physiology in the Elderly, in Pediatric Patients, and in Patients with Gastrointestinal Diseases. *J Pharm Sci*. 2016;105(2):476‐483. doi:10.1002/jps.24696

[5] Tremblay D, Dupront A, Ho C, Coussediere D, Lenfant B. Pharmacokinetics of cefpodoxime in young and elderly volunteers after single doses. *J Antimicrob Chemother*. 1990;26 Suppl E:21‐28. doi:10.1093/jac/26.suppl\_e.21

[6] Borin MT, Ferry JJ, Forbes KK, Hughes GS. Pharmacokinetics of cefpodoxime proxetil in healthy young and elderly volunteers. *J Clin Pharmacol*. 1994;34(7):774‐781. doi:10.1002/j.1552-4604.1994.tb02039.x

[7] Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. *Infect Dis Clin North Am*. 2009;23(4):791‐vii. doi:10.1016/j.idc.2009.06.008

[8] Mitra A, Kesisoglou F. Impaired drug absorption due to high stomach pH: a review of strategies for mitigation of such effect to enable pharmaceutical product development. *Mol Pharm*. 2013;10(11):3970‐3979. doi:10.1021/mp400256h

[9] Giarratano A, Green SE, Nicolau DP. Review of antimicrobial use and considerations in the elderly population. *Clin Interv Aging*. 2018;13:657‐667. Published 2018 Apr 17. doi:10.2147/CIA.S133640

[10] Trobec K, Kerec Kos M, von Haehling S, Springer J, Anker SD, Lainscak M. Pharmacokinetics of drugs in cachectic patients: a systematic review. *PLoS One*. 2013;8(11):e79603. Published 2013 Nov 8. doi:10.1371/journal.pone.0079603

[11] Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. *Clin Pharmacol Ther*. 2002;71(3):115‐121. doi:10.1067/mcp.2002.121829

[12] Faulkner CM, Cox HL, Williamson JC. Unique aspects of antimicrobial use in older adults. *Clin Infect Dis*. 2005;40(7):997‐1004. doi:10.1086/428125

[13] Falcone M, Paul M, Tiseo G, et al. Considerations for the optimal management of antibiotic therapy in elderly patients [published online ahead of print, 2020 Mar 9]. *J Glob Antimicrob Resist*. 2020;S2213-7165(20)30051-5. doi:10.1016/j.jgar.2020.02.022

[14] Schmucker DL. Liver function and phase I drug metabolism in the elderly: a paradox. *Drugs Aging*. 2001;18(11):837‐851. doi:10.2165/00002512-200118110-00005

[15] Corsonello A, Abbatecola AM, Fusco S, et al. The impact of drug interactions and polypharmacy on antimicrobial therapy in the elderly. *Clin Microbiol Infect*. 2015;21(1):20‐26. doi:10.1016/j.cmi.2014.09.011

[16] Halilovic J, Heintz BH. Antibiotic dosing in cirrhosis. *Am J Health Syst Pharm*. 2014;71(19):1621‐1634. doi:10.2146/ajhp140031

[17] Olivier P , Bertrand L , Tubery M , et al. Hospitalizations because of Adverse Drug Reactions in Elderly Patients Admitted through the Emergency Department[J]. *Drugs & Aging*, 2009;26(6):475 - 82. doi:10.2165/00002512-200926060-00004

[18] Noreddin AM, El-Khatib W, Haynes V. Optimal dosing design for antibiotic therapy in the elderly: a pharmacokinetic and pharmacodynamic perspective. *Recent Pat Antiinfect Drug Discov*. 2008;3(1):45‐52. doi:10.2174/157489108783413191

[19] Pea F. Pharmacokinetics and drug metabolism of antibiotics in the elderly. *Expert Opin Drug Metab Toxicol*. 2018;14(10):1087‐1100. doi:10.1080/17425255.2018.1528226

[20] Drenth-van Maanen AC, Jansen PA, Proost JH, et al. Renal function assessment in older adults. *Br J Clin Pharmacol*. 2013;76(4):616‐623. doi:10.1111/bcp.12199

[21] Gupta V, Ye G, Olesky M, Lawrence K, Murray J, Yu K. Trends in resistant Enterobacteriaceae and Acinetobacter species in hospitalized patients in the United States: 2013-2017. *BMC Infect Dis*. 2019;19(1):742. Published 2019 Aug 23. doi:10.1186/s12879-019-4387-3

[22] March A, Aschbacher R, Dhanji H, et al. Colonization of residents and staff of a long-term-care facility and adjacent acute-care hospital geriatric unit by multiresistant bacteria. *Clin Microbiol Infect*. 2010;16(7):934‐944. doi:10.1111/j.1469-0691.2009.03024.x

[23] Pinzone MR, Berretta M, Doerr HW, Nunnari G, Cacopardo B. The complexity of aging: cancer risk among elderly people and infectious risk among those with cancer. *Anticancer Agents Med Chem*. 2013;13(9):1444‐1448. doi:10.2174/18715206113136660346

[24] Yan L, Qing Y, Xingyi J, Hongbo Q. Etiologic diagnosis and clinical treatment of multiple drug-resistant bacteria infection in elderly patients with stroke-associated pneumonia after neurosurgery. *Cell Biochem Biophys*. 2015;71(2):731‐734. doi:10.1007/s12013-014-0256-2

[25] Ruscher C, Pfeifer Y, Layer F, Schaumann R, Levin K, Mielke M. Inguinal skin colonization with multidrug-resistant bacteria among residents of elderly care facilities: frequency, persistence, molecular analysis and clinical impact. *Int J Med Microbiol*. 2014;304(8):1123‐1134. doi:10.1016/j.ijmm.2014.08.006

[26] Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. *J Infect Dis*. 2017;215(suppl\_1):S28‐S36. doi:10.1093/infdis/jiw282

[27] Weber SG, Miller RR, Perencevich EN, et al. Prevalence of antimicrobial-resistant bacteria isolated from older versus younger hospitalized adults: results of a two-centre study. *J Antimicrob Chemother*. 2009;64(6):1291‐1298. doi:10.1093/jac/dkp349

[28] Borrego F, Gleckman R. Principles of antibiotic prescribing in the elderly. *Drugs Aging*. 1997;11(1):7‐18. doi:10.2165/00002512-199711010-00002

[29] Jespersen CM, Als-Nielsen B, Damgaard M, et al. Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial [published correction appears in BMJ. 2006 Jan 21;332(7534):151]. *BMJ*. 2006;332(7532):22‐27. doi:10.1136/bmj.38666.653600.55

[30] Morganroth J, Dimarco JP, Anzueto A, Niederman MS, Choudhri S; CAPRIE Study Group. A randomized trial comparing the cardiac rhythm safety of moxifloxacin vs levofloxacin in elderly patients hospitalized with community-acquired pneumonia. *Chest*. 2005;128(5):3398‐3406. doi:10.1378/chest.128.5.3398

[31] Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ*. 2018;360:k678. Published 2018 Mar 8. doi:10.1136/bmj.k678

[32] Bi LQ, Zhou J, Huang M, Zhou SM. Efficacy of linezolid on gram-positive bacterial infection in elderly patients and the risk factors associated with thrombocytopenia. *Pak J Med Sci*. 2013;29(3):837‐842. doi:10.12669/pjms.293.2925

[33] Britt NS, Potter EM, Patel N, Steed ME. Comparative Effectiveness and Safety of Standard-, Medium-, and High-Dose Daptomycin Strategies for the Treatment of Vancomycin-Resistant Enterococcal Bacteremia Among Veterans Affairs Patients. *Clin Infect Dis*. 2017;64(5):605‐613. doi:10.1093/cid/ciw815

[34] Godoy-Santos AL, Bruschini H, Cury J, et al. Fluoroquinolones and the Risk of Achilles Tendon Disorders: Update on a Neglected Complication. *Urology*. 2018;113:20‐25. doi:10.1016/j.urology.2017.10.017

[35] Parekh TM, Raji M, Lin YL, Tan A, Kuo YF, Goodwin JS. Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas. *JAMA Intern Med*. 2014;174(10):1605‐1612. doi:10.1001/jamainternmed.2014.3293

[36] Singh N, Jacob JJ. Levofloxacin and hypoglycemia. Clin Infect Dis. 2008;46(7):1127. doi:10.1086/529393

[37] Vardakas KZ, Kalimeris GD, Triarides NA, Falagas ME. An update on adverse drug reactions related to β-lactam antibiotics. Expert Opin Drug Saf. 2018;17(5):499‐508. doi:10.1080/14740338.2018.1462334

[38] Mattappalil A, Mergenhagen KA. Neurotoxicity with antimicrobials in the elderly: a review. Clin Ther. 2014;36(11):1489‐1511.e4. doi:10.1016/j.clinthera.2014.09.020

[39] Grahl JJ, Stollings JL, Rakhit S, et al. Antimicrobial exposure and the risk of delirium in critically ill patients. Crit Care. 2018;22(1):337. Published 2018 Dec 12. doi:10.1186/s13054-018-2262-z

[40] Apodaca K, Baker J, Bin-Bilal H, Raskin Y, Quinn DK. Ertapenem-Induced Delirium: A Case Report and Literature Review. Psychosomatics. 2015;56(5):561‐566. doi:10.1016/j.psym.2015.02.002

[41] Slobodin G, Elias N, Zaygraikin N, et al. Levofloxacin-induced delirium. Neurol Sci. 2009;30(2):159‐161. doi:10.1007/s10072-009-0027-9

[42] Lane MA, Zeringue A, McDonald JR. Serious bleeding events due to warfarin and antibiotic co-prescription in a cohort of veterans. Am J Med. 2014;127(7):657‐663.e2. doi:10.1016/j.amjmed.2014.01.044

[43] Lippi G, Favaloro EJ, Mattiuzzi C. Combined administration of antibiotics and direct oral anticoagulants: a renewed indication for laboratory monitoring?. Semin Thromb Hemost. 2014;40(7):756‐765. doi:10.1055/s-0034-1381233

[44] Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39(16):1330‐1393. doi:10.1093/eurheartj/ehy136

[45] Huang CR, Lin CH, Hsiao SC, et al. Drug interaction between valproic acid and carbapenems in patients with epileptic seizures. *Kaohsiung J Med Sci*. 2017;33(3):130‐136. doi:10.1016/j.kjms.2016.12.001

[46] Wu CC, Pai TY, Hsiao FY, Shen LJ, Wu FL. The Effect of Different Carbapenem Antibiotics (Ertapenem, Imipenem/Cilastatin, and Meropenem) on Serum Valproic Acid Concentrations. *Ther Drug Monit*. 2016;38(5):587‐592. doi:10.1097/FTD.0000000000000316

[47] Kieu V, Jhangiani K, Dadwal S, Nakamura R, Pon D. Effect of isavuconazole on tacrolimus and sirolimus serum concentrations in allogeneic hematopoietic stem cell transplant patients: A drug-drug interaction study. *Transpl Infect Dis*. 2019;21(1):e13007. doi:10.1111/tid.13007

[48] Vanhove T, Bouwsma H, Hilbrands L, et al. Determinants of the Magnitude of Interaction Between Tacrolimus and Voriconazole/Posaconazole in Solid Organ Recipients. *Am J Transplant*. 2017;17(9):2372‐2380. doi:10.1111/ajt.14232

[49] Laniado-Laborín R, Cabrales-Vargas MN. Amphotericin B: side effects and toxicity. *Rev Iberoam Micol*. 2009;26(4):223‐227. doi:10.1016/j.riam.2009.06.003