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Proceed with Caution: Antibiotic Considerations in the Geriatric Population

by Kelvin Gandhi, PharmD, Kelsey Zeeck, PharmD, Allison Gibble, PharmD, BCIDP

Individuals aged 65 years and older currently account for approximately 14.5% of the United States population. With aging baby boomers and advancements in medicine and technology, there is a rapidly increasing elderly population, which is projected to double over the next 25 years.[1] Age is a potential risk factor for infection, increased length of hospital stay, and many other complications. The elderly are generally more susceptible to infections than the younger population because of the potential association of aging with exposure to infections, anatomical and functional changes, and immune dysfunction.[2-4] A previous study showed that elderly patients used more antibiotics per person per year compared to the younger population.[1] With more medications being prescribed, there is an exponential increase in adverse effects.[5] Managing infections with antibiotic therapy in the elderly poses many obstacles to health care professionals, due to variable pharmacokinetic properties, decreased immune function, and increased risk for drug-drug interactions and adverse effects.[1] Using safe and effective pharmacotherapy is crucial in minimizing the collateral damage that can come with antibiotic agents, especially in the geriatric population.

Pharmacokinetic Considerations

As people age, their bodies undergo various anatomical and functional changes, potentially altering the safety and efficacy of medications. Changes in pharmacokinetic factors may impact the medication's absorption, distribution, metabolism, and elimination.

Absorption

There have been many proposed theories that gastric acid production decreases with age, although more recent studies have not found clinically significant alterations in gastric acid secretion.[1,5,6] Elderly patients are also more commonly on acid-suppressive medications (such as antacids, histamine-2 receptor antagonists, and proton-pump inhibitors) than the younger population, which may result in a higher gastric pH.[1] Many oral antibiotics, including azithromycin, amoxicillin, cephalexin, and cefadroxil, are dependent on gastric acid for optimal bioavailability.[7]

Distribution

Each drug has a specific volume of distribution; however, there can be interpatient variability, especially in the elderly.[7] Generally, the geriatric population has an increased proportion of adipose tissue and decreased lean body mass; decreased total body water; and decreased serum albumin.[1,5] This may have a considerable impact on drug pharmacokinetics, because an increase in the proportion of body fat increases the distribution of lipophilic agents (e.g. rifampin, metronidazole, fluoroquinolones, macrolides, and tetracyclines), prolonging their half-life.[1,5] With a lower proportion of lean body mass and total body water, this will result in reduced distribution of hydrophilic agents (e.g. aminoglycosides, beta-lactams, and glycopeptides), leading to a greater concentration within the intravascular compartment. Studies have shown decreased efficacy of highly protein-bound drugs (e.g. ceftriaxone and ertapenem) in patients with hypoalbuminemia.[1,5-9] Due to the reduced serum protein concentration, there is initially an increased free-fraction of active drug, but it is then rapidly cleared, leading to an overall reduced drug exposure and half-life.

Metabolism

With normal physiological aging effects on the liver, there may be decreased hepatic blood flow and cytochrome P450 (CYP450) enzyme activity, which can possibly prolong the half-life of hepatically metabolized drugs (e.g. metronidazole, macrolides, and fluoroquinolones). The high rate of polypharmacy in the older patient population further increases likelihood of drug-drug interactions,

which can affect the metabolism of certain antibiotics, potentially exposing the individual to toxicities or sub-optimal dosing.[1] In a recent cohort study assessing polypharmacy (≥ 5 drugs) in the aging population, the investigators found that polypharmacy and potential drug-drug interactions were much more prevalent in the elderly population.[10]

Elimination

Aging, even without accompanying renal disease, often results in reduced renal function due to decreased renal blood flow and glomerular filtration rate.[1,5] Serum creatinine concentration can be a misleading marker of renal function in the elderly because of reduced muscle mass, potentially overestimating the creatinine clearance (CrCl). However, it is still beneficial to trend this marker for renal function, especially when dosing antibiotics, since a change from baseline may indicate a need to reassess dosing for those requiring renal dose adjustments or a need to obtain levels for those requiring therapeutic drug monitoring (TDM). Antibiotics such as aminoglycosides, beta-lactams, and glycopeptides are heavily dependent on renal filtration for drug clearance and thus require dosing adjustments in the presence of renal impairment in order to prevent accumulation and supratherapeutic drug levels.

Antibiotic Considerations

Prior to antibiotic selection, one of the first considerations should be whether antibiotic use is necessary. Urinary tract infection (UTI) is one of the most common indications for antibiotic prescribing, but is often inappropriately diagnosed and managed, especially in the elderly population.[11] Inappropriate antibiotic use may lead to further resistance in uropathogens and an increase in adverse events.[12] Asymptomatic bacteriuria, which is the presence of bacteria in a urine culture without signs or symptoms of a UTI, is frequently seen in the elderly and often does not warrant antibiotic therapy.[13,14] The provider must weigh the risks and benefits of antibiotic selection, as they all carry potential toxicities, and cautious decision-making should be considered, especially in the geriatric population. Antibiotics discussed in this article include those that are commonly used for treatment of UTIs.

Nitrofurantoin

Nitrofurantoin is an antibacterial agent commonly used in treating an uncomplicated UTI. Previously, contraindication of nitrofurantoin in patients with a CrCl <60 mL/min was based on data with several major limitations and poorly defined clinical endpoints.[15] The American Geriatrics Society has revised its recommendation in the 2015 Beers Criteria Update to avoid nitrofurantoin in those with a CrCl <30 mL/min.[16,17] More cases of neurotoxicity, including peripheral neuropathy, dizziness, and cerebellar dysfunction, are reported in women than men, and more in the elderly than the younger population.[18,19] A retrospective study by Geerts et al. investigated treatment failure within 30 days or serious adverse events leading to hospitalization within 90 days in women with renal impairment treated for uncomplicated UTI with nitrofurantoin. Moderate renal impairment, defined as an estimated glomerular filtration rate (eGFR) between 30-49 mL/min/1.73 m^2, was not significantly associated with treatment failure. However, there was a significant increase in adverse events in individuals with renal impairment (eGFR <50 mL/min/1.73 m^2; adjusted hazard ratio =4.13) than in those without renal impairment.[17,20] Therefore, the health care provider should be cautious when using nitrofurantoin in renal impairment, especially in the elderly, because of the risk of adverse events that is still present.

Sulfamethoxazole-Trimethoprim

Another common first-line option for UTIs is sulfamethoxazole-trimethoprim (SMX-TMP). This drug should be used with caution in patients with renal impairment due to an increased risk of nephrotoxicity and hyperkalemia.[16,21-25] SMX-TMP plays a major role in the clearance of creatinine via inhibition of transporters in the kidney, and thus may lead to further enhancement of creatinine elevation, although it may not be an entirely accurate indicator of the degree of acute renal injury.[26] Inadequate hydration while on oral SMX-TMP may lead to crystal precipitate damaging the renal tubules. The trimethoprim component competitively inhibits the sodium channels in the kidney, thereby hindering renal excretion of potassium.[27] The geriatric population is also commonly prescribed angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or potassium-sparing diuretics, due to comorbidities, which can lead to an additive hyperkalemic effect when taken with SMX-TMP. A population-based, nested case-control study conducted in Ontario, Canada identified 6,903 hospital admissions due to hyperkalemia over an 18-year span.[22] Of that total, 10.8% of spironolactone users received at least one prescription for SMX-TMP. Compared with amoxicillin, SMX-TMP was associated with an increased risk of admissions due to hyperkalemia (adjusted odds ratio 12.4, 95% CI 7.1-21.6), and 60% of the elderly taking spironolactone and antibiotics for a UTI could have been avoided if an alternative agent to SMX-TMP was used.[22] SMX-TMP is an appropriate antibiotic option in the elderly but should be avoided or closely monitored in patients with renal impairment and concomitant agents increasing the risk of hyperkalemia.

Beta-lactam Antibiotics

Beta-lactam antibiotics are commonly prescribed for infections that affect the elderly population, such as pneumonia and UTI.[28] Aging patients often exhibit factors that impact beta-lactam pharmacokinetics, including decreased serum albumin, decreased renal blood flow, decreased hepatic blood flow, and increased fluid volume.[29] These pharmacokinetic changes could inhibit the ability to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets, such as time of drug concentration above the minimum inhibitory concentration, as well as put patients at increased risk for toxicities. This is evidenced by a population pharmacokinetic study by Lonsdale et al. that described a 50% decrease in clearance of beta-lactams by 71 years of age.[30] Appropriate dose adjustments are a necessity because of the potential for reduced clearance of beta-

lactam antibiotics, which may result in drug toxicities. Beta-lactam antibiotics are first-line agents for treatment of many infections, not only due to their efficacy but also because they are well-tolerated even in the elderly population. However, there are a few notable beta-lactam antibiotic toxicities to be particularly mindful of in the geriatric population. Cefepime and ertapenem neurotoxicity is theorized to be related to the concentration-dependent antagonism of gamma-aminobutyric acid. Kidney dysfunction and excessive cefepime dosing resulting in increased cefepime concentrations have been associated with neurotoxicity and are potential issues in the elderly population.[31] Similarly, decreased renal function, low body weight, and advanced age have all been identified as risk factors for ertapenem neurotoxicity.[32] Ertapenem mean AUCs have been reported to be 39% higher in the elderly compared with younger subjects.[33] Due to the increased risk for beta-lactam-associated toxicities in older patients, TDM is a potentially useful tool to optimize beta-lactam antibiotic dosing in this population.[34] Although use is increasing, it is still not commonly employed for beta-lactam antibiotics, which makes it even more crucial to optimize its use.[35] Beta-lactams, especially cefepime and ertapenem, should be monitored carefully for signs of neurotoxicity in elderly patients with decreased renal function and low body weight.

Fluoroquinolones

Fluoroquinolones are notorious for a multitude of adverse effects in any patient population. The Food and Drug Administration has issued a recommendation that fluoroquinolones be used only when other treatment options are not available for management of acute bacterial sinusitis, chronic bronchitis, and uncomplicated UTIs.[36] Special consideration should be given to the possible adverse effects and the subsequent implications specifically in the elderly patient population. For example, fluoroquinolones have been associated with risks of dysglycemia, QTc prolongation, and aortic aneurysm and aortic dissection.[36,37] Elderly patients may be at higher risk for these issues, due to the increased prevalence of comorbidities or interacting medications pre-disposing these issues.

Fluoroquinolones additionally carry Black Box warnings regarding the possibility of central nervous system (CNS) effects, exacerbation of myasthenia gravis, and tendonopathies, including tendon rupture.[36] In a large retrospective study of patients with quinolone-related tendonopathies, aged over 60, corticosteroid use and impaired renal function were associated with higher risk for tendonopathies.[38] CNS effects seen with fluoroquinolones may include psychosis, seizures, or delirium.[37] Despite the known CNS risks of fluoroquinolone use, increased risk specifically in the elderly population has not been well-characterized.[39,40]

In elderly patients who may have altered drug clearance as well as other comorbidities that may increase their risk for side effects, the decision to initiate fluoroquinolone therapy should not be taken lightly and alternate therapy should be considered.

Clostridioides difficile Infections

Clostridioides difficile infection (CDI) is an unfortunate risk that accompanies most antibiotic use, though the specific risk of CDI varies based on antibiotic class. Lincosamides, such as clindamycin, have been found to pose the highest risk.[41,42] Comparative rates of other antibiotics have varied in literature, but beta-lactams and fluoroquinolones do certainly carry a risk.[41,42] Elderly patients are disproportionately affected, with 70%-80% of global cases impacting patients over the age of 65.[43] Furthermore, patients with advanced age were at increased risk for hospitalization related to CDI and for recurrence of CDI.[43] Treatment of CDI is largely the same in elderly patients as in younger ones, but given the high morbidity and mortality associated with CDI in the elderly patient population, extra consideration should be given to prevention, such as infection prevention and antimicrobial stewardship.

Concluding Remarks

The elderly population is especially susceptible to the negative impacts of antibiotic use. Unfortunately, excessive and inappropriate use of antibiotics is common in this vulnerable demographic. Ensure appropriate indication, antibiotic selection, dose, and duration of therapy to minimize antibiotic exposure and the associated risks.[11] In a retrospective cohort study by Dylis et al., only 46% of antibiotics prescribed to elderly patients were in accordance with guidelines.[28] Furthermore, interviews conducted with primary care providers revealed that they are more likely to use broader spectrum antibiotics and longer durations of therapy for elderly patients as compared with the general population.[44] A potential driver of antibiotic use that deviates from guideline recommendations is the underrepresentation of aging patients in clinical trials. A systematic review by Avni et al. found that elderly patients were commonly excluded from randomized controlled trials for the management of pneumonia because of their comorbid diseases.[45] Additionally, there were limited subgroup analyses of specific age groups, which limits generalizability of results from these studies to the elderly population.[45] This data has shed light on the importance of increasing representation of elderly patients in infectious diseases literature in the future. In the meantime, it is important to use the information we do know about this unique population to help optimize antibiotic therapy.

Kelvin Gandhi is a PGY2 Infectious Diseases Pharmacy Resident at Froedtert Hospital in Milwaukee, WI. Kelsey Zeeck is an Infectious Diseases Clinical Pharmacist at Froedtert Menomonee Falls Hospital in Menomonee Falls, WI. Allison Gibble is an Infectious Diseases Clinical Pharmacist at Froedtert Hospital in Milwaukee, WI.

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