The Review Of
DIABETIC
STUDIES OPEN ACCESS

Clinical Challenges In Infectious Diseases With Multimorbidity And Complex Medication Regimens

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Abstract
Infectious illnesses among patients with multimorbidity create numerous difficulties in terms of therapeutic choices due to the pathophysiological changes, polypharmacy and increased susceptibility to adverse drug effects. With the world becoming older with the population, and the proliferation of chronic non communicable disease, the number of patients who require complex series of medication, whilst they are being managed against acute or chronic infection has also risen. Multimorbidity is also multifaceted, which frequently results in polypharmacy, which in turn adds to the risk of drug-drug and drug-disease interactions and medication non adherence, as well as cumulative organ toxicity which mainly causes renal and hepatic dysfunction. Aging-induced pharmacodynamic and pharmacokinetic alterations, such as immunosenescence and frailty complicate antimicrobial choice and dosing and therefore the therapeutic index between efficacy and toxicity. Nevertheless, this incorrect antimicrobial dosing within such a group can result in subtherapeutic exposure that will moderate the cultivation of antimicrobial resistance or supratherapeutic exposure that triggers severe adverse events. Large fraction of infections necessitating hospitalization are in patients harboring multimorbidity and taking complicated polypharmacy regimens, which increases emerging risks of pharmacotherapy that may be addressed by the centrality of the clinical pharmacist in practice as explained in this review. Clinical pharmacy interventions of critical importance include regimented medication review, therapeutic drug monitoring, deprescribing practice, compliance facilitation, risk stratification, and tailored antimicrobial therapy according to individualized patient determinants such as renal function, frailty, and comorbidity burden. There is strong evidence showing that pharmacist led interventions reduce drug related problems, adverse drug events, inappropriate polypharmacy and healthcare utilization and improve clinical outcomes. There is also an opportunity to use new complementary tools, such as: pharmacogenomic-guided therapy, digital and general health technologies, and clinical decision support systems, to guide therapeutic optimization in this particularly vulnerable group. In aggregate, clinical pharmacy services are critical to optimizing safe, effective, and patient centered infectious disease management for people with multimorbidity and complex medication regimens.

Keywords Multimorbidity; Infectious diseases; Polypharmacy; Clinical pharmacy; Antimicrobial therapy; Drug–drug interactions; Therapeutic drug monitoring.

Introduction

Infectious diseases, multimorbidity, and complex medication regimens together pose significant barriers to optimizing therapy and preventing adverse events, putting added burden on clinical

pharmacists as they seek to balance patient-centered outcomes with medication safety. However, the complexity in managing infectious disease is compounded by rising rates of multimorbidity particularly in areas with an increased communicable and non-communicable diseases burden (Etando et al., 2021). The complex inter-relationships between several chronic conditions may require polypharmacy, that although it is intended to treat disparate pathologies, its use can complicate their management by the potential drug-drug interactions and adverse drug reactions (Whitney et al., 2021). In fact, polypharmacy has been associated with serious health outcomes, including chronic kidney disease and liver impairment in at-risk communities (Whitney et al., 2021).

In addition, elderly individuals with multimorbidity often experience worse health outcomes (González-Bueno et al., 2021) such as lower health-related quality of life, higher healthcare utilization and greater frailty, challenges that are further exacerbated by the aging global population. Soraci et al. (2023) highlighted that due to the effect of aging, inappropriate drug dosing is even more likely to lead to sub-therapeutic exposure that selected for antimicrobial resistance, or supratherapeutic exposure that causes adverse events with loss of adherence. The fine line between efficacy and toxicity highlights an urgent importance in careful therapeutic manipulation, especially with regard to antimicrobial therapy, where improper dosing can accelerate antimicrobial resistance (Soraci et al., 2023; Whitney et al., 2021). These complications require the consideration of individual patient characteristics including frailty and renal function to help guide the optimal antimicrobial regimens in this vulnerable population whilst reducing the risk of immunotoxicity (Pea, 2022).

This rising cohort of elderly patients with frequent multimorbidity, expected to double before 2050, often require polypharmacy which can be further complicated by the fact that guidelines may not have geriatric evidence to guide optimal multidrug prescribing regimens (Urbańczyk et al., 2023). The absence of age-group specific recommendations can lead to overprescribing, especially near the end of life, since older adults with multiple morbidities are at higher risk for drug-drug interactions and adverse drug events (Cattaneo et al., 2021; Costanzo et al., 2024). The inconsistency of the mentioned investigations about using clinical pharmacists on polypharmacy, which defines the challenges of polypharmacy, patient safety, and better therapeutic outcome to optimize infective disease management for patients with multimorbidity (Stafford et al., 2021) further emphasize the role of clinical pharmacist. A complete response to this complex challenge requires careful and individualized consideration of medication reconciliation, therapeutic drug monitoring, and patient education, and so is well within the domain of practice for clinical pharmacy (Damasceno-Silva et al., 2023).

The growing burden of multimorbidity, particularly in older adults, suggests an expanding role for clinical pharmacists in the treatment of infectious diseases, including the optimization of antibiotic use and vaccination (Aremu et al., 2021, Bouza et al., 2020). Due to changed pharmacokinetics and pharmacodynamics of polymorbid elderly patients, which frequently burden the adequate selecting of antibiotics and dosing, their know-how is indispensable (Falcone et al. 2020).

Interaction Between Infections and Chronic Diseases

Cardiovascular, renal, hepatic and metabolic disease often occur in the context of infectious processes which further exacerbate disease severity and therapeutic management (Whitney et al., 2021). Such complex bidirectional relationship, on the one hand, makes them more prone to infections and less responsive to antimicrobial therapies (therefore necessitating a tailored nature of treatment) (Erdoğan & Günal, 2021). In addition, these chronic conditions can also further impair the immune function of polymorbid patients and alter drug metabolism, compromising patients by making them more susceptible to adverse drug reactions and therapeutic failures (Hernández-Ruiz, 2023). Immunosenescence associated with old age, combined with various chronic conditions leading to compromised physiological reserves in many older individuals make them more prone to severe infectious disease and even prolonged recovery times (Cillóniz et al., 2018; Erdoğan & Günal, 2021).

As a result, infectious disease management among multimorbidity patients is a multifaceted problem that needs a wide perspective that accounts not only for the management of infectious diseases but also makes effort to enhance chronic disease control, which would further improve patient prognosis with reduced health care burden (Gnjidic et al., 2018). The overlap between chronic and infectious disease also highlights the importance of public health policies that would shift towards the long-established approach of separating types of diseases to find common grounds of risk factors and population

vulnerability (Badawi et al, 2019). This method is essential in resource-limited environments to plan effective interventions to mitigate infectious as well as non-communicable disease burden (Mohiuddin, 2019).

Lastly, chronic inflammatory milieu of most non-communicable diseases and altered immune response to infection that has been described as inflammaging have a significant effect on disease progression and response to therapy in older individuals with multimorbidity (Doherty et al.,2019). The age-related low-grade persistent inflammation, together with the senescence features of the aged immune system, which undermine the ability to act as a defensive system, heightens the susceptibility to infections and weakens the vaccine reactions in this risk group (Chen et al., 2024). This convergence between chronic infectious diseases (e.g. HIV and TB) and non-communicable diseases in multimorbid people is an important area of management, especially in the area of low and middle-income countries (LMIC) 1 Since this convergence implies an understanding of how these conditions interact in terms of the course of the disease and treatment response, integrated care plans are required (Badawi et al., 2019; Editors & Editors, 2023).

Impact on pharmacotherapy

Complicated interactions between chronic, infectious diseases in multimorbid patients generate a significant impact on pharmacotherapy, which is also necessary to determine the possible applicability of drug-combines, define interactions and applicable pharmacokinetic properties (Bazrova et al., 2021). To illustrate this, polypharmacy is a common confounding variable of the treatment of many chronic conditions and may confound causal relationships between drug exposure and adverse events (Melo et al., 2021), which is why all drug benefit-harm studies are likely to get confused between causation and correlation. Besides the power to absorb, distribute, metabolize, and excrete a drug, alteration in aging and chronic diseases that interfere with the therapeutic drug concentrations and predispose to toxicity is also a critical issue (Domingo et al., 2019). It is crucial to minimize the negative effects and preserve therapeutic efficacy and the altered pharmacodynamics in this population provide unpredictable drug reactions (Domingo et al., 2019). This becomes even more evident in patients who have chronic pulmonary diseases with multimorbidity contributing significantly to the intensification of polypharmacy through the multiplicity of medications needed to address their complex health issues (Melo et al., 2021).

Not only do younger adults with multimorbidity possess more multimorbidity but also more medication burden due to polypharmacy seeming to indicate poor underlying health situation and not be a causal risk factor to harm (Melo et al., 2021). This gives the pharmacist an avenue to apply the pharmacogenomics and other fields of advanced pharmacokinetics on treating therapeutic regimens and design or avoid polypharmacy-related risks in such complex patient groups which demand a more complicated approach to medication administration. Since multimorbidity typically means that a patient needs more care, one should differentiate between polypharmacy as the reason behind bad outcomes and polypharmacy as an indicator of bad disease (Whitney et al., 2021). Such distinction is essential in the formulation of prescribing thresholds that are the most effective to treat the existing disease, though it also highlights the necessity to preserve organ functioning and keep the person alive (Whitney et al., 2021).

Polypharmacy in Infectious Disease Patients

Drug-drug interaction risks Polymorbid patients are at risk to be subjected to drug-drug interactions particularly those under treatment of infectious diseases and clinician has no easy way to enhance their pharmacological knowledge and use medication reconciliation techniques to prevent adverse events. It is more so in the case of the infectious diseases where the incorporation of strong microbicides can significantly alter the metabolism of other drugs given, leading to either under-therapy or toxic accumulation (Ghasemi et al., 2022). It, therefore, requires thorough medication reviews by clinical pharmacists to establish potential interactions as many patients with multimorbidity are already in the polypharmacy state (Feng et al., 2017). The prescribing cascade–the slow spiraling presence of unnecessary medications to control adverse drug reactions–can greatly compound the burden of medication a person with older-aged care needs carries, where inappropriate polypharmacy introduces both increasing drug burden and harm (Menditto et al., 2019). This situation is exacerbated by the

relative paucity of clinical guidelines regarding infectious diseases and multimorbidity for polypharmacy (Costanzo et al. 2024). Moreover, polypharmacy is also a risk factor for poor adherence to pharmacological treatment, increasing morbidity and mortality (Molist-Brunet et al., 2022), thus although polypharmacy itself is a risk compound, their association leads to a substantial challenge.
The absence of a uniform definition of polypharmacy in many of the utilized studies confounds the determination of its worldwide scope and significance and the establishment of clinical thresholds for intervention (Ghasemi et al., 2022). This variation highlights the importance of a qualitative not just a quantitative assessment of polypharmacy so that treated patients can be classified according to the appropriateness (versus none or overuse) of prescribed medications guided by clinical indication and patients' characteristics rather than by the number of prescribed drugs ["Primary Care Medicine - Theory and Practice," 2023]. With that in mind, the prevalence of polypharmacy differs greatly between settings and populations, as higher rates in nursing homes have been reported when compared to community-dwelling older adults (Michalik-Marcinkowska et al., 2025). Such differences illustrate the role of setting on medication burden and the need for setting-specific approaches to polypharmacy management in the wider community (Molist-Brunet et al., 2022).

Adherence challenges

The compliance with complicated treatment plans, especially those consisting of many drugs for chronic illness and even acute infections, is one of the greatest barriers to outcome effectiveness, often complicated by lack of cognitive capacity, poor understanding of treatment, or financial resources (Nwadiugwu, 2021). These unique challenges necessitate clinical pharmacist involvement in formulating patient-centered approaches to optimize adherence in these vulnerable groups, such as simplified dosing regimens and improved counseling (Sinnott et al., 2015). These interventions are necessary because polypharmacy, particularly in patients with multimorbidity and neurodevelopmental disabilities, has been strongly linked to increased risk of both non-adherence and adverse drug events (Bayona-Huguet & Bayona-Pizarro, 2023; Melo et al., 2021). Additionally, the physiological changes that accompany these patient populations can complicate their evaluation for adherence to treatments as drug metabolism and pharmacodynamics may be affected (Whitney et al., 2021). Therefore, the application of pharmacogenomic information combined with therapeutic drug monitoring is critical to optimizing outcomes and minimizing drug-related risk in patients with poor adherence in a context of polymorbidity (Bayona–Huguet & Bayona–Pizarro, 2023).
Identifying such nuance is critical, as the association of polypharmacy and adverse outcome (rather than a proxy of poor intrinsic health) is a hypothesis which cannot yet be fully accepted (Whitney et al., 2021). Hence, future research should attempt to untangle this association, investigating whether polypharmacy is a causal determinant or merely a marker of disease severity, through robust mechanistic studies and comparative effectiveness research (Melo et al., 2021). In adults, people with cerebral palsy have an earlier onset of chronic diseases which results in them having up to three times the prevalence of multimorbidity compared to their peers without the condition, often requiring them to take exponentially more medications than their peers to manage their complex health profiles (Melo et al., 2021; Whitney et al., 2021).

Clinical Pharmacy Evaluation Framework

A structured medication review is one of the cornerstones of clinical pharmacy, as it provides the foundation for systematically identifying, addressing, and preventing medication-related problems, especially in patients with complex infectious diseases and multimorbidity who are at high risk for polypharmacy (Feng et al., 2017). This includes a careful review of all medications that have been prescribed, and medications that the patient may also be taking, including over-the-counter and herbal medications to assess for therapeutic appropriateness, drug-drug or drug-disease interactions, and optimize dosing regimens (Mohiuddin, 2019). A patient-centered prescription model is at the centerpiece of an intervention with effectiveness to improve adherence and effective prescribing in multimorbidity patients (González-Bueno et al., 2021). Nonetheless, it is important to remember that polypharmacy is not necessarily a direct causal factor for the pathophysiology of many advanced chronic diseases but may be an adverse marker of individual health condition (Whitney et al., 2021).

However, apart from poor health measures, the increased risk of adverse events with polypharmacy and hyperpolypharmacy remains significant, even after extensive adjustment for multimorbidity, suggesting that their contribution is more than an indication of poor health (Whitney et al., 2021). In addition, how the clinical context and burden of multimorbidity should guide decisions about whether and how to use medications due to the fact that the concept of polypharmacy as defined by number of medications does not necessarily imply harm (("Primary Care Medicine - Theory and Practice [Working Title]," 2023). So, a comprehensive evaluation of medication practices, based on personal clinical history and risk of future organ damage, is fundamental for treatment optimization in complex populations (Melo et al., 2021; Whitney et al., 2021). This philosophy represents a paradigm shift away from purely disease-based care to a model of collaborative care that is especially vital for patients with either chronic conditions or multimorbidity (eg, coexisting chronic kidney disease or heart failure in addition to musculoskeletal conditions) who have a significantly increased risk of polypharmacy (Feng et al., 2017). Consequently, the implementation of medication review services, frequently conducted by expert clinicians such as clinical pharmacists, is crucial for optimizing therapeutic outcomes and minimizing medication-related damage in these risk groups (Molist-Brunet et al., 2022).

Table 1. Interactions Between Multimorbidity and Infectious Diseases Affecting Pharmacotherapy.

Chronic Condition / State	Effect on Infection Risk & Severity	Impact on PK/PD	Clinical Consequences	Clinical Pharmacy Focus
Cardiovascular disease	Reduced tissue perfusion, impaired immune response	Altered distribution and clearance	Delayed response to antimicrobials	Dose optimization; monitoring hemodynamic effects
Chronic kidney disease	Impaired immune defense; higher infection risk	↓ Renal clearance; drug accumulation	Nephrotoxicity, supratherapeutic exposure	Renal dose adjustment; TDM
Hepatic dysfunction	Altered metabolism; immune dysregulation	↓ Hepatic clearance; ↑ free drug	Hepatotoxicity, unpredictable exposure	Drug selection; hepatic monitoring
Diabetes mellitus	Impaired immunity; poor wound healing	Altered absorption and distribution	Prolonged infections, relapse	Glycemic control; regimen simplification
Frailty & aging	Immunosenescence, inflammaging	↓ Clearance; ↑ sensitivity	Adverse drug events, mortality	Conservative dosing; deprescribing
Chronic inflammatory states	Persistent immune activation	Variable PD response	Reduced antimicrobial efficacy	Individualized PK/PD targets

Risk stratification

Consequently, it is crucial to create efficient risk stratification models to pinpoint those patients that are at the highest risk for the outcomes explained above, facilitating the prioritization of intervention, and optimizing the organization of clinical pharmacy resources, especially among the aging population, who possess an increased risk for medication-related problems due to normal physiological and pathological changes associated with aging (Molist-Brunet et al., 2022; Reichenpfader, 2019). Those models should account for, for example, the number of medications, drug classes, patient comorbidities, and genetic risk to improve prediction (Barrio-Cortes et al., 2023; Whitney et al., 2021). These are advanced tools that may help distinguish between polypharmacy as a marker of advanced disease versus polypharmacy as a causal factor in an adverse event to inform more directed pharmacotherapy (Whitney et al., 2021). However, such a nuanced understanding is crucial because polypharmacy may represent

simply a marker of health status rather than a true causal factor for severe outcomes such as chronic kidney disease or liver disease (Whitney et al., 2021).

This is an important distinction since both kidney and liver health are often impaired in multimorbid individuals, and polypharmacy is known to contribute to deterioration of the function of these organs (Whitney et al., 2021). Consequently, the construction of functional risk stratification tools that consider these organ-specific susceptibilities as well as the unique drug-drug interactions will be essential for the implementation of anticipatory medication management. Moreover, risk assessment on an individual level should reflect the quantitative and qualitative burden of polypharmacy instead of a mere number of concomitant medications, and explore appropriateness and possible synergistic toxicities of specific drug combinations (Sozańska et al. 2025). In the context of, quantitative studies on polypharmacy have identified it as a key risk factor for mortality and incident severe chronic kidney disease and liver disease, especially in older adults (Melo et al., 2021; Whitney et al., 2021). However, it is equally important to determine whether polypharmacy is a direct contributor or merely a marker for more clinically severe conditions such as adults with cerebral palsy who have a propensity to develop multimorbidity and necessitate multiple medications (Whitney et al., 2021).

Research also calls into question the nature of the interrelationship between polypharmacy and patient outcome especially in terms of whether it be causation as opposed to association (Whitney et al., 2021). Therefore, utilization of precision medicine in polypharmacy management, using tools such as physiological-based pharmacokinetic-pharmacodynamic modeling may assist in personalizing medications according to patient profiles (Fujita et al., 2023). These complexities may be alleviated by using digital health innovations and clinical decision support systems to ensure that the prescribing decision-making process is as effective as possible, especially for older adults living with multiple chronic conditions (Foglia et al., 2023). In addition, machine learning algorithms will be useful in developing intelligent medication management systems that are able to predict adverse drug reactions and address deprescribing, both essential for reducing medication burden in this population (Fujita et al., 2023). Such systems may factor in physiologic changes associated with aging that affect drug pharmacokinetics and pharmacodynamics, minimizing the risk of iatrogenic decline in renal or hepatic function commonly encountered in older, multimorbid subjects (Villén et al. 2022; Wolf et al. 2023). This kind of pharmacotherapeutic strategies is necessary for the high risk of adverse drug events, especially in a population that has an altered drug metabolism and clearance due to age-associated organ decline (Huizer−Pajkos et al., 2015).

Antimicrobial Therapy Considerations

Antimicrobial therapy in multimorbid patients requires special consideration to ensure appropriate dose adjustments due to changes in physiological reserves, excessive burden of drug-drug interactions, and dynamicity of the organ dysfunction (especially the kidneys and/or liver) (Hughes et al., 2024; Silva, 2024). In cases of polypharmacy where multiple medications can interact to create cumulative toxicities or affect antimicrobial potency, the complexities only increase (Fujita et al., 2023). Hepatic and renal impairment, which is typical in the elderly and multimorbid individuals, may significantly change the pharmacokinetic properties of antimicrobials, necessitating precise dose modifications to prevent the possibility of drug accumulation and toxicity and maintain the desirable therapeutic concentrations (Fujita et al., 2023). Therefore, the limitation of intrinsic toxicity and pharmacological effectiveness of antimicrobials is essential to enhance the level of antimicrobial success at the lowest possible harm to the patient and the overuse of the maximum effect (Melo et al., 2021). The precision in dosing is even more pivotal due to therapeutic competition where potentially positive actions of a treatment on one disorder deteriorate another disorder; a phenomenon that makes administering antimicrobials to multimoral patients more difficult.

Furthermore, in such fields as antimicrobial stewardship, the entire course of medication including OTCs and supplements needs to be comprehended so that unforeseen interactions between drugs, which may lead to treatment failure and patient safety, could occur. This takes into account the cross-examination exercise of medication prescription to strengthen dosages on the basis of circumstantial essentials, retrogressive criteria and vulnerability to future organ harm, especially in medically congruent populations (Melo et al., 2021). And it is even harder to treat infectious diseases in this complicated structure where the elderly patients are very likely to exhibit untypical manifestations of

infections and are more prone to a negative outcome (Soraci et al., 2023; van Felton et al., 2023). It implies that in selecting an antimicrobial agent, as well as drug dosing, age-related alterations in pharmacokinetics and pharmacodynamics have to be considered (Clifford et al., 2015). Volume of distribution, renal clearance, or hepatic metabolism are all likely to alter and affect drug exposure and, as a result, the geriatric populations are more susceptible to adverse drug reactions (Soraci et al., 2023). As an example, improper use of antibiotics is common in elderly people and is associated with major negative outcomes, such as heart rhythm disturbances, delirium and increased risk of contracting Clostridioides difficile (Pulia et al., 2019). The comorbidities that are common among older adults and present alongside infections with pathophysiology characteristics of the aforementioned problems, which may contribute to the development of complications, are often present in already nephrotoxic antimicrobials that demand extra consideration given the high likelihood of supratherapeutic exposures manifesting in renal failure that provokes and exacerbates complications (Ngcobo,2025; Ture et al.,2025).

Table 2. Polypharmacy-Related Risks in Multimorbid Infectious Disease Patients.

Risk Domain	Mechanism	Clinical Impact	Examples	Pharmacist-Led Mitigation
Drug–drug interactions	Enzyme inhibition/induction	Toxicity or therapeutic failure	Macrolides + statins	Comprehensive medication review
Drug–disease interactions	Worsening comorbidities	Organ injury	NSAIDs in CKD	Drug–disease screening
Prescribing cascade	Treating ADRs as new diseases	Exponential polypharmacy	Anticholinergics for antibiotic-induced delirium	Deprescribing
Non-adherence	Regimen complexity	Treatment failure	Multiple daily dosing	Regimen simplification
Cumulative toxicity	Additive organ burden	AKI, liver injury	Vancomycin + aminoglycosides	Toxicity surveillance
Inappropriate polypharmacy	Lack of geriatric evidence	Increased mortality	End-of-life overtreatment	Patient-centered review

Findings Safer alternatives to traditional nephrotoxic antibiotics may be available, particularly in elderly and patients with impaired renal function, who are more vulnerable to adverse drug events (Falcone et al., 2023). Aminoglycosides are a good example of this issue; although effective, they can be nephrotoxic and ototoxic and require careful monitoring with consideration of dose adjustments, or less toxic alternatives, when possible (Clifford et al., 2015). Additionally, total body water and lean mass are decreased in older persons, which reduces the solubility of water-soluble drugs such as aminoglycosides and beta-lactams and increases the plasma concentration and risk of toxicity (Ngcobo, 2025). Yow et al. (2022) emphasize this, and comment on the clinical relevance of both pathogen diversity and a humanized prediction of PK/PD that specifically promotes dosing that optimally exposes a drug to a target pathogen to achieve the desired target while sparing a patient from the potential harm of excess drug exposure. Notably, in drugs such as teicoplanin, older patients may need to be prescribed higher doses than traditionally recommended to ensure adequate attainment of therapeutic concentrations despite fears of nephrotoxicity, highlighting that evidence-based dosing adjustments are needed for some agents (Liu et al., 2024).

This strategy is distinctly different than the general guidance for reduced dosing in this age group based on a decline in renal function affecting >40% of this population (Liu et al., 2024) and represents the unique considerations for improving antimicrobial treatment in older adults. Many antimicrobials are not accompanied by geriatric dosing guidelines, making receipt of appropriate therapy increasingly challenging, leading to suboptimal treatment, or sub and overtreatment [Wu et al After all, 2021; Yang et al. 2025]. This gap requires additional research to develop evidence-based dosing optimization

strategies which take both the physiological changes associated with aging as well as multimorbidity into account (Soraci et al., 2023).
In addition, increased risk of adverse drug events (ADEs) in older adults, with antibiotics as the most common culprit (Pulia et al., 2019), highlights the importance of appropriate use in this sensitive population. Moreover, the increased risk of antimicrobial-associated organ injury in older adults requires a detailed understanding of drug-specific toxicities and their possible persistent effects (Chinzowu et al., 2021). This is especially difficult in the setting of frailty, which typically correlates with deterioration of functional reserves altering antimicrobial contact and increasing the likelihood of antibiotic dosing-related toxicity (Pea, 2022). As such, the optimisation of drug levels is critical to maximise efficacy and minimise the risk of concentration-dependent adverse events in this population, and thus therapeutic drug monitoring is indispensable in this population (Saito et al., 2019). At the antibiotic level, achieving adequate trough concentrations (eg, levels below 10 μg/mL are associated with treatment failures, and levels above 15 μg/mL are recommended for serious infections) (Liu et al., 2011) is an example of an important PK-PD target for drugs such as vancomycin. Nevertheless, age-related pharmacokinetic alterations that result in disproportionately elevated vancomycin exposures for a given dose are often encountered in the elderly complicated by declining renal function further making the therapeutic targets elusive (Yahav et al., 2019).

Clinical Pharmacy Interventions

Deprescribing is the process of stopping medications that are no longer needed or that carry significant risk and burden; it is especially important in the polymedicated elderly where drug interactions and adverse effects are more likely (Gu et al., 2021).As such, the role of the pharmacist is crucial and highly regarded in the deprescribing process. It is in this context that this approach is especially relevant, because of the evidence gap over the effectiveness and safety of many drugs, including those used for type 2 diabetes and chronic kidney disease, in older populations where undertreatment or overtreatment may occur (Yang et al, 2025).
Deprescribing interventions, conducted by pharmacists in particular, have the potential to enhance medication-related outcomes by decreasing overall medication burden and reducing the risk for adverse drug events (Tesfaye et al., 2025). They are essential in promoting patient safety and quality of life through simplifying complex medication regimes; reducing potential for drug-drug interactions and medication non-adherence. Given that geriatric patients may present to the intensive care unit with multimorbidity and will often receive many intravenous medicines, the role of the clinical pharmacist to assess and optimize the medication regimen is invaluable (Gu et al., 2021). This includes an integrative assessment of medications, the patient´s comorbidities and current physiological status, and the risk of potential (drug-drug or drug-disease) interactions, which are commonplace among the older polypharmacy patients (Falcone et al., 2020).
Such reviews are crucial for the detection of potentially inappropriate medications that are prevalent in older population and often associated with adverse outcomes and to achieve optimal therapeutic regimens for adequate and effective care of elderly patients (Alwaddani et al., 2022; Kovačević et al., 2024). The role of reasons for high mortalities when studies are focused on infections also clinical pharmacists in the field of another strategy used to tackle this problems, antimicrobial stewardship, which is accomplished through optimizing of drug selections, dosages and durations of drug therapy, resulting in decreased of resistance and adverse effects (AlShehail 2025). Many studies have demonstrated dramatic reductions in both carbapenem and tetracycline consumption, allowing reductions in antibiotic use density to be achieved when pharmacist involvement is engaged in this targeted intervention (Gu et al., 2021). In addition, pharmacists play an active role in therapeutic drug monitoring (TDM) and modification of antimicrobial regimens to optimize pharmacokinetic/pharmacodynamic (PK/PD) target attainments and toxicity avoidance, particularly with narrow therapeutic index drugs (Gu et al., 2021). As older adults are usually polymedicated and the metabolism and clearance of many medications are changed by age-related physiological changes and/or multimorbidity, their skills in pharmacokinetics and pharmacodynamics assist in the management of complicated medication regimens (Ngcobo, 2025). In addition, pharmacist-led prospective medication reviews, particularly in the elderly population, can directly target polypharmacy, which is a marker of ill-health rather than a causal mechanism of adverse drug outcomes,

and optimize medication use to mitigate adverse drug events (Alwaddani et al., 2022; Whitney et al., 2021).

Table 3. Antimicrobial Therapy Considerations in Multimorbidity and Complex Regimens.

Antimicrobial Class	Key PK/PD Target	Multimorbidity-Related Challenge	Major Toxicities	Optimization Strategy
Vancomycin	AUC/MIC 400–600	Age-related ↓ clearance	Nephrotoxicity	AUC-guided TDM
Aminoglycosides	Cmax/MIC ≥8–10	↓ Total body water	Nephro-/ototoxicity	Once-daily dosing; alternatives
β-lactams	fT>MIC	ARC or renal failure	Neurotoxicity	Extended/continuous infusion
Polymyxins	Exposure-limited efficacy	Renal impairment	Severe nephrotoxicity	Individualized dosing; avoidance
Fluoroquinolones	AUC/MIC	QT prolongation risk	Arrhythmias, delirium	Risk stratification
Combination therapy	Synergistic targets	Interaction burden	Additive toxicity	Pharmacist-guided selection

Monitoring therapeutic effectiveness and safety

It is essential to monitor the effectiveness and safety of therapy, which leads to the overall success of the patient, especially in the case of older adults who have infectious diseases and complex medication regimens (Aksoy et al., 2025). This is accompanied by cautious observation of clinical response, laboratory parameters, and the adverse events related to the use of the drugs that are intensified by polypharmacy and physiological changes in older people (National Safety and Quality Health Service Standards User Guide of the Health Care of the Intellectually Disabled, 2024; Whitney et al., 2021). This close monitoring is particularly necessary because polypharmacy, in its turn, is a key risk factor of premature mortality, severe chronic kidney disease, and liver disease in the older populations (Whitney et al., 2021).

Moreover, the early onset of chronic disease in adults with cystic fibrosis, which may lead to a 3-fold higher frequency of multimorbidity in young adults, can also illustrate the wider aspect of polypharmacy as a marker of adverse health status rather than just a causal factor of pathophysiological processes (Melo et al., 2021; Whitney et al., 2021). Hence, the role of pharmacists is vital in interpreting if polypharmacy is an inevitable result of governing multiple chronic comorbidities or a potentially alterable determinant to adverse outcomes, particularly in complex populations (Whitney et al., 2021). The proactivity of the clinical informatician to optimise pharmacokinetic/pharmacodynamic parameters (e.g., adjusting dosing intervals or continuous infusions) is central to improving rational use of antibiotics and, as a result, attenuating the emergence of drug resistance (Zhou et al., 2023).

It is a careful strategy that enables maintaining therapeutic concentrations while limiting toxicity, a task that becomes difficult with aged people who had weakness in renal and hepatic (Melo et al., 2021). Because of such complexities, pharmacists often work with family physicians to facilitate discharge medication reconciling with current regimens, preventing inappropriate polypharmacy and timely cessation of unnecessary antibiotics as resistance and side effects (Susło et al., 2023). In addition, pharmacists are instrumental in-patient education, aiding in the compliance with complex medication schedules, counseling on potentially harmful drug interactions and side effects, and directing the patient to take an active role in their own care (Bouza et al., 2020).

Clinical Outcomes and Evidence

This has affected the significant reduction of adverse drug events due to drug-related problems including inappropriate prescribing, drug-drug interactions, and non-adherence in polymedicated older patients (Delgado-Silveira et al., 2021). Such interventions often focus on older adults, and especially those living in nursing homes (where both polypathology and related frailties are relatively frequent), since prescribing can often be reconciled against clinical practice guidelines to guide deprescription

with the goal of limiting adverse drug events (Zaij et al., 2023). In addition, pharmacists are central in analysing prescribing patterns with a view to optimising dosing based on current indications, past data and future risk of organ damage, particularly in medically diverse groups (Melo et al., 2021). This all-inclusive method encompasses an ongoing surveillance of pharmacological management, balancing the need for clinical effectiveness with minimizing untoward/unintended consequences through timely fine-tuning and patient education (Alwaddani, Bhagat, Mamat, & Khehra, 2022). Pharmacist involvement in the care team has been shown to reduce adverse events, decrease morbidity and mortality, reduce medication errors (including in the ICU, pediatric populations, etc.), and ultimately result in a more consistent pharmacotherapy management strategy (West et al., 2017).

The integrative and encompassing medication management services offered by pharmacists including reconciliation at transitions of care and monitoring for medication-related adverse drug reactions contribute to patient safety and effective pharmacotherapy, respectively (Alonazi et al., 2022). Research indicates that the addition of pharmacists to multidisciplinary care teams can significantly reduce polypharmacy and improve patient outcomes (Alkhamsan et al., 2024). This participation results in a significant improvement in the prescription appropriateness and higher cure rates with lower relapse rates of infectious diseases (Alghanim et al., 2025). Not only does this optimization of pharmacotherapy contribute to the prevention of adverse drug events amongst the population, which in turn leads to a considerable reduction in the burden of drug-related morbidity and mortality (Delgado-Silveira et al., 2021), but it also leads to additional cost savings for the healthcare system by reducing hospital readmissions. Clinical pharmacists avenant with these interventions tend to see acceptable patients again immediately and are also prevailed in the modernization of patient outcomes and decreasing polypharmacy, and its' benefits leaving aside demographic factors, neurodevelopmental disabilities and multimorbidity (Melo et al., 2021; Whitney et al., 2021).

Pharmacists' specialized knowledge in drug therapy and nutritional supplements places them uniquely in a position to reduce side effects due to iatrogenic polypharmacy and inappropriate use of drugs (Orehovački et al., 2023). They play a critical role in reviewing medication regimens and considering a patient's global health profile when addressing polypharmacy, which is frequently a marker of complex health rather than just a causal factor for adverse events (Whitney et al., 2021). This can be dissected in terms of whether polypharmacy is a natural output of effective disease management, or whether this is an indicator of worse clinical status, as might happen in cases where development of chronic disease and requirements of multiple medications happens early on (Melo et al., 2021; Whitney et al., 2021). Therefore, the pharmacist's detailed knowledge of individual patient profiles allows them to distinguish between appropriate polypharmacy necessary for multifaceted multimorbidity and excessive medication burdens (which are potentially harmful) (Whitney et al., 2021).

Improved patient-centered outcomes

Pharmacists help patients to follow medication guidelines and improve patients' health quality of life, particularly in managing the health needs of people coping with infectious disease in the context of complex multimorbidity (Almontashiri, 2024; Chumney & Robinson, 2006). Personalized medication management provides patients with the information they need to take charge of their conditions and health literacy (Almontashiri, 2024), while comprehensive education and continuous monitoring ensures that the most up-to-date treatment plan is in place. This approach is centered on the patient to maximize therapeutic effects and reduce adverse drug reactions and drug-drug interactions especially with large number of medications aimed at the same time (Melo et al., 2021; Whitney et al., 2021). In addition, based on the author's experience, this also helps decrease pharmaceutical expenses, which is an economic, in addition to clinical, advantage of the participation of pharmacists (Damasceno-Silva et al., 2023).

Pharmacists as Medication Therapy Optimizers This type of multifaceted role of pharmacists in optimizing therapy not only leads to optimal identification of medication therapy but also to improved health outcomes of patients with complex health profiles (Book, 2024). For example, the specialized knowledge that they bring can help with managing multimorbidity and polypharmacy, where a rising global population is living with multiple chronic conditions, of which over 70% of adult primary care patients can present with (Prazeres, 2024; Urbańczyk et al., 2023). This makes pharmacists a key driver of designing and executing deprescribing initiatives, especially in elderly patients, to achieve a net

reduction in the medication burden to optimize health outcomes without forgoing the therapeutic benefit of essential medication (Ali et al., 2022). Polypharmacy itself is a possible, direct cause of mortality and severe, chronic kidney disease and liver disease, emphasizing the need for careful medication management (Whitney et al., 2021) and so this is especially salient.

This type of careful management, which is often accomplished via patient-centered models of prescription, is intended to improve adherence and the evolvement of effective prescribing with the aim of reducing potential complicated drug regimen-associated risks in multimorbid patients (González-Bueno et al., 2021). Such careful optimization of medication regimens is needed to reduce harmful outcomes–including mortality, end-stage renal failure, and liver failure–that have been observed with polypharmacy and hyperpolypharmacy (Melo et al., 2021; Whitney et al., 2021). In addition, medication therapy management services performing by clinical pharmacists have been achieved significant in the management of blood pressure control, declining drug-related problems, and the medication therapy outcome in frequent multimorbid patients (Li et al., 2023).

Challenges in Real-World Practice

A shortage of evidence-based recommendations of patients with multiple chronic conditions in particular is one of the primary challenges encountered in the management of infectious disease in a multimorbid population, resulting in a therapeutic dilemma and difficulties with the personalization of prescriptions (Molist-Brunet et al., 2022). The mentioned deficiencies often lead to the necessity to resort to professional judgment and reasonable clinical experience to align conflicting treatment priorities and reduce adverse drug events in such multimorbid groups (Whitney et al., 2021). Such dependence is critical especially because much of the clinical practice guidelines are concerned with single disease conditions, which isolate the subject of polypharmacy and risk of adverse events in elderly adults with multimorbidity (Costanzo et al., 2024).

Therefore, there is an urgent need to modify current guidelines and/or develop new and combined strategies to address multifaceted pharmacological interactions and physiological changes that are involved in the treatment... This problem is exacerbated by the fact that evidence that proves that the use of single-disease guidelines may result in polypharmacy, which is negatively correlated with the compliance with the antibiotic prescription guidelines in patients with multiple comorbidities makes it difficult to make optimal treatment choices (Dylis et al., 2019). Therefore, to successfully manage the polypharmacy and its consequential effects, particularly since polypharmacy may exacerbate a deteriorating organ functionality (Whitney et al., 2021), one of the key conditions is to understand the complex relationships between various diseases and their treatments, to be able to implement the methods that balance the benefits and harms of treatment. This may result in clinical outcomes evaluating the worth of disease-focused treatment versus the numerous burdens of polypharmacy, with holistic directed integrated directions demonstrating the necessity (Costanzo et al., 2024). Besides that, the single-disease paradigm, prevalent in most other guidelines, also fosters polypharmacy and development of drug-drug interactions, as individual conditions are usually considered as a condition in and of themselves (Mangin et al., 2018).

Time and workforce constraints

The pressure on the providers is further burdened by the necessity to prescribe patients with multimorbidity the complex regimens of pills, which is complicated by the absence of time to conduct a proper consultation and communicate with interprofessional (Fabbri et al., 2015). This is particularly challenging since it is a considerable amount of training and time that would be required to provide effective psychosocial support as well as create individualized treatment plans (Bayona-Huguet and Bayona-Pizarro, 2023). Besides the above-mentioned issue, there is an increasing burden of multimorbidity especially in the elderly leading to a higher demand of complex pharmaceutical care which adds additional burden to health systems that are already overstretched. This is enhanced by the fact that individuals with multimorbidity, in most cases also have social, mental and physical health needs that need attention by various services and they are likely, in most cases, to need unplanned emergency care and hence, coordinated care is highly challenging (Nwidiugwu, 2021). These systemic pressures tend to result in care continuity shortage and decreased capacity to do complete medication

review and offer education that is crucial elements of effective complex regimen management (Cahill & Cahill, 2015).

An example of this is the necessity to adopt the concept of minimally disruptive medicine, the habit of ensuring to reduce the burden of treatment by transforming the tenor of ordinary care, guided by disease-focused guidelines, to a more personalized one where shared decision-making is prioritized (Lee et al., 2024), which is further exacerbated by such environment. Moreover, comorbidities such as chronic diseases (which are even observed to be more prevalent in the general population at earlier ages (Melo et al., 2021; Whitney et al., 2021) make the situation worse. As an example, comorbidity is especially prevalent in the case of autism spectrum disorder, and polypharmacy is more often the case in common comorbidities (Melo et al., 2021). Besides these problems, the fact remains that even more sophisticated healthcare systems, not to mention LMICs, are in most cases incapable of addressing multimorbidity and polypharmacy, and a so-called prescribing cascade in which one medication is prescribed to counteract the effects of another drug (Fraccaro et al., 2015). Polypharmacy is likely in people with multimorbidity and neurodevelopmental disabilities, including cerebral palsy, and poses a complicated polypharmacy-induced toxic environment that needs constant monitoring (Melo et al., 2021). This indicates the urgency of integrative management and specific training in the fields in which a combination can be the most accurate to meet the multifaceted needs of such groups of patients with the goal of maximizing treatment benefit and minimizing treatment burden (Lee et al., 2024; Moffat & Mercer, 2015).

Conclusion

In the current era of increased life expectancy with associated multimorbidity coupled with complex medication regimens, the management of infectious diseases is a major, and increasingly common, challenge to the clinician. Background physiological changes with age, chronic organ failure and frailty lead to marked alterations in pharmacokinetics and pharmacodynamics of drugs, that make traditional antimicrobial dosing strategies unhelpful. These, in conjunction with widespread polypharmacy, put patients at considerable risk of drug–drug interactions, adverse drug reactions, treatment non-adherence, and antimicrobial resistance. Key messages Polypharmacy in multimorbid patients represents not only a simple number of medications but a complex clinical phenomenon and should be qualitatively assessed in terms of appropriateness, trailogenic need and cumulative toxicity. Clinical pharmacists have the potential to overcome these challenges by performing thorough medication reviews, making dose adjustments, therapeutic drug monitoring, and deprescribing when necessary. Numerous studies provide evidence that interventions by pharmacists decrease medication errors; drug-related problems; adverse events; hospital readmissions; and healthcare costs, thereby enhancing patient safety and outcomes. In addition, the pharmacist is a key member of the health team in regard to patient education, adherence support, and antimicrobial stewardship, making sure antimicrobial therapy is used efficiently and safely within the competing priorities brought by chronic diseases. However, barriers to real-world implementation include lack of evidence to drive clinical practice guidelines, limitations in pharmacist workforce capacity to implement these guidelines, and limited incorporation of pharmacy services into multidisciplinary care models. Advancing clinical care will involve the creation of multimorbidity-inclusive clinical guidelines, greater availability of clinical pharmacy services, and the implementation of digital decision-support tools and precision pharmacotherapy approaches.

Conflict of Interest

The authors declare they don’t have any conflict of interest.

Author contributions

The initial author and the supervisor of the cross-ponding author write the first manuscript drafts. Each author contributed to the manuscript's writing, gathered information, edited it, made tables, and received approval to submit it for publication in a journal.

Acknowledgement

The authors thank numerous resources for providing open access materials, including DOAJ, Cochrane Library, BMJ Clinical Evidence, Google Scholar, Embase, PubMed, and Medline.

Ethical Approval
Not Applicable

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