Pharmacokinetics and Pharmacodynamics in Special Populations in Admitted Patients

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Abstract:

Pharmacokinetics and pharmacodynamics are critical in optimizing medication therapy for special populations, including pediatric, geriatric, and those with compromised organ function. In hospital settings, understanding how factors such as age, weight, genetic makeup, and co-existing conditions affect drug absorption, distribution, metabolism, and excretion (ADME) is essential for effective treatment. For instance, in pediatric patients, liver and renal functions are still maturing, which can lead to altered drug clearance and necessitate age-specific dosing adjustments. In geriatric patients, polypharmacy and altered physiological parameters can significantly influence drug interactions and efficacy. Monitoring these pharmacokinetic changes ensures that patients are receiving the appropriate therapeutic doses to maximize efficacy while minimizing toxicity. Pharmacodynamics, the study of drug effects and mechanisms of action, is also crucial in special populations. Variability in receptor sensitivity and signaling pathways can result in altered drug responses among different patient groups. For example, older adults often experience increased sensitivity to central nervous system (CNS) depressants, which can lead to adverse effects, such as sedation or confusion. In patients with chronic diseases, comorbidities can further complicate drug action, necessitating careful selection of pharmacotherapy. Tailoring treatment plans based on pharmacodynamic considerations in these populations helps healthcare providers avoid adverse drug reactions and improve patient outcomes in hospital settings.

Keywords: Pharmacokinetics, Pharmacodynamics, special populations, hospital settings, pediatric, geriatric, organ function, drug absorption, distribution, metabolism, excretion, therapeutic dosing, drug interactions, receptor sensitivity, CNS depressants, comorbidities.

Introduction:

The field of pharmacology is intricately intertwined with the principles of pharmacokinetics and pharmacodynamics, domains that explore the behavior of drugs within biological systems and their respective effects on the body. Pharmacokinetics encompasses the absorption, distribution, metabolism, and excretion (ADME) of drugs, whereas pharmacodynamics focuses on the biological and physiological effects of drugs and their mechanisms of action. In routine clinical practice, these principles are often generalized based on average adult patients, potentially overlooking the unique considerations required for special populations [1].

Special populations are groups that may respond differently to medications due to factors such as age, gender, genetics, disease states, and organ function. These populations commonly include pediatric patients, geriatric patients, pregnant and lactating women, and individuals with coexisting medical conditions or genetic polymorphisms. Hospital settings are critical environments in which understanding the nuances of pharmacokinetics and

pharmacodynamics is essential for safe and effective patient care. The dynamic interplay of drugs with altered physiology, concurrent medications, and varying treatment goals underscores the necessity of tailoring pharmacologic therapy to meet the specific needs of these patients [2].

The pediatric population presents distinct pharmacokinetic and pharmacodynamic challenges due to their ongoing developmental processes. Differences in body composition, organ maturity, and enzyme activity can significantly alter drug behavior and effectiveness. For example, neonates and infants exhibit immature liver and kidney function, leading to reduced clearance rates of medications and potential for accumulation and toxicity. Likewise, pharmacodynamics in children can diverge sharply from adults, as pediatric patients often exhibit heightened sensitivity to certain medications, necessitating careful dose adjustments to avoid adverse effects while achieving therapeutic goals [3].

Conversely, the geriatric population faces its own unique set of challenges. Age-related physiological changes, such as decreased renal function, altered body composition, and changes in receptor sensitivity, can considerably affect both pharmacokinetics and pharmacodynamics. Additionally, polypharmacy—a common scenario in elderly patients—can lead to increased risk of drug-drug interactions and adverse effects, complicating treatment strategies. Understanding the geriatric population’s pharmacologic profiles is essential for optimizing medication therapy in these often fragile patients [4].

Pregnant and lactating women represent another critical area of study within pharmacokinetics and pharmacodynamics in special populations. Physiological changes during pregnancy—such as increased plasma volume, altered drug clearance rates, and placental transfer of medications—necessitate careful consideration of drug therapy. Certain medications may pose risks to fetal development, while lactation introduces additional considerations regarding drug exposure in breastfed infants. Research into teratogenic potentials and the safe use of medications during pregnancy and lactation is vital for informed clinical decision-making [5].

Furthermore, individuals with comorbid conditions often exhibit altered pharmacological responses due to complex interactions between their diseases and prescribed treatments. Diseases such as diabetes, hypertension, and chronic kidney or liver disease necessitate adjustments in dosing or the selection of alternative medications due to impaired absorption, altered drug metabolism, or modified therapeutic effect. Genetic polymorphisms can also play a significant role in pharmacodynamic variability, as certain populations may metabolize drugs at different rates, leading to therapeutic failures or toxicities [6].

In light of these complexities, the integration of pharmacogenomics into clinical practice can enhance our understanding of individual responses to pharmacotherapy. By identifying genetic variations that influence drug metabolism and response, personalized medicine approaches can be employed to maximize therapeutic effects while minimizing adverse outcomes [7].

Influence of Age on Drug Absorption and Metabolism:

The human body's ability to absorb and metabolize drugs is a complex interplay of various physiological factors that can significantly change over a person's lifetime. Age, in particular, is a critical factor affecting pharmacokinetics, which encompasses the processes of drug absorption, distribution, metabolism, and excretion (ADME). As individuals progress from infancy through childhood, adolescence, adulthood, and into the elderly phase of life, the body undergoes numerous changes that can alter drug behavior [8].

Drug Absorption Across the Lifecycle

Neonates and Infants:
Drug absorption in neonates and infants is notably unique due to several anatomical and physiological factors. The gastrointestinal (GI) tract is immature at birth, leading to alterations in gastric pH, gastric emptying time, and intestinal motility. For instance, the higher gastric pH in neonates means that weakly acidic drugs, which are usually better absorbed in an acidic environment, may not be as effectively absorbed. Conversely, weakly basic drugs may have enhanced absorption. Additionally, longer gastric emptying times can delay the absorption of certain medications [9].

The skin of infants is thinner and more permeable than that of adults, which can lead to increased systemic absorption of topical medications. This heightened sensitivity necessitates careful dosing and monitoring of topical therapies in this population [10].

Children and Adolescents:
As children grow, their GI tract matures, and the

absorption characteristics gradually resemble those of adults, although some differences persist, particularly in very young children. The onset of puberty introduces hormonal changes that can further affect drug response. Differences in body composition during childhood and adolescence—such as increased body water and decreased body fat relative to adults—can also alter how drugs are distributed in the body. For instance, hydrophilic drugs may have a greater volume of distribution in children due to higher total body water, which necessitates weight-based dosing adjustments [11].

Adults:
In young and middle-aged adults, drug absorption is generally stable and predictable; however, factors such as diet, co-administered drugs, and overall health can introduce variability. The GI tract is fully developed, and while first-pass metabolism primarily occurs in the liver, certain systemic factors can influence absorption rates. Illness, stress, and hormonal fluctuations can also play roles in modifying how drugs are absorbed and utilized by the body [12].

Elderly:
As individuals age, numerous physiological changes can significantly impact drug absorption. Reduced gastric acid secretion, slower gastric emptying and intestinal motility, and changes in enzyme levels can all contribute to decreased bioavailability for certain medications. For instance, drugs requiring an acidic environment for optimal absorption may see diminished absorption in older adults due to increased gastric pH levels. Reduced blood flow to the GI tract can also affect absorption rates. Although drug absorption may be slower, it is not always necessarily reduced; some drugs may still be absorbed effectively, but the onset of action may be delayed [13].

Drug Metabolism with Age

Drug metabolism primarily occurs in the liver and involves enzymatic processes that transform lipophilic compounds into more hydrophilic metabolites for easier excretion. Enzyme activity is influenced not only by age but also by genetic factors, diet, health status, and concurrent medications—a phenomenon known as drug-drug interactions [14].

Neonates and Infants:
In neonates, liver enzymes responsible for drug metabolism are immature, which can lead to reduced clearance of drugs and a prolonged half-life, especially for drugs that undergo extensive first-pass metabolism. For example, the metabolism of medications such as phenytoin and theophylline is significantly slower in infants than in adults, necessitating lower dosages or more careful monitoring. By six months of age, metabolic capacity begins to increase, approaching that of adults, though variations may still exist [15].

Children and Adolescents:
In childhood, metabolic enzyme activity levels typically increase, and in some cases, children may exhibit an increased clearance for certain medications, requiring higher doses compared to adults on a weight-adjusted basis. During puberty, hormonal shifts can again influence enzyme expression and activity, leading to further variability in drug metabolism [16].

Adults:
In healthy adults, drug metabolism is generally efficient, and the liver's enzymatic pathways are well-established. However, lifestyle factors such as diet, exercise, and substance use (e.g., alcohol, tobacco) can also impact drug metabolism. For example, substances that induce liver enzymes may lead to decreased drug levels for medications metabolized by those same pathways, necessitating careful monitoring [17].

Elderly:
In older adults, metabolic processes tend to decline due to reduced liver size and hepatic blood flow, leading to decreased metabolic clearance for many medications. This decline can result in a higher risk of drug accumulation and toxicity. The "beer criteria," a list of potentially inappropriate medications for older adults, highlights the importance of assessing metabolic capacity when prescribing medications to this population. Metabolic variability can be exacerbated in the elderly due to comorbidities and polypharmacy, where multiple medications may interact and affect metabolism rates [18].

Clinical Implications

Understanding the influence of age on drug absorption and metabolism is essential for clinicians in order to optimize therapeutic regimens across the lifespan. Consideration should be given to age-related changes when prescribing medications to ensure safety and efficacy. Dosing strategies often require adjustment based on age, weight, organ function, and overall health status [18].

In pediatrics, weight-based dosing formulas are routinely employed, tailored to the unique needs and

developmental stages of children. In geriatrics, careful consideration of polypharmacy and potential drug-drug interactions is crucial to avoid adverse effects. Additionally, medication reconciliation during transitions of care is vital to minimize risks associated with medication changes due to shifting pharmacokinetic profiles [18].

Pharmacokinetic Considerations in Pediatric Populations:

Pharmacokinetics, the study of how drugs are absorbed, distributed, metabolized, and excreted in the body, plays a pivotal role in ensuring the safe and effective use of medications. Particularly in pediatric populations, pharmacokinetic principles take on heightened importance due to the unique physiological and developmental characteristics of children compared to adults. Adequate understanding of these variations is essential for optimizing therapeutic outcomes and minimizing adverse effects in pediatric patients [19].

Pediatric populations encompass a broad age range from neonates to adolescents. Each stage of development presents distinct pharmacokinetic profiles influenced by factors such as body composition, organ maturity, and metabolic capacity. For instance, neonates and infants present a vastly different pharmacokinetic landscape compared to older children due to immature organ systems, particularly the liver and kidneys, which are crucial for drug metabolism and excretion.

Absorption of drugs can vary significantly in children owing to differences in gastrointestinal (GI) physiology. In neonates, gastric pH is higher (less acidic), which impacts the solubility and, consequently, the absorption of certain medications. The gastric emptying and intestinal transit times are also longer in neonates and infants compared to adults, which can delay the onset of drug action. Moreover, the immature skin in young children affects the transdermal absorption of medications; potentially leading to both increased systemic exposure to topical medications and altered efficacy of treatments administered dermally [19].

The distribution of drugs in the body is influenced by body composition, which changes as children grow. Neonates have a higher total body water percentage (approximately 80% of body weight), whereas older children and adults typically have a higher proportion of body fat and lower total body water. This difference necessitates adjustments in dosing regimens, as hydrophilic drugs may require larger dosing adjustments in younger patients to achieve therapeutic concentrations, while lipophilic drugs may require smaller doses due to their altered distribution in fat tissues [20].

Protein binding also plays a critical role in drug distribution. These binding proteins, such as albumin and alpha-1 acid glycoprotein, are less abundant and bind less effectively in neonates and infants, resulting in higher free drug concentrations. This situation can lead to increased pharmacological effects and a higher risk of toxicity.

The metabolic pathway for drugs can differ significantly in pediatrics. The liver, where the majority of drug metabolism occurs, undergoes dramatic maturation from the neonatal stage through adolescence. Phase I reactions (oxidation, reduction, hydrolysis) may be immature in neonates, while Phase II reactions (conjugation) develop more slowly. These variations can lead to unpredictable drug metabolism in children, necessitating the need for vigilant monitoring in pediatric patients to prevent potential overdoses or therapeutic failures [21].

An example is the metabolism of theophylline, where neonates metabolize the drug at a much slower rate than older children who may demonstrate significantly enhanced clearance as they grow. As a result of these variations, dosing regimens established in adults cannot be directly extrapolated to pediatric populations.

Renal function is another important consideration in pediatric pharmacokinetics. In neonates, renal clearance of drugs is significantly reduced due to immature glomerular filtration rates. This insufficiency gradually matures and reaches adult levels by the age of 1 year. As such, dosing regimens for renally excreted drugs must be carefully tailored based on the patient's age and developmental stage to avoid drug accumulation and toxicity [22].

The unique pharmacokinetic profile of pediatric patients necessitates an individualized approach to medication management. Common complications arise from the lack of rigorous pediatric studies that can lead to the misapplication of adult dosing regimens in children. This misapplication can inadvertently cause an increased risk of adverse drug reactions or therapeutic failures.

One prominent example of the impact of pharmacokinetics is evident in the treatment of infections, where antibiotics like ceftriaxone display substantial variability in pharmacokinetic parameters across different pediatric age groups.

Guidelines for dosing in children must take into consideration not only weight or body surface area but also maturation of organ function to achieve effective and safe drug administration [23].

Another area of concern is the risk of drug-drug interactions which can arise due to the dietary habits and physiological differences in children. Clinicians must remain vigilant, particularly for commonly prescribed medications that may interact adversely with each other or with over-the-counter preparations often administered to children [24].

Future Directions in Pediatric Pharmacology

To improve pharmacotherapeutic strategies in pediatric populations, ongoing research and development are crucial. This includes:

- **Pediatric Clinical Trials**: Conducting more studies specifically aimed at understanding drug pharmacokinetics in children, allowing for the establishment of evidence-based dosing guidelines.
- **Use of Pharmacogenomics**: Incorporating pharmacogenetic testing to understand individual variations in drug metabolism due to genetic factors, ensuring personalized and optimized therapy for children.
- **Formulation Development**: Creating child-friendly formulations that cater to the unique needs of pediatric patients. This includes age-appropriate dosages and alternative delivery methods for those who resist oral medications [25].

Pharmacodynamics in Geriatric Patients: Sensitivity and Response Variability:

The field of pharmacodynamics explores the relationship between drugs and their physiological effects on the body, encompassing critical aspects such as the mechanism of action, the time course of drug effects, and the relationship between drug concentration and effect. This understanding is particularly vital in geriatric patients, a demographic that often presents unique challenges in medication management. As individuals age, physiological changes occur that can significantly impact both drug sensitivity and variability in response [26].

Physiological Changes in the Elderly

One of the primary reasons for increased variability in drug responses among geriatric patients is the array of age-related physiological changes. These modifications include alterations in body composition, organ function, and metabolic processes, all of which can influence how drugs act within the body.

1. **Alterations in Body Composition**: As individuals age, there is typically an increase in body fat and a decrease in lean body mass and total body water. These changes can affect the volume of distribution for hydrophilic and lipophilic drugs. Drugs that are distributed in water, such as many antibiotics, may have higher plasma concentrations due to decreased volume distribution, leading to increased toxicity. Conversely, lipophilic drugs may persist longer and accumulate in body fat, potentially prolonging their effects and side effects [27].
2. **Organ Function Decline**: Aging is associated with decreased efficiency of various organs, primarily the liver and kidneys. Since these organs are crucial for drug metabolism and excretion, their diminished function can lead to altered drug clearance and extended half-lives, impacting the pharmacodynamics of various medications. For instance, drugs that require hepatic metabolism may become increasingly potent and produce unanticipated effects if dosages do not account for reduced metabolic capacity.
3. **Altered Receptor Sensitivity**: Aging may also bring about changes at the receptor level. Receptors can become less sensitive to neurotransmitters and other signaling molecules, resulting in changes in therapeutic effects. For example, older adults may require higher or more frequent dosing of certain medications to achieve the desired pharmacological effect, such as increased sensitivity to sedatives and analgesics, which could enhance the risk of side effects or adverse events [28].

Sensitivity to Medications

Geriatric patients can exhibit heightened sensitivity to medications, posing significant risks for adverse drug reactions (ADRs). This increased sensitivity may stem from several factors including polypharmacy, co-existing health conditions, and unique pharmacokinetic and pharmacodynamic interactions [29].

1. **Polypharmacy**: The phenomenon of polypharmacy, which is defined as the concurrent use of multiple medications, is

prevalent in aging populations. Geriatric patients frequently suffer from multiple chronic conditions requiring complex therapeutic regimens. Each additional medication increases the risk of drug-drug interactions that can amplify or diminish the effects of individual drugs, leading to unpredictability in treatment responses. Inappropriate prescribing or inability to adequately monitor these interactions can elevate the probability of ADRs.

2. **Co-Morbidities**: The presence of multiple health conditions in elderly patients can result in altered pharmacodynamic profiles. For instance, an older individual with both diabetes and hypertension may respond differently to antihypertensive medications than a younger counterpart. The interplay between medications for different conditions can complicate treatment, necessitating careful consideration by healthcare professionals regarding alterations in drug effects due to comorbidities.
3. **Unique Adverse Effects**: Certain elderly patients may also be predisposed to atypical reactions to medications that are not well-documented in younger populations. For instance, sedative-hypnotics can lead to prolonged sedation and confusion in older adults, whereas younger individuals may metabolize the same drug without such pronounced effects. The nuanced interplay between aging, pharmacodynamics, and individual variability makes it imperative that clinicians adopt a cautious and individualized approach to prescribing [30].

Response Variability in Geriatric Patients

The variability in response to medications among elderly individuals cannot be overstated. Even among patients receiving identical doses of the same drug, differences in outcomes can be profound. Several factors contribute to this variability:

1. **Genetic Factors**: Genetic polymorphisms can influence drug absorption, distribution, metabolism, and excretion. Pharmacogenomic variations can result in some geriatric patients metabolizing drugs more slowly (or quickly) than others, potentially leading to under-treatment, toxicity, or adverse effects. Understanding these genetic differences is crucial in personalizing medication regimens for older adults.
2. **Psychosocial Factors**: Beyond the biological aspects, psychosocial factors also play a significant role in drug response variance among the elderly. Cognitive impairment, socio-economic status, and adherence to medication regimens can significantly impact treatment effectiveness. Cognitive decline may lead to difficulties in understanding medication instructions, increasing the likelihood of improper use or non-compliance that affects overall therapeutic outcomes.
3. **Comorbidity and Health Status**: The overall health status of geriatric patients can influence drug responses. Patients with more extensive comorbidities may experience compounded effects of their conditions, making it essential to evaluate the individual's entire clinical picture when prescribing and monitoring medications. Documenting and considering a patient's functional status, severity of illness, and quality of life are vital in anticipating and mitigating variability in drug response [31].

Clinical Implications

The intricacies of pharmacodynamics in geriatric patients necessitate a multifaceted approach to medication management. Clinicians must be vigilant in monitoring older patients for both intended outcomes and potential ADRs. Several strategies can help optimize pharmacotherapy:

1. **Individualized Dosing**: Personalized medicine, grounded in thorough patient assessment and understanding of geriatric pharmacokinetics and pharmacodynamics, can substantially improve therapy outcomes. Clinicians should consider starting at lower doses and titrating slowly to find the optimal therapy for each patient.
2. **Comprehensive Medication Reviews**: Regular medication reviews can identify drug duplications, interactions, and medications that may no longer be necessary due to changes in health status. Encouraging open communication regarding medication efficacy and side effects can guide therapeutic adjustments.
3. **Education and Advocacy**: Empowering patients through education about their medications can enhance adherence and self-management. Patients, their families, and caregivers should be encouraged to

engage actively in discussions about their treatment plans [32].

Impact of Renal and Hepatic Function on Drug Clearance:

Drug clearance is a critical pharmacokinetic parameter that defines the rate at which a drug is removed from the body. It greatly influences the drug's efficacy and toxicity. The clearance process is primarily governed by two organ systems: the kidneys and the liver. Renal and hepatic functions play a pivotal role in drug metabolism and elimination, and their impairments can lead to significant clinical consequences, including altered drug dosages, enhanced adverse effects, and therapeutic failures. Understanding the intricate relationship between renal and hepatic functions and drug clearance is essential for optimal drug therapy, particularly in vulnerable patient populations such as those with chronic diseases, the elderly, and those receiving polypharmacy [33].

The kidneys are essential for preserving the body's homeostasis, including regulating fluid balance, electrolyte levels, and waste product elimination through urine formation. One of the primary mechanisms by which the kidneys facilitate drug clearance is through glomerular filtration. The glomeruli filter blood plasma, allowing low-molecular-weight substances, including many drugs, to be excreted via urine [34].

In addition to glomerular filtration, drugs can also undergo tubular secretion and reabsorption within the nephron. Tubular secretion actively transports certain drugs from the blood into the tubular fluid, thereby increasing the drug's elimination. Tubular reabsorption, on the other hand, can reclaim some drugs and metabolites back into the bloodstream, decreasing their elimination; this process is largely dependent on the drug's physicochemical properties, such as its pKa and lipid solubility [35].

Renal function is typically assessed through the measurement of glomerular filtration rate (GFR), which can be estimated from serum creatinine levels, age, body weight, and gender using various formulas, such as the Cockcroft-Gault equation or the Modification of Diet in Renal Disease (MDRD) study equation. Impaired renal function, as seen in conditions such as chronic kidney disease (CKD) or acute kidney injury (AKI), can lead to diminished drug clearance, resulting in increased drug concentrations in the plasma. This accumulation can enhance the risk of drug toxicity, particularly for drugs that have a narrow therapeutic index, such as aminoglycosides, digoxin, and certain anticoagulants [36].

The liver is the body's primary site for drug metabolism, which transforms lipophilic compounds into more hydrophilic metabolites, facilitating their excretion. Hepatic clearance involves two phases: Phase I (drug metabolism) and Phase II (conjugation). In Phase I, drugs undergo oxidation, reduction, or hydrolysis, largely mediated by cytochrome P450 enzymes. These metabolic transformations can activate prodrugs or detoxify harmful substances. Phase II reactions typically involve conjugation, where molecular groups (like glucuronidation or sulfation) are added to the metabolite, enhancing its water solubility for excretion.

Liver function is evaluated through various clinical parameters, including liver enzyme levels, the presence of jaundice, and, more specifically, through assessments such as the Model for End-Stage Liver Disease (MELD) score or Child-Pugh classification in chronic liver disease contexts. Conditions such as cirrhosis, hepatitis, and liver tumors can significantly impair hepatic function, leading to reduced drug metabolism. This reduction can result in increased half-lives and plasma concentrations of drugs, potentiating the risk of adverse effects and drug interactions [37].

Complicating the impact of liver function on drug clearance is the concept of first-pass metabolism, which refers to the initial metabolism of orally administered drugs in the liver before they reach systemic circulation. If liver function is compromised, the first-pass effect may be diminished, leading to increased bioavailability of certain medications. Thus, adjustments in drug dosing regimens become critical to avoiding toxicity in patients with liver impairment [37].

The interplay between renal and hepatic function may not always be straightforward. Several drugs undergo both hepatic metabolism and renal excretion. For instance, the pharmacokinetics of drugs like morphine involve significant hepatic metabolism before renal clearance of the resulting metabolites. Therefore, in patients with coexisting hepatic and renal impairments, predicting drug clearance becomes complex, requiring careful attention to drug selection, dosing, timing, and monitoring [38].

Furthermore, renal impairment can also affect hepatic clearance. Reduced renal function can elevate serum levels of certain drugs that are

primarily metabolized by the liver, thus affecting their clearance and potential therapeutic effects. Conversely, hepatic impairment may also affect renal function indirectly, owing to fluid overload or functional changes in the glomeruli due to altered hemodynamics.

The clinical implications of altered renal and hepatic function on drug clearance are profound. For healthcare providers, it necessitates a thorough understanding of pharmacokinetics, careful patient evaluation, and sometimes the need for therapeutic drug monitoring. Drug dosing adjustments, based on function assessments and the pharmacological profiles of various drugs, must be meticulously performed to achieve drug effectiveness while minimizing toxicity [39].

Patients with decreased renal or hepatic function may require medication reviews to exclude nephrotoxic or hepatotoxic agents. Polypharmacy, or the use of multiple medications, significantly raises the risk of drug-drug interactions, particularly in patients with compromised organ function where clearance pathways are already challenged. Thus, the identification of potential interactions through screening and communication with clinical pharmacists is fundamental [39].

Moreover, there is a burgeoning interest in pharmacogenomics, the study of genetic variability in response to drugs, which may provide further insights into the variability of drug clearance in populations with varying degrees of renal and hepatic function. Genetic polymorphisms affecting drug-metabolizing enzymes can provide additional rationale for individualized dosing and treatment strategies [39].

Drug Interactions and Polypharmacy in Special Populations:

The use of multiple medications, known as polypharmacy, is a prevalent issue among various patient populations, particularly the elderly, individuals with chronic diseases, and those who are critically ill. Polypharmacy raises significant concerns regarding drug interactions, which can lead to adverse drug reactions, reduced therapeutic efficacy, and overall increases in healthcare costs. Understanding these complications, particularly in special populations, is crucial for ensuring the safe and effective use of medications [40].

Polypharmacy is generally defined as the concurrent use of five or more medications. While it can sometimes be necessary to manage multiple health conditions effectively, the growing trend of polypharmacy reflects changes in demographics, clinical practices, and prescribing habits. In the elderly population, for instance, polypharmacy often arises from the treatment of age-related comorbidities such as hypertension, diabetes, arthritis, and heart disease. Similarly, patients with chronic illnesses may require a combination of medications to control symptoms, prevent complications, and improve their quality of life [40].

While polypharmacy is often unavoidable, it can lead to an increased risk of drug interactions, where the pharmacokinetic or pharmacodynamic effects of one drug are altered by the presence of another. Such interactions can manifest in various ways, from diminished efficacy—which might lead to treatment failure—to increased toxicity, resulting in serious health compromises.

Drug interactions can occur at several levels, including absorption, distribution, metabolism, and excretion. They can also lead to additive, synergistic, or antagonistic effects. For example, two drugs that have similar side effects may compound these effects, leading to increased toxicity. Conversely, one drug might inhibit the metabolism of another, resulting in elevated serum levels and potential overdose [41].

The consequences of such interactions can be particularly severe in special populations. Elderly patients, for instance, often exhibit altered pharmacokinetics due to age-related physiological changes—reduced renal function, hepatic metabolism, and changes in body composition—making them more susceptible to adverse drug effects. Furthermore, cognitive decline can hinder their ability to manage complex medication regimens, effectively escalating the risk of non-adherence and unintentional overdoses [41].

In children, where dosing is often weight-based or gleaned from adult data, the risk of interactions is equally critical. Pediatric patients may have conflicting metabolic capacities compared to adults, necessitating careful evaluation of drug combinations. Similarly, in pregnant or breastfeeding women, unique pharmacokinetic alterations can occur, and medications that are safe for non-pregnant individuals may pose risks to fetal development or lactation.

To mitigate the dangers associated with polypharmacy, healthcare professionals must be equipped to identify and assess high-risk drug interactions. Several databases and tools exist that

help clinicians evaluate drug interactions, taking into account the comprehensive medication lists of their patients. Tools such as the Beers Criteria have been developed to guide clinicians in identifying potentially inappropriate medications and reducing the risk of adverse effects among older adults [42].

Critical consideration must also be given to the therapeutic index of medications, which outlines the range between effective and toxic doses. High-risk categories include anticoagulants, antiepileptics, and certain cardiovascular agents, which can have life-threatening interactions if not managed properly. Additionally, physicians should routinely review the patient's medication regimen at every patient visit and employ shared decision-making to optimize therapy and simplify complex medication regimens where necessary [43].

Collaboration among healthcare providers, including physicians, pharmacists, nurses, and specialists, is essential in managing polypharmacy effectively. Pharmacists, in particular, play a critical role in medication reconciliation, advising prescribers on potential interactions, and assisting patients in understanding their medication regimens. By working as part of a multidisciplinary team, healthcare professionals can help ensure optimized therapeutic outcomes while minimizing the risk of adverse drug interactions.

Furthermore, patient education cannot be overstated. Patients should be empowered to understand their medications, including the purpose, potential side effects, and how to recognize possible interactions. Encouraging patients to maintain an updated medication list, including over-the-counter drugs and supplements, can also significantly reduce the occurrence of harmful drug interactions [44].

Tailoring Pharmacotherapy: Clinical Implications and Dosing Strategies:

The landscape of pharmacotherapy is witnessing a paradigm shift, motivated by emerging evidence on the importance of personalized medicine. The traditional “one-size-fits-all” approach in prescribing medications is giving way to more nuanced strategies that recognize the inter-individual differences in drug metabolism, efficacy, and safety. Tailoring pharmacotherapy is not merely an innovative idea; it is becoming a clinical necessity [45].

The Rationale Behind Tailoring Pharmacotherapy

The acknowledgment that patients respond differently to medications is founded on several interplaying factors. Genetic variations, known as pharmacogenomics, play a crucial role in how a patient metabolizes drugs. For instance, polymorphisms in genes encoding drug-metabolizing enzymes, such as cytochrome P450 isoenzymes, can lead to significant differences in medication efficacy and the risk of adverse effects. In addition to genetic factors, patient-specific characteristics such as age, sex, weight, comorbidities, and concomitant medications further complicate drug response profiles.

A tailored pharmacotherapy approach aims to align drug selections and dosages with these individual characteristics. For example, in the management of chronic diseases like hypertension or diabetes, clinicians now often rely on biomarkers and genetic tests to guide their choice of medications. This personalized method enhances the effectiveness and safety of treatment regimens, ultimately improving patient adherence, satisfaction, and health outcomes [45].

Clinical Implications of Tailored Pharmacotherapy

The clinical implications of tailoring pharmacotherapy are vast, impacting not only the effectiveness of treatment but also healthcare costs and patient quality of life. One significant advantage of personalized medicine is the reduction in the trial-and-error process typically associated with prescribing. When clinicians can predict which medications are more likely to be beneficial for individual patients, it decreases the time to therapeutic efficacy and reduces the frequency of adverse drug reactions [46].

For instance, in oncology, understanding the molecular profile of a tumor can guide the selection of targeted therapies, yielding considerably better outcomes in terms of survival and quality of life. Patients with breast cancer often benefit from hormonal therapies tailored to the expression of estrogen and progesterone receptors, where treatments can include Tamoxifen or aromatase inhibitors based on the specific tumor characteristics.

Moreover, tailoring pharmacotherapy can also alleviate the economic burden on healthcare systems. Adverse drug reactions are not only

harmful to patients but also costly, resulting in increased hospitalizations and healthcare costs. By carefully selecting and dosing medications based on individual profiles, healthcare providers can mitigate these risks, leading to more efficient resource utilization. The adoption of pharmacogenetic testing, for example, has shown potential in reducing healthcare expenditures associated with adverse drug events, especially in populations suffering from polypharmacy [46].

Dosing Strategies in Tailored Pharmacotherapy

Dosing strategies play a pivotal role in maximizing the benefits of personalized pharmacotherapy. Optimizing dose not only targets therapeutic effectiveness but also minimizes toxicity, and various methods have been devised to achieve this goal [47].

1. **Therapeutic Drug Monitoring (TDM)**: TDM is a clinical practice where drug concentrations in the bloodstream are measured to inform dose adjustments. This practice is especially valuable for medications with narrow therapeutic indices, such as lithium or warfarin, where both under-treatment and over-treatment can have significant consequences. By regular monitoring of drug levels, healthcare providers can adjust dosages based on the specific pharmacokinetics of each patient, ensuring that medication stays within effective and safe ranges [48].
2. **Weight-Based Dosing**: For many medications, particularly in pediatric populations and those undergoing chemotherapy, dosing is often adjusted according to body weight. This approach helps account for the volume of distribution and clearance, tailoring the treatment to the physiological characteristics of the individual.
3. **Age-Adjusted Dosing**: Clinicians frequently have to consider the age of patients when prescribing medications, particularly in elderly populations who may exhibit altered pharmacokinetic and pharmacodynamic responses to drugs. Adjustments might be needed based on renal or hepatic function, which often declines with age, necessitating more conservative dosing strategies to prevent adverse events [49].
4. **Adaptive Dosing**: This novel approach involves modifying the dosing regimen based on the patient's response over time. For example, in chronic disease management, the initial dose may be escalated or de-escalated based on the patient's clinical response and tolerability. Such dynamic adjustment requires ongoing monitoring and comprehensive communication between patient and provider.
5. **Genotype-Guided Dosing**: Exploiting advances in pharmacogenetics allows healthcare professionals to tailor dosages based on an individual's genetic makeup. The application of genotype data can influence the initial dosing decision for specific medications, particularly those in areas such as anticoagulation or psychotropic treatments, thereby optimizing both efficacy and patient safety [49].

Challenges and Future Directions

Despite the demonstrated benefits of tailored pharmacotherapy, several challenges remain. One significant barrier is the integration of pharmacogenomics into routine clinical practice. Many healthcare providers may lack the necessary training and resources to interpret genetic testing results meaningfully. Additionally, the cost of implementing comprehensive pharmacogenetic testing can be prohibitive [50].

Furthermore, issues related to data sharing and electronic health records need addressing. Facilitating seamless communication between laboratories, healthcare providers, and pharmacies is critical for efficient implementation.

As research progresses, and more evidence emerges supporting the efficacy of personalized pharmacotherapy, a cultural shift within the medical community will be essential. Educational initiatives aiming to enhance awareness and understanding of pharmacogenomics among healthcare providers are imperative to foster a more personalized treatment paradigm [51].

Future Directions and Research Gaps in Pharmacotherapy for Special Populations:

Pharmacotherapy, the treatment of disease through the use of medications, has expanded significantly over the last few decades, particularly with advancements in biopharmaceuticals and personalized medicine. However, despite these advancements, there remain critical gaps in our understanding and application of pharmacotherapy for special populations, such as children, the elderly,

pregnant and lactating women, and individuals with comorbidities or polypharmacy. Addressing these gaps is essential for optimizing treatment outcomes and ensuring health equity across diverse demographics [52].

Special populations encompass groups that may respond differently to medications due to physiological, developmental, metabolic, or psychosocial factors. For example, children often require pediatric-specific formulations and dosages due to their different body compositions and developing organ systems. The elderly might have altered pharmacokinetics and pharmacodynamics owing to age-related physiological changes, comorbidities, and polypharmacy issues. Pregnant and lactating women require careful consideration of the pharmacological effects on both the mother and the fetus or infant, necessitating a delicate balance between benefits and risks. Finally, individuals with multiple chronic conditions or those on multiple medications face unique challenges regarding drug interactions and adherence [53].

One of the main challenges in pharmacotherapy for special populations is the historical lack of research specifically targeting these groups. Many clinical trials typically focus on a homogeneous adult population, leading to limited data on how various demographics respond to treatments. This oversight not only hampers the ability of healthcare providers to make informed decisions but may also expose special populations to avoidable risks [54].

For instance, many medications that are deemed safe for adults may have significantly different safety profiles in children or pregnant women. The Thalidomide tragedy in the 1960s serves as a historical reminder of the potential dangers of using a single population's data to inform treatment protocols for all. Consequently, there is a pressing need for more inclusive clinical research practices that encompass a variety of demographic factors [55].

Future Directions in Research

1. **Enhanced Research Funding and Incentives**: One of the critical steps toward bridging the existing research gaps is to increase funding and provide incentives for studies focused on special populations. Organizations such as the National Institutes of Health (NIH) and pharmaceutical companies should prioritize research that emphasizes diverse participant inclusion. Public-private partnerships could help in pooling resources to conduct large-scale studies, ensuring that findings are translatable across different demographics [56].
2. **Development of Pediatric and Geriatric Formulations**: There remains a pressing need for the development of age-specific formulations and delivery systems. Pharmaceuticals tailored for children and the elderly can improve adherence and minimize adverse effects. In particular, research into liquid formulations, as well as transdermal and inhalation therapies for children, could enhance therapeutic efficacy while reducing the likelihood of medication errors.
3. **Implementation of Pharmacogenomics**: Pharmacogenomic testing, which examines how genetic variations affect individual responses to drugs, holds significant promise for optimizing pharmacotherapy, particularly among special populations. This personalization of medicine can aid in predicting adverse drug reactions and therapeutic outcomes. Future directions should include the integration of pharmacogenomic testing into routine clinical practice for vulnerable populations, aiming to create more individualized treatment plans that minimize harm and maximize benefits [57].
4. **Interdisciplinary and Collaborative Approaches**: Future pharmacotherapy research must adopt interdisciplinary methodologies that encompass insights from genetics, pharmacology, pediatrics, geriatrics, and obstetrics. Collaborative efforts among stakeholders—clinicians, researchers, policymakers, and patient advocacy groups—are essential for evaluating the multifaceted aspects of drug therapy across special populations [58].
5. **Use of Real-World Evidence (RWE)**: Utilizing RWE through observational studies and patient registries can enrich our understanding of how medications perform outside the controlled environment of clinical trials. This can provide invaluable insight into the effectiveness, safety, and adherence patterns among special populations, aiding healthcare providers in making informed decisions that are grounded in real-world experiences [59].
6. **Educational Initiatives**: A concerted effort is needed to enhance the education of healthcare professionals regarding the unique pharmacotherapy considerations for special populations. Educational

programs that target pharmacology and pediatric or geriatric care can better prepare clinicians to make informed prescribing decisions and advocate for appropriate therapies tailored to these groups [60].

Addressing Social Determinants of Health

Social determinants of health (SDOH) play a critical role in pharmacotherapy outcomes and must be integrated into future research agendas. Socioeconomic status, access to healthcare, cultural beliefs, and environmental factors can all influence medication adherence and efficacy. Research that incorporates SDOH can help identify barriers to effective treatment, enabling healthcare systems to design more inclusive and accessible pharmacotherapeutic strategies [61].

Conclusion:

In conclusion, understanding pharmacokinetics and pharmacodynamics in special populations within hospital settings is vital for optimizing patient care and improving therapeutic outcomes. Variations in drug absorption, distribution, metabolism, and excretion, as well as differences in drug response among pediatric, geriatric, and patients with compromised organ function, require clinicians to adopt a personalized approach to pharmacotherapy. By considering factors such as age, comorbidities, and organ function, healthcare providers can tailor medication regimens to minimize adverse effects and maximize efficacy.

The findings of this study underscore the importance of ongoing education and training for healthcare professionals in recognizing and managing these complexities. As drug therapies continue to evolve, further research is needed to fill knowledge gaps and develop evidence-based guidelines that specifically address medication management in these vulnerable populations. Ultimately, a thorough understanding of pharmacokinetics and pharmacodynamics will enhance clinical decision-making and lead to safer, more effective treatment strategies in hospital settings.

References:

1. Bamberger DM, Herndon BL, Suvarna PR. The effect of zinc on microbial growth and bacterial killing by cefazolin in a Staphylococcus aureus abscess milieu. J Infect Dis. 1993;168(4):893–6. doi: 10.1093/infdis/168.4.893.
2. Garrison MW, Vance-Bryan K, Larson TA, et al. Assessment of effects of protein binding on daptomycin and vancomycin killing of Staphylococcus aureus by using an in vitro pharmacodynamic model. Antimicrob Agents Chemother. 1990;34:1925–31. doi: 10.1128/aac.34.10.1925.
3. Tan JS, Salstrom SJ. Levels of carbenicillin, ticrcillin, cephalothin, cefazolin, cefamandole, gentamicin, tobramycin, and amikacin in human serum and interstitial fluid. Antimicrob Agents Chemother. 1977;11:698–700. doi: 10.1128/aac.11.4.698.
4. Chambers HF, Mills J, Drake TA, et al. Failure of a once-daily regimen of cefonicid for treatment of endocarditis due to Staphylococcus aureus. Rev Infect Dis. 1984;6(Suppl 4):s870–4. doi: 10.1093/clinids/6.supplement_4.s870.
5. Leeming JP. Treatment of ocular infections with topical antibacterials. Clin Pharmacokinet. 1999;37(5):351–60. doi: 10.2165/00003088-199937050-00001.
6. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet. 2001;358(9276):135–8. doi: 10.1016/s0140-6736(01)05321-1.
7. Tamai I, Yamashita J, Kido Y, et al. Limited distribution of new quinolone antibacterial agents into brain caused by multiple efflux transporters at the blood–brain barrier. J Pharmacol Exp Ther. 2000;295(1):146–52.
8. Pascual A, Ballesta S, Garcia I, et al. Uptake and intracellular activity of linezolid in human phagocytes and nonphagocytic cells. Antimicrob Agents Chemother. 2002;46(12):4013–5. doi: 10.1128/AAC.46.12.4013-4015.
9. Quie PG, Belani KK. Coagulase-negative staphylococcal adherence and persistence. J Infect Dis. 1987;156(4):543–7. doi: 10.1093/infdis/156.4.543.
10. Buijk SE, Mouton JW, Gyssens IC, et al. Experience with a once-daily dosing program of aminoglycosides in critically ill patients. Intensive Care Med. 2002;28(7):936–42. doi: 10.1007/s00134-002-1313-7.
11. Lamer C, de Beco V, Soler P, et al. Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. Antimicrob Agents Chemother. 1993;37:281–6. doi: 10.1128/aac.37.2.281.
12. Meagher AK, Ambrose PG, Grasela TH, et al. Pharmacokinetic/pharmacodynamic

profile for tigecycline—a new glycylcycline antimicrobial agent. Diagn Microbiol Infect Dis. 2005;52(3):165–71. doi: 10.1016/j.diagmicrobio.2005.05.006.
13. Smith A, Pennefather PM, Kaye SB, et al. Fluoroquinolones: place in ocular therapy. Drugs. 2001;61(6):747–61. doi: 10.2165/00003495-200161060-00004.
14. Turnidge J. Pharmacodynamics and dosing of aminoglycosides. Infect Dis Clin North Am. 2003;17(3):503–28. doi: 10.1016/s0891-5520(03)00057-6.
15. Neu HC. General concepts on the chemotherapy of infectious diseases. Med Clin North Am. 1987;71(6):1051–64. doi: 10.1016/s0025-7125(16)30796-9.
16. Chambers HF, et al. Effects of protein binding on antibiotics. In: Gorbach S, Bartlett JG, Blacklow NR, editors. Infectious diseases. Vol. 3. Lippincott Williams & Wilkins; Philadelphia: 2004. pp. 172–9.
17. Tod M, Lortholary O, Seytre D, et al. Population pharmacokinetic study of amikacin administered once or twice daily to febrile, severely neutropenic adults. Antimicrob Agents Chemother. 1998;42(4):849–56. doi: 10.1128/aac.42.4.849.
18. Bryan LE, Van den Elzen HM. Streptomycin accumulation in susceptible and resistant strains of Escherichia coli and Pseudomonas aeruginosa. Antimicrob Agents Chemother. 1976;9(6):928–38. doi: 10.1128/aac.9.6.928.
19. Rodriguez I, Kilborn MJ, Liu XK, et al. Drug-induced qt prolongation in women during the menstrual cycle. JAMA. 2001;285:1322–6. doi: 10.1001/jama.285.10.1322.
20. El-Eraky H, Thomas SH. Effects of sex on the pharmacokinetic and pharmacodynamic properties of quinidine. Br J Clin Pharmacol. 2003;56:198–204. doi: 10.1046/j.1365-2125.2003.01865.x.
21. Taylor HA. Monitoring adherence to the NIH policy on the inclusion of women and minorities as subjects in clinical research. In: Committee NTI, editor. Comprehensive report. Silver Springs, MD, USA: United States Federal Agency; 2008. 2011–2012.
22. CDC. Births and natality. [accessed 1 November 2014]; 2013.
23. NIH. Human clinical trials. [accessed 3 Nov 2014]; 2001.
24. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. Nature. 2014;509:282–3. doi: 10.1038/509282a.
25. Hutson WR, Roehrkasse RL, Wald A. Influence of gender and menopause on gastric emptying and motility. Gastroenterology. 1989;96:11–17. doi: 10.1016/0016-5085(89)90758-0.
26. Fine JS. Reproductive and perinatal principles. In: Nelson LS, editor. Goldfrank's toxicologic emergencies. New York, NY: McGraw Hill; 2010. pp. 423–46.
27. Mazer-Amirshahi M, Samiee-Zafarghandy S, Gray G, van den Anker JN. Trends in pregnancy labeling and data quality for us-approved pharmaceuticals. Am J Obstet Gynecol. 2014;211:690.e1–e11. doi: 10.1016/j.ajog.2014.06.013.
28. Atuah KN, Hughes D, Pirmohamed M. Clinical pharmacology: Special safety considerations in drug development and pharmacovigilance. Drug Safety Int J Med Toxicol Drug Experience. 2004;27:535–54. doi: 10.2165/00002018-200427080-00006.
29. GAO. Report to congressional requestors, women sufficiently represented in new drug testing, but fda oversight needs improvement. [accessed 9 Nov 2014]; 2001.
30. Mitchell AA, Gilboa SM, Werler MM, et al. National Birth Defects Prevention Study. Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. Am J Obstet Gynecol. 2011;205:e51–8. doi: 10.1016/j.ajog.2011.02.029.
31. Du S, Itoh N, Askarinam S, et al. XY sex chromosome complement, compared with XX, in the CNS confers greater neurodegeneration during experimental autoimmune encephalomyelitis. Proc Natl Acad Sci USA. 2014;111:2806–11. doi: 10.1073/pnas.1307091111.
32. Heitkemper MM, Chang L. Do fluctuations in ovarian hormones affect gastrointestinal symptoms in women with irritable bowel syndrome? Gender Med. 2009;6:152–67. doi: 10.1016/j.genm.2009.03.004.
33. Cleary KL, Roney K, Costantine M. Challenges of studying drugs in pregnancy for off-label indications: Pravastatin for preeclampsia prevention. Sem Perinatol. 2014;38:523–7. doi: 10.1053/j.semperi.2014.08.019.
34. Sadik R, Abrahamsson H, Stotzer PO. Gender differences in gut transit shown with a newly developed radiological procedure. Scand J Gastroenterol.

2003;38:36–42. doi: 10.1080/00365520310000410.
35. FDA. Guidance for industry. United States Federal Agency; 2001.
36. FDA. Safety Announcement 5-14-2013, Drug Safety Communication. Silver Springs, MD, USA: United States Federal Agency; 2013.
37. Singer AJ, Brandt LJ. Pathophysiology of the gastrointestinal tract during pregnancy. Am J Gastroenterol. 1991;86:1695–712.
38. FDA. Safety Announcement 5-14-2013, Drug Safety Communication. Silver Springs, MD, USA: United States Federal Agency; 2013.
39. Abbott M., Byron G., Tailor Diana. The role of PK/PD analysis in the development and evaluation of antimicrobials. Pharmaceutics 13 (833), 833. 10.3390/pharmaceutics13060833.
40. Luepke K. H., Mohr J. F. The antibiotic pipeline: reviving research and development and speeding drugs to market. Expert Rev. Anti. Infect. Ther. 15 (5), 425–433. 10.1080/14787210.2017.1308251.
41. Drusano G. L. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat. Rev. Microbiol. 2, 289–300. 10.1038/nrmicro862.
42. Kaye K. S., Bowmick T., Metallidis S., Bleasdale S. C., Sagan O. S., Stus V., et al. Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. JAMA 319 (8), 788–799. 10.1001/jama.2018.0438.
43. Rubino C. M., Bhavnani S. M., Loutit S. J., Morgan E. E., White D., Dudley M. N., et al. Phase 1 study of the safety, tolerability, and pharmacokinetics of vaborbactam and meropenem alone and in combination following single and multiple doses in healthy adult subjects. Antimicrob. Agents Chemother. 62 (4), e02228–17. 10.1128/AAC.02228-17.
44. Jorda A., Zeitlinger M. Preclinical pharmacokinetic/pharmacodynamic studies and clinical trials in the drug development process of EMA-approved antibacterial agents: a review. Clin. Pharmacokinet. 59, 1071–1084. 10.1007/s40262-020-00892-0.
45. Griffith D. C., Loutit J. S., Morgan E. E., Durso S., Dudley M. N. Phase 1 study of the safety, tolerability, and pharmacokinetics of the β-lactamase inhibitor vaborbactam (RPX7009) in healthy adult subjects. Antimicrob. Agents Chemother. 60 (10), 6326–6332. 10.1128/AAC.00568-16.
46. Rubino C. M., Bhavnani S. M., Loutit J. S., Lohse B., Dudley M. N., Griffith D. C. Single-dose pharmacokinetics and safety of meropenem-vaborbactam in subjects with chronic renal impairment. Antimicrob. Agents Chemother. 62 (3), e02103–17. 10.1128/AAC.02103-17.
47. Bhavnani S. M., Rex J. H. Editorial overview: use of PK-PD for antibacterial drug development: decreasing risk and pathways forward for resistant pathogens. Curr. Opin. Pharmacol. 38, vii–xii. 10.1018/j.coph.2017.11.008.
48. CDC. Antibiotic resistance threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services.
49. Bhavnani S. M., Krause K. M., Ambrose P. G. A broken antibiotic market: review of strategies to incentivize drug development. Open Forum Infect. Dis. 7 (7), ofaa083. 10.1093/ofid/ofaa083.
50. European Medicines Agency. Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. Committee for Medicinal Products for Human Use.
51. Gallo J. M. Pharmacokinetic/pharmacodynamic-driven drug development. Mt. Sinai J. Med. 77 (4), 381–388. 10.1002/msj.20193.
52. European Medicines Agency. Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products.
53. Rizk M. L., Bhavnani S. M., Drusano G., DAne A., Eakin A. E., Guina T., et al. Considerations for dose selection and clinical pharmacokinetics/pharmacodynamics for the development of antibacterial agents. Antimicrob. Agents Chemother. 63 (5), e02309–18. 10.1128/AAC.02309-18.
54. European Medicines Agency. Xerava. Xerava, INN-eravacycline. Committee for Medicinal Products for Human Use.
55. Safir M. C., Bhavnani S. M., Slover C. M., Ambrose P. G., Rubino C. M. Antibacterial drug development: a new approach is needed for the field to survive and thrive. Antibiotics 9 (412), E412. 10.3390/antibiotics9070412.
56. Labreche M. J., Graber C. J., Nguyen H. M. Recent updates on the role of pharmacokinetics-pharmacodynamics in antimicrobial susceptibility testing as

applied to clinical Practice. Clin. Infect. Dis. 61, 1446–1452. 10.1093/cid/civ498.
57. Griffith D. C., Loutit J. S., Morgan E. E., Durso S., Dudley M. N. Phase 1 study of the safety, tolerability, and pharmacokinetics of the β-lactamase inhibitor vaborbactam (RPX7009) in healthy adult subjects. Antimicrob. Agents Chemother. 60 (10), 6326–6332. 10.1128/AAC.00568-16.
58. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. Clin Pharmacokinet. 1986;11:257–82. doi: 10.2165/00003088-198611040-00001.
59. Ambrose PG, Bhavnani SM, Owens RC. Clinical pharmacodynamics of quinolones. Infect Dis Clin North Am. 2003;17:529–43. doi: 10.1016/s0891-5520(03)00061-8.
60. Bush LM, Levison ME. Antibiotic selection and pharmacokinetics in the critically ill. Crit Care Clin. 1988;4(2):299–324.
61. Westphal JF, Brogard JM. Drug administration in chronic liver disease. Drug Saf. 1997;17(1):47–73. doi: 10.2165/00002018-199717010-00004.