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Adverse Effects of Antimicrobial Therapeutic Agents in Common Use: A Review

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Abstract

Antimicrobial agents play critical roles in reducing the burden of bacterial infectious diseases and their associated fatalities but may also come with unintended consequences that in some cases may lead to other health burdens, disability and death in extreme cases. Unwanted effects occur commonly in the administration of a wide variety of drugs, but antimicrobial agents garner less attention as some of these agents pose extensive diversities of objectionable side effects. This review focuses on highlighting the dangers that may accompany the administration of antimicrobial agents. Literature search applying keys words on the subject matter was conducted and related materials were assembled. Adverse effects of antimicrobial agents ranged from hypersensitivity to penicillins, bleeding disorder with members of the fourth generation cephalosporins, nephrotoxicity and ototoxicity common to gentamycin, tendon rupture, liver toxicity and induction of hypoglycemic state with some fluoroquinolones. The interference and constitutional alteration in intestinal bacterial community and consequential overgrowth of resistant *Clostridioides difficile* is prominent in the administration some antimicrobial agents and especially with the clindamycins. The attendant side effects of each antimicrobial agent demand re-evaluation, expediency of personalized prescription and proper patient education to minimize and circumvent the adverse drug effects of antimicrobial agents.

Keywords*: Adverse drug effects, antimicrobial agents, disease burden, morbidity, microbiome alteration, patient education, personalized prescription*

1. Introduction.

Antimicrobial agents play a key role in preventing millions of deaths worldwide since their introduction into medical care in the 1940s. Antimicrobial agents also possess adverse drug effects or reactions, ADEs/ADRs that can immensely affect the outcomes of their administration [1,2]. Gerhard Domagk – a German Chemist initiated the first true antimicrobial therapy with prontosil (sulfonamide compound) in 1935 to treat different infections including syphilis but the patients experienced severe ADEs that included nausea and neurological disturbances [2]. Prontosil

became the precursor of modern sulfonamides [3] Alexander Flemming researching independently at the time of prontosil's introduction had previously observed the activity of penicillin against bacteria in 1928. Each of these early researchers were spurred into action by the horrific wound infections that were common place during the World War I, culminated in discovery of penicillin, eventual purification and availability for treatment of major human infections, marking a major turning point in treatment of bacterial infections [4]. The treatment of several bacterial illnesses that included pneumonia, septicemia, diphtheria, tetanus, typhoid and tuberculosis, all with elevated fatality rates became possible [5]. Following the introduction of penicillin into clinical practice there was a rapid discovery of other antimicrobial agents. This review highlights the adverse effects of common groups of antimicrobial agents regularly available for the management of bacterial infections.

2. Methodology

The execution of this review was with the aid of search engines applying the key words – antimicrobial agents, antibiotics, antibacterial agents, adverse effects/reactions/events, side effects combined with the different groups of antimicrobial agents. Literature that contained related information to the major review themes that included penicillins, cephalosporins, aminoglycosides, quinolones, macrolides, sulfonamides, tetracyclines, chloramphenicol, lincosamides, carbapenems, glycopeptides, monobactams oxazolidinones, rifampicin ethambutol and isoniazid in English language were extracted for compilation.

3. Antimicrobial agents and ADEs

3.1. Penicillins.

The availability of penicillin for the treatment of a wide variety bacterial infection in 1945 marked a great leap forward in human development and emancipation from the era of fatal infectious diseases [6]. Penicillin act by inhibiting the transpeptidation steps in bacterial cell intermediate macromolecules that are crucial for peptidoglycan formation [7, 8]. Extensive excretion of penicillins happens in the renal system and this can result in prolonged biological half-lives and elevated serum levels that can exacerbate the tendency for toxicity [9]. The kidneys are able to eliminate virtually all penicillins without the need for dosage adjustment to circumvent hepatotoxicity. The most prominent side effect of the penicillins is the propensity to bind to serum proteins forming hapten-protein complex to become antigenic as the basis of the hypersensitivity reactions commonly seen in piperacillin administration that may lead to hemolytic anemia if the drug binds to red blood cells [10, 11, 12]. This can occur at any age, but notably between the ages of 20 and 49 years, there is an increased risk for anaphylactic reaction during a second period in about 15% of patients administered with a penicillin agent [13]. The commonest adverse events in treatment with penicillins are usually intestinal discomfort involving nausea, vomiting, epigastric pain and antibiotic induced *Clostidioides difficile*. Hepatic effects and thrombophlebitis may spike transaminases with high doses of nafcillin in patients with renal limitations [14].

3.2. Cephalosporins

These agents have structural similarities with the penicillins by also possessing the beta-lactam ring and well tolerated like most penicillins and effective substitutes. They inhibit bacteria cell wall enzyme by binding to penicillin binding proteins, PBPs [15]. The ADEs of cephalosporins are similar to those of the penicillins with the exception of occasional biliary effect, bilirubinemia and a very rare fatal hemolysis observed with ceftriaxone [16]. Cephalosporins have low toxicity

without serious adverse events even in patients with evidence of previous hypersensitivity to penicillins {17]. The toxicity of cephalosporins are restricted to minor differences in the chemical and structural constitution of modern cephalosporins molecules that potentiate undesired reactions in up to 3.2% of patients [18]. The general reactions reported in cephalosporins include fever, arthralgia and exanthema in groups of children administered with cefaclor [16] and hypersensitivity in patients with liver disease and asthma [19,20]. Nephrotoxicity is uncommon in modern cephalosporins except for significant decline in renal activity with large regimens of ceftazidime, ceftriaxone and cefoperazone that each has a fraction of 3-methyl-thiotetrazole side-chain that interferes in the biosynthesis of prothrombin with consequential increase in the tendency for bleeding disorder with concomitant increase in disulfiram-like effects in individuals concurrently taking alcohol containing substances [21]. Cephalosporins ADEs are commoner in children aged four years and spikes with the age of the child especially with the use of ceftazidime, ceftriaxone and cefoperazone are sometimes fatal [22]. Neurological and psychological disturbances including epidermal and arthritic effects have been reported to be associated with the use of cefaclor [23, 24].

3.3. Aminoglycosides.

These agents are some of the foremost and very effective antibacterial agents that have continued to retain a key position in the treatment of serious Gram-negative bacterial infections including urinary tract infections and bacteremia [25]. Aminoglycosides inhibit 30S bacterial ribosomes thereby preventing the synthesis of essential proteins [26]. The glomeruli rapidly filter the agents unchanged within two hours. This can however be extended to 30-60 hours in patients with impaired renal function thereby requiring dosage modification [27]. Some of the most commonly used aminoglycosides include gentamycin, amikacin, tobramycin, streptomycin, neomycin and kanamycin. The initial application of streptomycin was for the treatment of tuberculosis while neomycin and kanamycin are effective in gut sterilization and wound infections on account their toxicity. Aminoglycosides are polar agents that are poorly absorbed through oral route of administration necessitating the parenteral route. The most pronounced ADEs of aminoglycosides are nephrotoxicity and ototoxicity. The nephrotoxicity is worrisome as it affects creatinine clearance causing a build-up of concentrations that can induce nephrotoxicity and the possibility of neurotoxicity that affects the kidneys due to the agents binding to phospholipid in the liposomes hindering permeability and leading to accumulation [27], and inhibition of their function [26]. Exposure to aminoglycosides in-utero can result in permanent deafness [28], whereas neurotoxicity can be reversible [25]. The mechanism of neurotoxicity is through the drugs ability to freely pass into hair cell and induce reactive oxygen species, ROS to damage the mitochondria resulting in cell death. Aminoglycosides nephrotoxicity is bothersome on the account of their significant effect on the proximal tubule epithelial cells arising from selective endocytosis and build-up of aminoglycosides in the renal cortex that can activate acute kidney injury [29]. Kidney injury initiated as the agents filter unchanged in the glomeruli, and reabsorbed by the proximal epithelia where they concentrate into liposomes after encounter with the phospholipids on the brush border membranes thereby interfering with phospholipid metabolism. This in addition, affects the functions of the cells of the kidneys greatly, influenced by the dosage and length of administration [27]. The pressure to use an aminoglycoside has dissipated immensely with the availability of less toxic and effective agents for treating Gram-negative bacterial infections [30].

3.4. **Fluoroquinolones**.

The arrival of the fluoroquinolones into the clinical arena with their wide spectrum of activity displaced some other frequently administered agents like the aminoglycosides administered parenterally with notable adverse effects. The fuoroquinolones combine the advantage of being available for oral use and outstanding bioavailability [31]. The fluoroquinolones inhibit bacterial gyrase and topoisomerases II and IV [32, 33]. The fluoroquinolones are associated with arthro-arthritis in immature animals, which formed the basis of their restriction during pregnancy, and in the young [34]. These agents exhibit a range of intense and permanent forms of ADEs that include tendon atrophy, tendon rupture, and induction of hypoglycemic states, peripheral neurological toxicity, retinal detachment and aneurism of the aorta [35,36]. Teratogenic effects have with ciprofloxacin in mice even at low doses has been reported [37], and significant declines in spermatozoa concentration of infertile men treated with ciprofloxacin [38]. In 2008, the Food and Drug Administration, FDA issued a warning concerning the side effects of fluoroquinolones. The was followed by the European Medicine Agency, EMA and other countries' regulatory authorities issuing similar warnings on the ADEs involved in the use some fluoroquinolones [39]. Gatifloxacin was a major quinolone that fell under the hammer due to its marked depression of glucose utilization leading to hypoglycemic state [40, 41]. Trovafloxacin is associated with induction of severe liver injury and fatal outcome [42]. In consequence, the twin agents fell into disuse for oral or systemic administration. Studies have indicated that ciprofloxacin initiate DNA damage, chromatin abnormalities of sperm cells that could contribute in the observed low fertilization rates and retarded embryo development [43]. The risk of tendonopathy, peripheral neuropathy, retinal detachment, cardiac arrhythmia and central nervous system involvement are higher in individuals who are 60 years or older [36,39].

3.5. Sulfonamides.

These agents are in use in a wide array of human and animal situations that include the treatment of toxoplasmosis when used in combination with antimalarial agents [44]. Sulfonamides have a wide spectrum of activity and the foremost agents applied for the treatment of bacterial infections [45]. Some of the earlier sulfonamides (prontosil) are associated with grave ADEs. Sulfonamides with better tolerability have since been developed that can be administered for specific indications. Sulfonamides competitively inhibit the synthesis of protein with adverse reactions of modern sulfonamides including lethal toxidermia, severe liver injury, pulmonary reactions and blood dyscariasis [46]. The mechanism of the side effects remains unclear, it is presumed that the metabolites of sulfamethoxazole of the most regularly prescribed sulfonamide bind covalently to protein due to the chemical reactivity leading to the formation unique adverse events [47]. Immune responses that follow could also trigger hematological complications antecedent to hemolytic anemia, agranulocytosis and or suppression of hematopoietic activity of the pluripotent stem cell in the bone marrow [48]. Renal involvement usually manifests from the crystallization of sulfonamide bye-products in the renal tubules to precipitate kidney stones exhibiting as interstitial nephritis and or acute kidney injury, AKI [49,50].

3.6. Tetracyclines

The tetracyclines discovered in the 1940s possess activity against a wide spectrum of microorganisms including Gram-positive and Gram-negative bacteria, chlamydiae, mycoplasma, rikettsiae and protozoa [51]. They are inexpensive and used extensively as prophylactic agents in

human treatment and incorporated into livestock feeds at the sub-therapeutic levels as growth promoter thereby creating a high pressure for the emergence of resistance to these agents, this has severely limited their use in clinical settings [52]. Tetracyclines interfere with the 30S ribosomal subunit binding to the amino-acyl-tRNA to the receptor site on the mRNA-ribosome complex thereby hindering the process. Photosensitivity is a well-documented major ADE of the tetracyclines that involves the development of a complex with calcium ions capable of absorbing ultra-violet, UV light. This complex then generates reactive oxygen species, ROS that can damage DNA and cell membrane on exposure to sunlight leading to dermatological complications, initiation of lupus erythematosus, LE and pressure within cranium [53,54].

3.7. Macrolides

These agents have a spectrum of activity that includes viruses, fungi and protozoa [54] and recommended in the management of respiratory infections with anti-inflammatory activity [55-57]. Macrolides typically impair the synthesis of protein by attaching to 23S of the 50S ribosomal unit of bacteria [58]. Macrolides are very safe agents, with side effects usually limited to minor intestinal disturbances occurring in 15-20% of individuals taking erythromycin and less than 5% with the newer macrolides that rarely initiate motolin release *in-vivo*, such as clarithromycin, azithromycin, dirithromycin and rikamycin except for high doses of troleandomycin and erythromycin [59].

3.8. Lincosamides

This group consists of two main antibiotics that are used in human medicine and veterinary settings. Lincomycin and its derivative – clindamycin are agents with inhibitory effect on both Gram-positive and anaerobic Gram-negative bacteria as well as on protozoa especially in combination those of malaria [60]. Lincosamides hinder 23S on the RNA bigger subunit, thereby cutting off the path by which emerging intermediates substrates needed for the next step in protein synthesis [61-63]. The major side effects is the ability to create pseudomembranous colitis, nausea and abdominal cramps or vomiting following administration. The significant interference and modification of resident intestinal bacteria community (microbiome) by clindamycin confer selective advantage on resistant *Clostridioides difficile* to overgrow and produce toxins that lead to the development of micro-abscesses on the intestinal mucosae that coalesce into pseudo-membranes and may necessitate the discontinuation of the agent or intervention with treatment with vancomycin in extreme cases [64].

3,9. Chloramphenicol

Chloramphenicol is lowly priced antibiotic that binds to bacterial 50S subunit of the 70S ribosome thus interfering with the peptidyl-transferase chain of the nascent protein molecules [65]. The agent is particularly effective in treating cases of meningitis due to *Neisseria meningitides*, *Streptococcus pneumoniae* and *Haemophilus influenza* - the main bacterial agents of meningitis [66]. The key concern in prescribing chloramphenicol lies in its neurotoxicity and irreversible hematopoietic damage to pluripotent stem cells of the bone during extended period of use [66]. Chloramphenicol is still useful in life threatening infections especially in resource-poor countries and with the rising spate of multidrug resistant, MDR bacteria worldwide, there is a reawakening of attention on old antibiotics and intense focus on chloramphenicol as candidate for many infections [67-71].

3.10. Carbapenems

These are beta-lactam agents as the penicillins and cephalosporins representing the most efficacious agents in infections involving resistant bacterial strains as well as demonstrating a unique level of destructive effects on beta-lactamases [72-74]. The deployment of the agents is often as the antibiotics of last resort in the management of refractory Gram-negative bacterial infections [75]. The carbapenems act by blocking the synthesis of cell wall as the penicillins [73]. The general ADEs of this group of agents involve abdominal pain, nausea and vomiting in about 20% of patients with swelling and pain at the injection site. There are reports of nephrotoxicity about imipenem when not administered with cilastatin to shield the drug from renal dihydropeptidase degradation [73].

3.11. Glycopeptides

This are naturally occurring and semisynthetic agents with wide spectra of action, which are especially effective against Gram-positive and methicillin-resistant *Staphylococcus aureus*, MRSA [76-80]. The spiral of MDR bacteria in clinical settings all over the world has placed immense reliance on these agents as the drugs of last resort [76,80]. The ADEs associated are also partly responsible their restricted use [81]. The major members include vancomycin, teicoplamin, oritavancin and dalbavancin, all of which act by inhibiting cell wall synthesis [78,82-84]. The prominent ADEs experienced include infusion reaction or red man's syndrome, nausea, vomiting, diarrhea, rash pruritis and a rare hypersensitivity and *Clostridioides difficile* when given oral route [78].

3.12. Monobactams

Aztreonam is the main member of this group possessing a narrow range of activity with activity essentially against Gram-negative bacteria and remarkably effective in treating MDR bacterial infections with stability in the presence of metallo-beta-lactamases, MBLs except for the variant serine-metallo-beta-lactamases, SBLs that often occur concurrently with MBLs [85]. Aztreonam act by preventing the assembly peptidoglycan intermediates resulting in failure of cell wall synthesis [86]. High doses are associated with neutropenia in 11.3% of young patients, elevated transaminases and there are no reports of nephrotoxicity, ototoxicity or hematopoietic disorders [87].

3.13. Oxazolidinones

Linezolid is the first member of this group of synthetic antimicrobial agents introduced into human medical practice [88-91]. Linezolid acts by blocking both 30S and 50S ribosomes, halting the initiation of complexes during protein synthesis [90,91]. Linezolid is especially useful in vancomycin resistant *Enterococcus*, VRE and methicillin resistant *Staphylococcus aureus*, MRSA and in hospital acquired infections, HAIs, in addition to treating multidrug resistant tuberculosis, MDR-TB [92] and has an excellent bioavailability in both oral and parenteral routes [93,94]. Linezolid is well tolerated with low toxicity compared to the higher degree of adverse events associated with vancomycin. The main ADEs of linezolid involve diarrhea nausea, vomiting and headache that are often not severe [95]. Other ADEs of linezolid involve thrombocytopenia, leukocytopenia, anemia, hypoglycemia [95] and a rare coloration of the tongue during extended periods of administration [96].

3.14. Rifampicin, Ethambutol and Isoniazid

Rifampicin is a major agent for treating a wide range of bacterial infections especially Gram-positive bacteria including *Clostridioides difficile* [97] and an effective antituberculosis agent

arising from its ability to bind RNA-polymerase leading to the inhibition of essential protein formation [98,99]. The concurrent use of rifampicin with other antituberculosis agents as ethambutol and isoniazid are often the main cause of ADEs that alter metabolism and regularly involve the gastric and hepatic functions [97,100]. Rifampicin rarely elicits acute side effects, while ethambutol may induce dose related retrobulbar neuritis [101]. Ethambutol and isoniazid as first line agents in tuberculosis treatment capable of initiating nephrotoxicity particularly in individuals with nephrotic syndromes arising from a decline in renal elimination [102]. Rifampicin use may lead to urticaria, flu-like manifestations, thrombocytopenia states and orange colouring of body fluids [99].

4. Antimicrobial disturbance of microbiome

The administration of antimicrobial agents is a major cause in the ecological shift in the microbial communities of the gastrointestinal tract, GIT [103-108]. The impacts of antimicrobial agents on the GIT microbial community (microbiome/microbiota) leads to the alteration in the constitution of the microbiome and optimal function of the GIT [109-113]. Recent evidence indicates that most microbiome interactions during the first year of life is critical for infant development, as early life antibiotic exposure ultimately disrupts the conventional microbiome maturation and adversely affects well-being, in addition to increasing the abundance of antibiotic resistant bacteria [103,104,107,108,110]. The disturbance of the microbiome is associated with short-term and long-term implications [112,113]. Focusing on new source of antimicrobial agents that selectively targets the infective agent will diminish the constitutional change of gut microbiome and function [112].

Table 1. Summary of some prominent ADEs of antimicrobial therapeutic agents

Agents and specific members	ADEs
Penicillins	Hypersensitivity, hemolytic anemia, anaphylaxis in 15% 20-49 years group [13], vomiting, *Clostridioides difficile* infection [10,14].
Nafcillin	Spikes in transaminases, thrombophlebitis [14]
Cephalosporins	
Cefaclor	Fever, arthralgia, exanthema in 3.2% of children in age range of 4 years [16,21]
Ceftazidime/ceftriaxone/ cefoperazone	Interference with prothrombin, bleeding disorder disulfiram-like reaction [22]
Aminoglycosides	Nephrotoxicity and ototoxicity [29,30] Irreversible ototoxicity or permanent deafness in embryonic administration [28].
Fluoroquinolones	Arthropathy in immature animals, tedonopathy tendon rupture, peripheral neuropathy and aortic aneurism [35,36].
Ciprofloxacin/ofloxacin	DNA damage and chromatin abnormalities [35] Decline in spermatozoa concentration [38]. Retardation of embryo growth [43]
Gatofloxacin	Hypoglycemia and liver injury [35,40-42].
Trovafloxacin	Fatal hepatic injury [43]. Increased risk of retinal detachment, arrhythmia, neurological disorder at 60+ years [36,39].
Sulfonamides	Fatal toxidermia, acute liver injury, AKI, Pulmonary reaction and blood dyscariasis [46,47,50].
Macrolides	Intestinal disturbances in 15-20% of individuals [58]
Domycin	Motilin release in high doses [59].
Lincosamides	Nausea, vomiting, *Clostridioides difficile* infection (or pseudomembranous colitis) [64].
Chloramphenicol	Neurotoxicity, irreversible depression of hematopoiesis with prolonged use [66
Carbapenems	Abdominal pain nausea, vomiting, neuropathy site irritation or swelling in 20% of patients [73].
Glycopeptides	Red man's syndrome, nausea vomiting, diarrhea, rare hypersensitivity, *Clostridioides difficile* [78].
Monobactams	neutropenia in 11.3% of patients, elevated transaminases, no reports of nephrotoxicity or ototoxicity or hematopoietic disorders [87]
Oxazolidinones	Nausea, vomiting, diarrhea, headache and nephrotoxicity in high doses [95]. Other ADEs

	of linezolid – thrombocytopenia, leukocytopenia anemia, hypoglycemia [95,96] and rare colored coated tougue [96].
Rifampicin/Ethambutol/Isoniazid	
Rifampicin	Urticaria, flu-like illness, thrombocytopenia, orange colored body fluids [97,99,100].
Ehtambutol	Retrobulbar neuritis [101].
Isoniazid	Nephrotoxicity in individuals with renal Syndromes, combination of ethambutol and isoniazid alter gastric and hepatic functions [97,100].

6. Addressing ADEs of antimicrobial agents

The deployment of antimicrobial therapeutic substances classically based on intervention in many infections or for prophylaxis in human medical care and in veterinary services globally. This sometimes necessitates the need for more accountability in their administration through deliberate effort to adhere to the general guidelines for their application [114]. Significant progress recorded in the last couple of years on the logical use of antimicrobial agents aims to harness the benefits, encourage sound use and stave off the occurrence of antimicrobial selective pressure in microbial populations, and as a measure to decrease the rising spate of resistant bacterial mutants as well as reduce ADEs [114]. Adverse drugs effects are responsible for a noteworthy number of deaths globally estimated to be the forth runner in causing death in the United States [115]. There is an abysmal level of ADEs reporting on antimicrobial agents indicating that death toll may be much higher in most African health settings [116]. It is crucially important to understand the adverse reaction that could follow each agent and drug-to-drug combination as a pathway to reducing the detrimental outcome of ADEs [115-120]. The application of personalized antimicrobial prescription based on history of ADEs, patients with a history of hypersensitivity reaction reduces the potential for allergies when the agents are avoided [10]. Agents exhibiting higher frequencies of ADEs at specific age groups as the fluoroquinolones for patients who are 60 years or older. The interference with prothrombin activity and bleeding disorder is thus avoidable with this pre-knowledge and as well as in ceftazidime, ceftriaxone or cefoperazone adverse event in children in the age range of 4 years or older becomes circumventable [22, 121].

6.1. Antimicrobial agent monitoring

Agents that have the potential for to induce renal or hepatic toxicity need monitoring as in the administration of aminoglycosides and glycopeptides with the sole purpose of obtaining a better outcome of therapy and minimizing harm to the patient has been proven to be rewarding [114,122-124]. Additionally, drug monitoring is essential for agents with narrow margins for toxicity as the inhibition of the pathogen relies on the concentration in the blood or tissue that is equal to or higher than the minimum inhibitory concentration, MIC for the pathogen [122].

6.2. Patient education

Education of the patient is pivotal to proper monitoring of ADEs, prevention and intervention [125,126]. The tetracyclines, especially deoxycycline may cause photosensitivity that in most

cases are not so severe requiring no serious course of action [127]. It is expedient that the patient receive appropriate and timely information on the possibility of sunburn and use of sunscreen. Similarly, patients administered will clindamycin need to be aware of the unintended intestinal condition associated with overgrowth of *Clostridioides dificille* and toxin production when the microbiota is disturbed. A patient with the prior knowledge of a likely ADE has a better prognosis for resolution when it occurs.

Conclusion

Antibacterial agents remain the cornerstone in the treatment of bacterial infections since introduction in the 1940s with massive decline in the hitherto mortality rates of many infectious diseases. The use of antimicrobial therapeutic agents also come with some adverse drug effects requiring clear and critical evaluation in their deployment to circumvent harm that may lead to disability or fatality. The toxicity of some fourth generation cephalosporins – ceftazidimw, ceftriaxone and cefoperazone leading to bleeding disorders; initiation of nephrotoxicity and ototoxicity of aminoglycosides; hypoglycemia, tendon rupture, retinal detachment and liver toxicity associated with some members of the fluoroquinoloes or development of kidney stones, fatal toxidermia, acute liver injury of sulfonamides are well documented. Disruption and functional modification of gut microbiome with short-range or enduring consequences conjoint with many orally administered agents is prominent with the lincosamides. Maximizing the benefits of antimicrobial therapeutic agents demands personalized focus with the knowledge of interactions in the host and based on the nature of the infective agent will markedly decrease ADEs incidences in the use of antimicrobial therapeutic agents.

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