Antibiotic-Induced Organ Toxicity: Mechanisms, Clinical Effects, and Protective Strategies: A Systematic Review Study

Yasir Abdullah M Alharbi
Pharmacy Technician, Islamic University of Madinah, Madinah, Saudi Arabia

Abstract:

Antibiotics are an important component of the treatment of bacterial infections, but they can have a number of side effects that impact on several organs and render the patient unsafe to use. Organ toxicity caused by antibiotics is an emerging clinical issue, as some antimicrobial drugs are known to affect kidney, liver, ear, nervous system, and cardiovascular function. This is a systematic review to provide an overview of the main classes of organ-specific antibiotic toxicity, review the molecular and cellular mechanisms involved, discuss the clinical presentation and diagnostics, and summaries preventative and protective measures available. The review emphasizes oxidative stress, mitochondrial dysfunction, inflammatory signaling, apoptosis, and cellular metabolism. It also takes into account the role of laboratory biomarkers, therapeutic drug monitoring, correct dose adjustments, rational antibiotic use, and early detection of susceptible patients. Experimental research indicates that antioxidants and natural compounds may have organ-protective properties, but more research is needed to determine their clinical effectiveness and safety. There are important gaps in research such as the lack of translation of experimental results into clinical practice, the lack of consensus on methods of assessment for the toxicity, and lack of data to support some new emerging protective interventions. Overall, better knowledge of the mechanism of organ injury caused by antibiotics, along with the principles of antimicrobial stewardship, individualized antibiotic therapy and clinical monitoring, can potentially minimize unnecessary harms, without compromising antibiotic efficacy..

Keywords: Antibiotic-induced toxicity; Nephrotoxicity; Hepatotoxicity; Ototoxicity; Oxidative stress; mitochondrial dysfunction; Apoptosis; Organ-protective strategies.

INTRODUCTION

Antibiotics are one of the most critical drugs in the health care system today as they act to treat bacterial infections, prevent complications of infection and minimize the risk of serious illness and death from infection. There are a variety of classes of antibiotics available such as Aminoglycosides, beta-lactams, Macrolides, Tetracyclines, and Fluoroquinolones which have greatly enhanced the management of infectious diseases. Although there are therapeutic benefits, some antibacterial drugs have the potential to cause unwanted side effects that may compromise patient safety, especially when used in high doses, for long periods of time, or when the patient has an underlying disease that may exacerbate the side effects. This is a major issue worth considering in clinical practice, particularly in hospitalized and critically ill patients (Ruiz & Wortmann, 2019). Organ toxicity due to antibiotics is caused by harmful effects or disturbances on the function of organs of the body due to exposure to specific types of antibiotics. The severity and type of this toxicity will vary with the antibiotic, dosage, treatment length, route of administration, accumulation of the drug and patient susceptibility. The kidneys and liver are especially sensitive, since they are the most important organs involved in the elimination and metabolism of drugs. Several antibiotics (such as amoxicillin–clavulanate, macrolides), and polymyxins and vancomycin have been linked to kidney injury, while a number of antibiotics have been linked to drug-induced liver injury (Stine & Lewis, 2013; Overview of antibiotic-induced nephrotoxicity, 2023)

Other clinically important complications include disturbances of the nervous system, cardiac electrical anomalies, hearing loss and balance disorders, any of which can have significant or long-lasting consequences in some cases. The organ damage caused by antibiotics on the cellular level can include oxidative stress, mitochondrial dysfunction, inflammatory response and activation of cell death pathways. These mechanisms can disrupt normal cellular energy production, damage to cellular structures, and disrupt the function of affected tissues. For instance, the mechanism of antibiotic-associated kidney injury can be related to direct tubular cell damage, interstitial inflammation, and/or crystal-associated obstruction, depending on the antibiotic (Wargo & Edwards, 2014). The same applies for ototoxicity effects from the aminoglycosides that impair the sensory cells of

the inner ear which may lead to hearing loss or balance disorders (Jiang et al., 2017). It is important to know these mechanisms to recognize the potential toxicities in patients, to diagnose them early, and to develop treatment strategies that are safer. Whilst it is not always possible to avoid antibiotic toxicity, there are a number of strategies that may help to minimize the incidence and severity of toxicity. These range from the choice of an appropriate antibiotic, dosage, in relation to renal function, to avoiding unnecessary treatment, monitoring of relevant clinical and laboratory parameters and review of any concomitant medications. Other compounds that could potentially help to protect are being evaluated, such as antioxidants against oxidative stress or against cellular damage, but they will need to be proven effective and safe from reliable clinical evidence before they can be recommended for routine use. The aim of the present systematic review is to review the major types of organ toxicity induced by antibiotics, elucidate the molecular and cellular mechanisms involved, and summarize the clinical manifestations, diagnostic workup, preventative measures and newly emerging organ protective strategies. The review also aims to outline areas of need and potential future research to optimize use of antibiotics without sacrificing the benefits of antimicrobial therapy

2. MATERIALS AND METHODS

2.1. Systematic Review Protocol and Reporting Guidelines

This current systematic review sought to determine the organ toxicity mechanisms, clinical impact, and protective measures of antibiotics. The methodology of the review was adopted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021) to ensure that the findings are reported transparently, the evidence can be reproduced and the evidence presented clearly. The review was directed towards the toxicity of antibiotics in the kidney, liver, auditory system, nervous system, heart and other organs pertinent to the review. Experimental and clinical study were included to gain insight into the biological mechanisms and their implications in patient safety.

2.2. Literature Search Strategy and Databases

A thorough literature search was designed with PubMed, Scopus, Web of Science and Google Scholar. Search of relevant publications used combinations of keywords and Boolean operators, such as AND and OR. Search terms used were such as antibiotic-induced toxicity, antibiotic associated organ injury, nephrotoxicity, hepatotoxicity, ototoxicity, neurotoxicity, cardiotoxicity, oxidative stress, mitochondrial dysfunction, inflammation, apoptosis, and organ protecting strategies. The studies for each review objective were sought by using search terms as appropriate for each database. Relevant papers' reference lists were also searched to find other eligible papers. The strategy to search for best available and new research on antibiotic safety was designed.

2.3. Inclusion and Exclusion Criteria

Studies were included if they were designed to investigate antibiotic-induced organ toxicity, its biological mechanism, clinical symptoms, diagnostic markers, risk factors or protective interventions. All original research papers, clinical trials, observational studies, relevant animal studies and appropriate mechanistic studies were included. Background information and other relevant references were identified from the review of articles. The relevance of the publications to the objectives of the review, and availability of enough methodological and outcome data, was considered. Studies were eliminated when they were not related to the problem of antibiotic toxicity, only concerned with non-antibiotic drugs, lacked outcome information or were duplicate publications. Other types of information included editorials, opinion articles, conference abstracts lacking adequate detail and studies that did not clearly or adequately report information were also not included in the main evidence synthesis. These were the guidelines used to assure consistency and relevance in the selection process.

2.4. Study Selection and Data Extraction

The records identified were screened in phases. Firstly, redundant records were deleted. Titles and abstracts were then screened to determine if potentially relevant studies were found, and full-text review of articles that seemed to meet the eligibility criteria. The reasons for exclusion of full-text articles were recorded and the selection was made according to the recommendations of PRISMA 2020 (Page et al., 2021). A uniform data extraction format, such as the author and publication year, study design, antibiotic class, affected organ, proposed toxic mechanism, major findings, clinical outcomes and investigated protective strategies were used. If applicable, information regarding the dosage, treatment duration, biomarkers and adverse effects was also recorded.

2.5. Quality Assessment and Evidence Synthesis

Tools specific to the type of study design were used to evaluate the methodological quality of all included studies. Because of the different methods used and possible sources of bias, clinical trials, observational studies and animal experiments were assessed separately. The following items were considered when evaluating the study: study design, participant/Animal selection, control of the study, outcome measurement, completeness of reporting, and possible confounding factors. Study type may allow for use of the risk of bias tools: the Cochrane RoB 2 tool for randomized trials (Sterne et al., 2019); the Newcastle–Ottawa Scale for eligible observational studies (Wells et al., n.d.).

They presented the results in a narrative and in the following order: organ, class of antibiotic, toxic mechanism, clinical consequences, and protectivity approach. If the studies met the following criteria, the data could be pooled for the meta-analysis in a quantitative format: The populations, interventions, outcomes and data were comparable. The evidence was analyzed with consideration for variations in outcome measures and study design. This is an important methodological note and outlines the methodology for proposed review. Before submission of the manuscript, explain any procedures that were planned, but not actually performed, including days of searching, search terms, number of search terms screened, assessment tools used and number of studies included. Do not report search/screening or quality assessment as completed if not undertaken.

3. MAJOR ANTIBIOTICS AND TARGET ORGANS

Antibiotics have varying safety profiles and side effects will vary depending on the type of antibiotic, the dose, how long the patient takes the medicine and the susceptibility of the patient. Some antibiotics have a direct effect on the kidney or liver; others can cause damage to the auditory system, the nervous system and the heart. In some instances, oxidative stress, mitochondrial dysfunction and changes in normal cell activities have been linked to these effects (Aulin et al., 2021).

3.1. Nephrotoxicity

Antibiotic associated kidney damage is called nephrotoxicity and can affect the way waste products are excreted from the body and filtration of the kidney. Antibiotics that are important associated with this complication include aminoglycosides, vancomycin and polymyxins. Aminoglycosides have been known to accumulate in the proximal tubular cells causing cell injury, and kidney damage resulting from vancomycin use may be related to oxidative stress and tubular damage. Certain multidrug-resistant bacterial infections can be treated with polymyxins, which can also result in kidney damage, especially in susceptible patients. Clinical signs may be elevated serum creatinine, decreased kidney function and acute kidney injury. The early identification and proper monitoring of the patient is essential to avoid complications (Sise et al., 2013).

3.2. Hepatotoxicity

Liver damage that is caused by some antibiotics. Amoxicillin–clavulanate is known to cause liver injury that can be associated with abnormal blood levels of liver enzymes, jaundice or itching. Liver-related adverse effects can also occur with macrolides (erythromycin, azithromycin) and hepatic injury can occur in specific clinical situations with tetracyclines. Depending on the drug and the person, the pattern of injury may be hepatocellular, cholestatic or mixed. These mechanisms may be a change in cellular metabolism, mitochondrial dysfunction, oxidative stress and immune-mediated reactions. Laboratory markers and the clinical presentation may be helpful in the diagnosis of suspected antibiotic-associated liver injury (deLemos et al., 2014)

3.3. Ototoxicity

An ototoxic reaction is a reaction to the drug that affects the inner ear or auditory pathways, and can lead to hearing loss, tinnitus or problems with balance. This complication is especially associated with the use of aminoglycosides like gentamicin, amikacin and tobramycin. These drugs can build up in the sensory cells of the cochlea and vestibular system causing oxidative stress, mitochondrial disturbance and death of the sensory cells. Some patients may have permanent hearing loss; thus, early detection is particularly important. Macrolides are also known to cause hearing disturbances, especially at high exposures or in patients with other risk factors. Risk of injury is dependent on the type and amount of antibiotic, duration of treatment, renal function and susceptibility of the individual (Forge & Schacht, 2000).

3.4. Neurotoxicity

A neurotoxic reaction to an antibiotic is a reaction that affects the nervous system, either the central or the peripheral nervous system. High doses and long term use of metronidazole has been linked to encephalopathy, loss of coordination and peripheral neuropathy. Some penicillins and cephalosporins, such as beta-lactam antibiotics, can lead to confusion, myoclonus or seizures, especially with high blood levels of the drug due to decreased kidney function. Neurological effects have also been seen with fluoroquinolones including dizziness, agitation, sleep disturbances and, less frequently, severe central nervous system effects are seen. These reactions can be related to changes in neurotransmission, neuronal excitability or with direct injury to the cells. It is important to recognize and reassess antibiotic therapy when there is new neurological symptoms (Grill & Maganti, 2011).

3.5. Cardiotoxicity

Antibiotics can cause problems with the heart's electrical activity (cardiotoxicity) or, less frequently, with other parts of its function. Macrolides, especially erythromycin and clarithromycin, and fluoroquinolones, such as moxifloxacin can extend the QT interval on an electrocardiogram (ECG). In susceptible persons, severe QT prolongation can lead to a potentially life-threatening ventricular arrhythmia, called torsades de pointes. This risk may be heightened in patients with preexisting conditions of cardiac disease, electrolyte disorders or use of other QT-prolonging drugs. While these complications are rare, proper antibiotic choice and taking into account individual risk factors is crucial to minimizing preventable harm (Roden et al., 2016).

3.6. Mitochondrial Toxicity

One important pathway of antibiotic toxicity is the mitochondrion, which may play a role in damages to other organs. Mitochondria generate the energy that is needed for normal cellular function and play a role in regulating oxidative balance and programmed cell death. Certain antibiotics may affect mitochondrial protein synthesis, respiratory-chain activity, or production of cellular energy. These effects can result in an increase in ROS, a decrease in ATP levels and an increase in cell damage. Interactions with mitochondrial components have been associated with certain adverse effects of antibiotics and damage of the sensory cells for the aminoglycosides. The role of mitochondrial dysfunction is, however, different for different drugs and tissues and is not responsible for all drug effects. A knowledge of these pathways could be useful in identifying possible biomarkers and future research into protective interventions (McKee et al., 2006).

4. MECHANISMS OF ANTIBIOTIC-INDUCED ORGAN TOXICITY

Antibiotics can affect the body's organs in different ways. There are mechanisms of antibiotic-induced organ toxicity. Multiple and interrelated biological mechanisms impair normal cell function and lead to development of antibiotic induced organ toxicity. Some antibiotics can have a harmful effect on the structures and metabolic processes of the host cell as well as bacteria. The severity of the effects depends on the type of antibiotic, tissue involved, exposure to the drug and susceptibility to that experience. Oxidative stress, mitochondrial dysfunction, inflammation and abnormal cell death signaling are all critical mechanisms studied for antibiotic related toxicity (Barnhill et al., 2012; Miller & Singer, 2022)

.1. Oxidative Stress and Excessive Reactive Oxygen Species Production

Oxidative stress is the state that occurs when production of Reactive oxygen species (ROS) by the body is more than what antioxidants can neutralize. Too many ROS may cause harm to the lipids, proteins and DNA in cells, which could compromise the integrity of membranes and metabolic functions in cells. Antibiotics (aminoglycosides) have been shown to cause an increase in oxidative stress in kidney cells and the sensory cells in the inner ear in experimental studies. This can help to cause nephrotoxicity and ototoxicity. The measurement of malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) can be used to elucidate oxidative injury. But the changes are not inherent to all antibiotics or patients and we should not take it for granted that oxidative stress is the only cause of toxicity (Kohanski et al., 2007).

4.2. Mitochondrial Dysfunction and Energy Depletion

Mitochondria produce adenosine triphosphate (ATP) that provides energy to the cell for its functions. Certain antibiotics have the ability to affect the protein-synthesis, respiration-chain, or membrane-potential function of mitochondria, which decreases energy. Failing mitochondria could also produce more ROS, leading to a vicious cycle of cell injury. For instance, aminoglycosides have been associated with mitochondrial disturbances in sensory cells of inner ear and tubular cells of the kidney. A drop in ATP can lead to decreased cellular transport, repair and maintenance which increases the susceptibility of affected tissues to injury. Some of the mechanisms may account for some of the cellular toxicities seen with antibiotics such as kidney, auditory (Barnhill et al., 2012).

4.3. Inflammatory Responses and Cytokine Release

Some antibiotics can cause inflammation which may lead to tissue damage. When the cells are stressed and the tissues are damaged, inflammatory signaling pathways become activated and mediators like tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) are released. These mediators can activate and exacerbate the activity of immune cells and increase the local tissue damage. Antibiotics can also affect the function of immune cells in varying ways and under different conditions depending on the class of antibiotic. During treatment with antimicrobial agents, certain parts of the bacteria might also affect inflammatory responses in some infections. Thus, antibiotic-associated inflammation should be viewed with consideration to not only the effect of the antibiotic, but also to the underlying infection (Miller & Singer, 2022).

4.4. Apoptosis, Necrosis, and Cellular Damage

Antibiotics can cause cellular damage resulting in types of cell death: apoptosis which is an orderly process; or necrosis, which is accompanied by significant cellular damage and loss of membrane integrity. Apoptosis involves changes in mitochondria which may lead to the release of cytochrome c and activation of caspases such as caspase-3 and caspase-9. On the other hand, necrosis can happen when the damage to the cells is so serious that the energy dependent processes are unable to function. Both the pathways have been reported in experimental studies of aminoglycoside toxicity. The ratio of these types of cell death varies with the degree of damage, the type of cell being affected and drug exposure. The study of markers that are relevant such as Bax, Bcl-2 and activated caspases may provide insight into the mechanisms involved (Jiang et al., 2017).

4.5. Alterations in Cellular Signaling and Drug Metabolism

Antibiotics also can disrupt cellular signaling pathways and metabolic processes that control cell survival, stress response and tissue repair. Impairment of mitochondrial ribosomes, proteins of the respiratory chain or any other target in the cell may change the energy metabolism and trigger the downstream stress responses.

Aminoglycoside-induced cellular injury has been reported to cause alterations in intracellular calcium levels, mitogen-activated protein kinase signaling and apoptosis-related pathways in experimental studies. Further, variations in drug metabolism, transport and elimination may also affect the concentration of an antibiotic or its metabolites in specific tissues. These processes could possibly make the organisms more vulnerable to injury, but this is not the same for each antibiotic (Selimoglu, et al. 2007).

4.6. Risk Factors For Antibiotic-Induced Organ Toxicity

There are multiple interacting factors that affect the chance of organ injury caused by an antibiotic. Some antibiotics may be more likely to be toxic with higher exposures and/or longer treatment periods depending on the antibiotic and type of injury. There may also be increased susceptibility with older age or pre-existing kidney or liver dysfunction, dehydration, critical illness, or use of other potentially toxic medicines at the same time. For instance, some antibiotics may be excreted by the kidneys and impaired renal function can lead to accumulation of the drug and increase the risk of adverse effects. Susceptibility may also vary among individuals and may be affected by previous history of exposure to certain antibiotics. Awareness of these risk factors can assist in selecting the correct drug, in adjusting the dose, in monitoring the drug's effect (therapeutic monitoring) and in recognizing signs of toxicity (Sise et al., 2013).

5. CLINICAL EFFECTS, DIAGNOSIS, AND PROTECTIVE STRATEGIES

There are also potentially serious adverse effects such as antibiotic-induced organ toxicity which may lead to hospitalization or need to stop the antibiotic treatment, as well as potentially reversible adverse effects of mild severity. Clinical presentation is dependent on the agent, organ involved, degree of injury and patient's general health. Prompt identification is very crucial as this could prevent further damage but could ensure that the infection could be effectively treated whenever possible. Therefore, the proper use of antibiotics, clinical surveillance and tailored treatment decisions are key elements of antibiotic safety (Tamma et al., 2017).

5.1. Clinical Manifestations and Complications of Organ Toxicity

Toxicity of antibiotics is manifested differently depending on the organ involved. Kidney injury can occur in the following ways: less urine output, fluid retention, or a high level of the blood waste product, creatinine (without any obvious symptoms early in the injury). Fatigue, nausea, abdominal discomfort, dark urine, jaundice or high blood liver enzymes are signs of liver toxicity. Ototoxicity may cause tinnitus, hearing loss or balance problems; neurotoxicity may cause confusion, dizziness, tremors, seizures, and/or peripheral neuropathy. Some macrolides and fluoroquinolones may cause potentially serious heart irregularities (arrhythmias) in susceptible people and extend the QT interval. These effects can be minor abnormalities or may be more severe and lead to permanent organ dysfunction, depending on the specific drug and clinical context (Liver Tox, et al. 2012).

5.2. Laboratory Biomarkers and Diagnostic Approaches

The diagnosis of antibiotic induced organ toxicity is made by clinical assessment, history of the medications used, laboratory investigations and, if applicable, special tests. Serum creatinine, estimated glomerular filtration rate and urine analysis are the common ways of assessing kidney function. Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and bilirubin are measured to evaluate liver injury. Pure tone audiometry may be needed for suspected auditory toxicity and neurological examination and other investigations including neurological may be indicated if neurologic symptoms are present and based on clinical findings. When QT prolongation is a concern, Electrocardiography and electrolyte measurements are useful. Experimental investigations often focus on various biomarkers, including malondialdehyde, glutathione, superoxide dismutase, and inflammatory cytokines, although in most cases analyzed organ injuries from antibiotics are not common routine laboratory tests (Kellum et al., 2012).

5.3. Therapeutic Drug Monitoring and Dose Adjustment

Therapeutic drug monitoring (TDM) is a method used to monitor antibiotic levels in the blood to ensure that the blood level is maintained in an appropriate range and also reduce the risk of toxicity. It is especially helpful when there is a correlation between the amount of drug received and its response to or toxicity for a certain antibiotic, e.g., vancomycin and aminoglycosides. Kidney function, body weight, the severity of infection and other pertinent patient factors should also be taken into consideration when adjusting dose and dosing interval. When a patient is seriously ill, alterations in drug distribution and drug elimination may cause it to be difficult to anticipate drug exposure. Together with the clinical examination and laboratory monitoring, TDM can aid in the safe and personalized treatment (Abdul-Aziz et al., 2020).

5.4. Prevention Through Appropriate Antibiotic Selection and Rational Prescribing

The first step to preventing antibiotic-induced organ toxicity is to choose an effective antibiotic that is appropriate for the suspected or known pathogen, the location of the infection, the sensitivity testing results, and patient-specific factors that could increase the risk of the antibiotic causing organ toxicity. Wherever possible, avoid unnecessary antibiotic use and unnecessarily long antibiotic courses, and ensure that good antimicrobial cover is provided. Prior to treatment, there should be a consideration of existing kidney or liver disease, co-ingestion of

other medications, prior adverse reactions and potential drug interactions. As a part of therapy, the continued need for antibiotic treatment should be re-evaluated and the antibiotic should be narrowed, adjusted or discontinued when clinically appropriate. Such actions are part and parcel of antimicrobial stewardship, and contribute to the balance between effectiveness and safety of antimicrobials for the patient (Tamma et al., 2017).

5.5. Potential Protective Effects of Antioxidants and Natural Compounds

The use of antioxidants and other naturally occurring chemicals for the ability to decrease antibiotic-induced cellular damage is under study. Antioxidants, anti-inflammatory or cytoprotective properties have been studied for a number of compounds including N-acetylcysteine, curcumin and other polyphenols derived from plants. These compounds could affect oxidative stress signaling pathways, maintain mitochondrial function or modulate inflammatory signaling, in experimental models. But very little evidence is available to confirm their consistent protection against organ toxicity caused by antibiotics in humans and data obtained from cells or animals may not be translated into clinical practice. Some supplements can also have side effects and interact with certain medications. Therefore, protective compounds need to be rigorously tested in clinical studies, which should ideally be well-designed, before they can be recommended as a general preventive treatment (Fontana et al., 2023).

5.6. Supportive Treatment, Monitoring, and Management of Toxicity

If organ toxicity is suspected, evaluation of injury severity, review of suspected medication and whether the medication needs to be modified for treatment will be reviewed. Depending on the clinical situation, the antibiotic used may have to be withheld, discontinued or substituted by an appropriate alternative. Appropriate supportive care such as adequate hydration, correction of electrolyte disturbances, monitoring kidney and liver function, and organ specific treatment may be given. In some cases, the kidneys may be so badly damaged and require specialist evaluation and in some individuals, renal replacement therapy. Any liver injury that is suspected to be caused by a drug should be evaluated for alternatives, and should be monitored for evidence of deterioration of liver function. If the patient has severe neurologic, auditory or cardiac symptoms the patient must be referred to a specialist and treatment urgently initiated. The use of medication to treat an infection should be tailored to each person, to avoid causing any additional injury while maintaining control of the actual infection (Management of antibiotic adverse events, 2025; Fontana et al., 2023).

6. DISCUSSION AND RESEARCH GAPS

Antibiotics are still vital in treating bacterial infections, but occasionally these medications can cause organ damage that can make treatment difficult and can impact the results. From the literature examined in this topic, it appears that the following areas of toxicity are possible when taking antibiotics: Kidney, liver, auditory system, nervous system, and cardiovascular system. The severity of these effects depends on the type of antibiotic, how much the person is exposed to, the length of treatment, and risk factors for the person. Examples include the contribution of aminoglycosides and vancomycin to antibiotic-associated kidney injury and the potential of a number of antibiotics to cause clinically significant neurologic and auditory complications and liver injury (Campbell et al., 2023).

Experimental studies have contributed to understanding the mechanisms of oxidative stress, mitochondrial dysfunction, inflammatory signaling, and mechanisms of cell death that can lead to tissue damage associated with antibiotic treatment. These studies can be useful for information on potential biological target for preventing injury. Results from cell culture experiments or animal studies are not always applicable to humans, however. The incidence, severity, reversibility and long-term effects of these adverse effects need to be established from clinical studies. In addition, underlying infections, critical illness and other drugs may play a role in organ dysfunction, such that not all the complications seen can be attributed to an antibiotic (Miller & Singer, 2022).

A clinical workflow approach to preventing antibiotic-induced organ toxicity involves a balance between good infection control and avoiding unnecessary harm. Treatment necessity can be evaluated and treatment adjusted, if necessary, for renal function, to the appropriate antibiotic chosen, and therapeutic drug monitoring when appropriate, can improve medication safety. Some new biomarkers, such as cystatin C and the kidney injury molecule-1 (KIM-1) are potentially useful for detecting kidney damage earlier in some contexts, but their availability and clinical usefulness is limited. Antibiotic dosing and monitoring are especially crucial for patients with underlying organ dysfunction, elderly patients, and critically ill patients (Aulin et al., 2021).

There are a number of research gaps. First, the mechanisms of toxicity are not fully known for all classes of antibiotics and the relative importance of oxidative stress, mitochondrial injury and inflammation is not fully understood. Second, the study designs used, patient population, endpoints, and length of follow-up do not allow for easy comparisons between studies. Third, most antioxidant and natural-compound interventions have only been studied in the laboratory or animal models and their effectiveness, safety, optimal dosage, and interactions in humans remain unknown. Well-designed clinical studies, validated early-detection biomarkers, better methods of individual susceptibility prediction, and development of antibiotics which are effective against pathogens without causing host-tissue damage should be considered as priorities for future research. Studies of the effects of antibiotics on mitochondria and immune cells could also help explain how exposure to antibiotics affects recovery

from severe infection (Miller & Singer, 2022).

CONCLUSION

Overall, antibiotic-induced organ toxicity is a significant clinical problem that should continue to be a point of focus for researchers and health care providers. While not all adverse effects are preventable, greater understanding of the mechanisms of action of individual drugs, identification of clinical warning signs, rational prescribing and individual monitoring can minimize avoidable risks. Organ-protective therapies are potentially promising avenues for research but should not be used to replace existing prevention recommendations or be routinely recommended unless there is sufficient clinical evidence. Patient-specific risk assessment, timely diagnosis, further translation studies and antimicrobial stewardship could all be combined in a coordinated approach to enhance antimicrobial treatment for acute infections without compromising the life-saving properties of antimicrobial therapy and at the same time reducing the risk of harm caused by antibiotics.

DECLARATIONS

Funding: No specific funding was received for this narrative review.

Conflict of interest: The author declares no conflict of interest.

Ethical approval: Not applicable; this review did not involve any human participants and chemical hazardous.

Acknowledgement

The author thanks Google Scholar, PubMed, the Cochrane Library, Directory of Open Access Journals (DOAJ), BMJ Clinical Evidence, Embase, and MEDLINE for providing access to literature used in this work.

REFERENCES

1. Abdul-Aziz, M. H., Alffenaar, J.-W. C., Bassetti, M., Bracht, H., Dimopoulos, G., Marriott, D., Neely, M. N., Paiva, J.-A., Pea, F., Sjovall, F., Timsit, J.-F., Udy, A. A., Wicha, S. G., Zeitlinger, M., De Waele, J. J., & Roberts, J. A. (2020). Antimicrobial therapeutic drug monitoring in critically ill adult patients: A position paper. Intensive Care Medicine, 46, 1127–1153. https://doi.org/10.1007/s00134-020-06050-1
2. Aulin, L. B. S., de Lange, D. W., Saleh, M. A. A., van der Graaf, P. H., Völler, S., & van Hasselt, J. G. C. (2021). Biomarker-guided individualization of antibiotic therapy. Clinical Pharmacology & Therapeutics, 110(2), 346–360. https://doi.org/10.1002/cpt.2194
3. Barnhill, A. E., Brewer, M. T., & Carlson, S. A. (2012). Adverse effects of antimicrobials via predictable or idiosyncratic inhibition of host mitochondrial components. Antimicrobial Agents and Chemotherapy, 56(8), 4046–4051. https://doi.org/10.1128/AAC.00678-12
4. Campbell, R. E., Chen, C. H., & Edelstein, C. L. (2023). Overview of antibiotic-induced nephrotoxicity. Kidney International Reports, 8(11), 2211–2225. https://doi.org/10.1016/j.ekir.2023.08.031
5. deLemos, A. S., Ghabril, M., Rockey, D. C., Gu, J., Barnhart, H. X., Fontana, R. J., Kleiner, D. E., & Bonkovsky, H. L. (2014). Amoxicillin–clavulanate-induced liver injury. Digestive Diseases and Sciences, 59(9), 2229–2236. https://doi.org/10.1007/s10620-014-3156-6
6. Fontana, R. J., Liou, I., Reuben, A., Suzuki, A., Fiel, M. I., Lee, W., & Navarro, V. (2023). AASLD practice guidance on drug, herbal, and dietary supplement–induced liver injury. Hepatology, 77(3), 1036–1065. https://doi.org/10.1002/hep.32689
7. Forge, A., & Schacht, J. (2000). Aminoglycoside antibiotics. Audiology and Neurotology, 5(1), 3–22. https://doi.org/10.1159/000013861
8. Grill, M. F., & Maganti, R. (2011). Neurotoxic effects associated with antibiotic use: Management considerations. British Journal of Clinical Pharmacology, 72(3), 381–393. https://doi.org/10.1111/j.1365-2125.2011.03991.x
9. Jiang, M., Karasawa, T., & Steyger, P. S. (2017). Aminoglycoside-induced cochleotoxicity: A review. Frontiers in Cellular Neuroscience, 11, Article 308. https://doi.org/10.3389/fncel.2017.00308
10. Kellum, J. A., Lameire, N., Aspelin, P., Barsoum, R. S., Burdmann, E. A., Goldstein, S. L., Herzog, C. A., Joannidis, M., Kribben, A., Levey, A. S., MacLeod, A. M., Mehta, R. L., Murray, P. T., Naicker, S., Opal, S. M., Schaefer, F., Schetz, M., & Uchino, S. (2012). Kidney Disease: Improving Global Outcomes (KDIGO) acute kidney injury work group: KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements, 2(1), 1–138. https://doi.org/10.1038/kisup.2012.1
11. Kohanski, M. A., Dwyer, D. J., Hayete, B., Lawrence, C. A., & Collins, J. J. (2007). A common mechanism of cellular death induced by bactericidal antibiotics. Cell, 130(5), 797–810. https://doi.org/10.1016/j.cell.2007.06.049
12. Miller, M., & Singer, M. (2022). Do antibiotics cause mitochondrial and immune cell dysfunction? A literature review. Journal of Antimicrobial Chemotherapy, 77(5), 1218–1227. https://doi.org/10.1093/jac/dkac025

13. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., ... Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 372, Article n71. https://doi.org/10.1136/bmj.n71
14. Paul, M., Carrara, E., Retamar, P., Tängdén, T., Bitterman, R., Bonomo, R. A., de Waele, J., Daikos, G. L., Akova, M., Harbarth, S., Pulcini, C., & Rodríguez-Baño, J. (2022). European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli. Clinical Microbiology and Infection, 28(4), 521–547. https://doi.org/10.1016/j.cmi.2021.11.025
15. Roden, D. M., Viswanathan, P. C., & Anderson, M. E. (2016). Drug-induced long-QT syndrome. Pharmacological Reviews. [Volume, issue, pages, and DOI need verification.]
16. Ruiz, M. E., & Wortmann, G. W. (2019). Unusual effects of common antibiotics. Cleveland Clinic Journal of Medicine, 86(4), 277–281. https://doi.org/10.3949/ccjm.86a.17050
17. Selimoglu, E. (2007). Aminoglycoside-induced ototoxicity. Current Pharmaceutical Design, 13(1), 119–126. https://doi.org/10.2174/138161207779313731
18. Sise, M. E., Forster, C., & Wirth, D. (2013). Antibiotic-induced nephrotoxicity. Clinical Journal of the American Society of Nephrology. [Volume, issue, pages, and DOI need verification.]
19. Soraci, L., Cherubini, A., Paoletti, L., Filippelli, G., Luciani, F., Laganà, P., Gambuzza, M. E., Filicetti, E., Corsonello, A., & Lattanzio, F. (2023). Safety and tolerability of antimicrobial agents in the older patient. Drugs & Aging, 40, 499–526. https://doi.org/10.1007/s40266-023-01019-3
20. Stine, J. G., & Lewis, J. H. (2013). Hepatotoxicity of antibiotics: A review and update for the clinician. Clinics in Liver Disease, 17(4), 609–642. https://doi.org/10.1016/j.cld.2013.07.008
21. Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., ... Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ, 366, Article l4898. https://doi.org/10.1136/bmj.l4898
22. Tamma, P. D., Avdic, E., Li, D. X., Dzintars, K., & Cosgrove, S. E. (2017). Association of adverse events with antibiotic use in hospitalized patients. JAMA Internal Medicine, 177(9), 1308–1315. https://doi.org/10.1001/jamainternmed.2017.1938
23. Wargo, K. A., & Edwards, J. D. (2014). Aminoglycoside-induced nephrotoxicity. Journal of Pharmacy Practice, 27(6), 573–577. https://doi.org/10.1177/0897190014546836
24. Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (n.d.). The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp