REVIEW ARTICLE

A Comprehensive Review on Sulfonamide Resistance: Recent Trends and Implications in Primary Care Clinical Settings

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Abstract

Sulfonamides, once widely effective antibiotics, now face escalating resistance due to decades of overuse in clinical and agricultural settings. This narrative review synthesizes evidence (2000-2024) on the evolutionary drivers of resistance, highlighting key mechanisms such as folP gene mutations, the acquisition of sul1, sul2, and sul3 resistance genes *via* mobile genetic elements, and efflux pump activation. Resistance proliferation is exacerbated by environmental contamination—particularly in hospital effluents and manure-treated soils—where antibiotic residues select for resistant strains and facilitate gene transfer to human pathogens. Clinical misuse (*e.g.*, subtherapeutic dosing) further accelerates resistance, complicating infections like UTIs and respiratory diseases. Emerging data underscore the need for integrated strategies: antimicrobial stewardship to curb unnecessary prescriptions, surveillance of resistance hotspots (*e.g.*, wastewater, livestock), and policy reforms to limit agricultural overuse. Combination therapies (*e.g.*, trimethoprim-sulfamethoxazole) may delay resistance, but long-term solutions require a One Health approach. This review equips clinicians with insights to navigate sulfonamide resistance while advocating for systemic interventions to preserve antibiotic efficacy.

Keywords: *Sulfonamides, infection, resistance, gene, sul, folP.*

INTRODUCTION

One of the earliest synthetic antimicrobial agents in the 1930s was the sulfonamide, also referred to as sulfa drug. Sulfa drugs function by inhibiting the bacterial enzyme dihydropteroate synthase (DHPS); which is involved in the synthesis of folate [1]. Bacteria require folate to produce DNA and other vital biomolecules. Sulfonamides have played an enormous role in the treatment of many infections, such as urinary tract infections, pneumonia, and wound infections [2]. However, in the last few decades, the emergence and proliferation of resistance have derailed their effectiveness [3]. The evolution of sulfonamide resistance is associated with a variety of adaptive mechanisms, which include the accumulation of point mutations in the gene encoding DHPS, such as the folP gene and horizontally transferred resistance genes such as sul1, sul2, and sul3 [4]. These pathways allow pathogens to circumvent or surpass the inhibition of folate synthesis, making treatment with sulfonamide less effective [5]. Resistance has also been noted in several different bacterial species including *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus*; the concern is that sulfonamides have low effectiveness in contemporary clinical settings [6].

However, in the last few years research efforts have been focused on innovative therapeutic strategies to overcome sulfonamide resistance. Some of the approaches included novel inhibitors of folate pathways, combination therapies with synergistic antibiotics and bacteriophage therapy, which demonstrate promise in preclinical models [7, 8]. Furthermore, genomic surveillance and molecular diagnostics are more frequently used for the surveillance of resistance patterns and for the facilitation of personalized treatment strategies and for optimizing the use of sulfonamides [9]. In an environmental study, research was done on multiple water samples and the result showed that the presence of sul1, sul2, and sul3 is associated with resistance [10]. Research reports the rising threat of infections caused by multi-drug resistant (MDR) bacteria anti-microbial resistance (AMR), which is a significant challenge [11]. Research also described sulfonamide resistance mechanisms from the literature and claims that enzyme production, efflux systems, target site modification and genetic factors are frequently involved in drug resistance [12].

Therefore, the purpose of this narrative review article was to conduct a complete analysis of the evolutionary aspects of sulfonamide resistance in bacterial pathogens. This also entailed a comprehensive search for the mutant genes and sites, including the DHPS gene, which helps gain insight into how bacteria acquire new genetic information to evade the effects of sulfonamides. At the same time, the review will account for the individual ecological and environmental factors that contribute to the selection of resistant strains and further release them into different environments where such release may favor the proliferation of resistance.

METHODOLOGY

The methodology of our current narrative review comprises the following sub-elements: an article search, eligibility criteria, information resources, search strategy, study selection, extraction of data, synthesis of the

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data, risk of bias assessment, statistical analysis, and results reporting after qualifying the eligibility criteria. Studies considered were based on the inclusion criteria of reporting mechanisms of resistance to sulfonamide, the prevalence of resistance genes and new therapeutic approaches published between 2000 and 2024. In qualifying studies, exclusion criteria included those written in a language other than English, reviews, case reports, and research lacking original information regarding mechanisms of resistance and treatment strategies. A thorough search was conducted from the databases of PubMed, web of science, google scholar, sciencedirect, springer and directory of open access journals. The keywords "sulfonamide resistance", "DHPS mutations", "antibiotic resistance" and "therapeutic strategies" were employed for carrying out this work.

Data extraction was carried out using a standardized form to record the following: study type, design, publication year, resistance mechanisms, objectives of the study and main findings. Qualitative synthesis was carried out on the incorporated studies; findings related to resistance mechanisms and the appropriate therapeutic approaches for them were thematically consolidated.

RESULTS AND DISCUSSION

After the careful review of the literature, the results were summarized in Table **1** pertaining to the resistance of sulfonamides. This review tries to detail the evolutionary dynamics of sulfonamide resistance and discuss modern therapeutic strategies by efficiently combating resistant infections [13]. Among the general goals, one of the most important is the explanation of the reasons why resistance genes have stable conditions, such as an absence of the effects of antibiotics [14]. It is also imperative to discuss how sulfonamide resistance is maintained by the conjugational transfer in bacteria; processes of adaptations in bacteria and sustainability of sulfonamide resistance [15]. Further research indicated that sulfonamide resistance is due to sul2 gene and the resistance rate is 5.2%-100% (avg. 57.4%) [16]. In Biochemical and microbiological analysis, the mechanism for resistance is primary mutations (F17L, S18L, and T51M) and secondary mutations (E208K, KE257 dup) that result in resistant structural transformation as observed in 56 *S. aureus* reference strains and 80 non-redundant *S. aureus* [17]. One of the studies where two soil-type samples were treated with manure shows that sul1 and sul2 genes are resistant to sulfadiazine [18].

Several studies make an excellent contribution to understanding the mechanisms of sulfonamide resistance development across various settings, especially from a clinical and laboratory perspective. [19]. One important aspect that recurs in these works is the various mutations, gene additions, or even drug efflux that lead to the development of resistance [19]. The various studies, for example, observe that mutations within the DHPS and folP genes are implicated in resistance by changing the enzyme's ability to bind to the drug target [20]. Several studies have detected sul1, sul2, and sul4 genes in soils and aquatic environments, especially those that have been subject to farming

Table 1: Findings of studies about sulfonamide resistance mechanisms.

S. #	Study Type	Study Design	Study Year	Resistance Mechanism(s)	Study Objective	Key Findings	Citation
1	Genomic Analysis	*In vivo* experimental study	2024	Horizontal gene transfer of sul genes	To study sul gene horizontal transfer among *Staphylococcus aureus* clinical isolates and prevalence of sul1 and sul2 in hospital settings.	Detected sul gene transfer among various strains, demonstrating sul1 and sul2 prevalence in hospital settings	[24]
2	Comparative Study	Review and genomic epidemiology	2024	Mutations in folP and DHPS genes	To study the differences in resistance due to folP and DHPS mutations in clinical isolates compared to environmental bacterial isolates.	Noted significant variation in resistance based on folP mutations among strains from different sources	[25]
3	Genomic	Environmental Study	2024	Multi-drug resistance	To explore public health implications of multidrug-resistant bacteria in water.	Genomic analysis found of multidrug-resistant *E. coli* in water sources	[26]
4	Environmental Genomics	Surveillance study	2024	Detection of sul genes	Monitor the prevalence and distribution of sul genes, especially sul1 in urban sewage samples, in order to highlight their potential role in environmental dissemination of resistance genes.	Widespread sul1 gene presence noted in urban waste-water, indicating environmental spread	[23]
5	Environmental Study	Cross-sectional analysis	2024	sul1 and sul2 genes	Determine the frequency of sul1 and sul2 among sediments and Water samples of rivers surrounding areas of high density of livestock, and assess their freshness in aquatic ecosystems.	sul gene prevalence linked to high-density livestock areas; resistance genes persist in water bodies	[21]
6	Laboratory-based Study	Experimental and genomic study	2024	Gene mutation in sul2	Define the distribution and frequency of sul1, sul2, and sul4 genes in environmental bacteria from samples of industrial waste-water, soil, and water, linking their existences with genetic adaptation at polluted sites.	Found that sul2 gene mutations provided partial resistance to sulfonamide drugs	[22]

S. #	Study Type	Study Design	Study Year	Resistance Mechanism(s)	Study Objective	Key Findings	Citation
7	Experimental	Case-control study	2024	Gene mutations in folP	To examine mutations directly responsible for sulfonamide resistance in 150 clinical isolates through specific mutations of the folP gene and correlate this with treatment failure in the clinical setting.	Established folP mutations' role in resistance; sulfonamide treatment failure linked to specific mutations	[27]
8	Genomic study	Genomic analysis study	2024	Antimicrobial resistance, Virulence factors	To understand the genomic features of *E. coli* in urban settings.	Virulence, antimicrobial resistance, and adaptation observed in *E. coli* from urban environments	[18]
9	Environmental Study	Cross-sectional analysis	2023	Presence of sul1 and sul3 genes in environmental bacteria	To check the occurrence of sul1 and sul3 genes among environmental bacteria isolated from soil and water samples and determine the linkage between agricultural run-off of antibiotics and increasing sul gene occurrence.	Significant rise in sul gene prevalence linked to antibiotic run-off from agricultural sites	[28]
10	Case-control Study	Case-control analysis	2023	Gene mutations in sul genes and efflux pump activation	To compare resistant and susceptible bacterial strains and draw conclusion on the types of sul gene mutations that have efflux pump activation associated with sulfonamide resistance.	Showed a correlation between efflux activity and sul gene expression in resistant strains	[29]
11	Laboratory-based Study	*In silico* and structural study	2023	Mutation in sul2 and overexpression of efflux pumps	Investigate the function of efflux pumps with sul2 mutations in facilitating antibiotic resistance in *Pseudomonas* isolates.	Demonstrated efflux pumps' role in combination with sul2 mutations in resistance	[30]
12	Basic Research	Experimental study investigating sul4 resistance gene in marine bacteria	2023	Sulfonamide resistance mediated by sul4 genes without mobile genetic elements	To understand the prevalence and characteristics of the sulfonamide resistance gene sul4 in marine bacterial isolates.	Identified sul4 in diverse marine bacteria and highlighted its potential role in intrinsic resistance, independent of horizontal gene transfer	[11]
13	Biochemical and microbiological analysis.	Research about trends and mechanisms of resistance, and therapeutic strategies against microbes	2021	Primary mutations (F17L, S18L, T51M) and secondary mutations (E208K, KE257 dup) enhancing sulfonamide resistance	To identify and characterize primary and secondary DHPS mutations in *S. aureus* strains, evaluate their association with sulfonamide resistance, and assess the structural changes associated with resistance.	Five DHPS mutations increase sulfonamide resistance; F17L is most prevalent structural changes	[31]
14	Genomic Surveillance study	Longitudinal genomic study	2018	Evolution of sul genes under selective pressure	A survey on how sul genes evolve in clinical settings under selection pressure keeping a watchful eye on developing profiles of resistance over time.	Observed the evolution of sul genes in clinical settings, with increased resistance rates over time	[32]
15	Genomic Surveillance study	Longitudinal genomic study	2018	Detection of sul genes in bacteria from treated soil	Study the spreading of sul genes in bacteria from agricultural fields that are manure-fertilized, in truth, all what manure will affect in the resistance of soil bacteria.	Agricultural application of manure identified as a significant contributor to sul gene dissemination in soil bacteria	[32]
16	Microbiome study	Expiremental study	2017	Sulfonamide resistance gene	To identify a novel resistance gene.	Discovery of the fourth mobile sulfonamide resistance gene	[17]
17	Environmental study	Observational study	2015	sul1, sul2, sul3 genes: DHPS with low sulfonamide affinity; found in transposons/ plasmids	To determine the effect of manure application on the abundance of sulfonamide resistance genes (sul1, sul2, sul3) in soil and the specific bacteria genera presenting resistance to it in the different soil types in the study.	Manure application increases ARG gene abundance; *Bacillus*, *Pseudomonas*, and *Shigella* are prevalent with this resistant gene	[20]

S. #	Study Type	Study Design	Study Year	Resistance Mechanism(s)	Study Objective	Key Findings	Citation
18	Genomic analysis study	Observational study	2014	sul4 gene: Clonally transferred; most prevalent. Other genes: sul1, sul2, sul3 detected	To study how sulfonamide resistance genes (sul1, sul2, sul3, sul4) occur in the marine bacterial isolates in terms of their dissemination, particularly for sul4, which is thought to have implications for folate metabolism.	sul4 is found in 45% of isolates; followed by sul2, sul3 and sul1. sul4 may affect folate metabolism; not linked to mobile genetic elements	[19]
19	Laboratory-based study	Experimental study	2013	sul1 and sul2 genes	To assess the impact of manure application on the prevalence of sul1 and sul2 genes in soil, and link it to application of manure treatment and increase in sulfonamide resistance.	sul1 and sul2 in soils treated with sulfadiazine manure; links manure application to rising sulfonamide resistance	[33]
20	Environmental study	Cross-sectional observational study	2013	Presence of sul1, sul2, and sul3 associated with DHPS mutation	To analyze sulfonamide resistance gene (sul1, sul2, sul3) prevalence and distribution in urban river water samples, and analyze their association with DHPS mutations.	sul1 and sul2 are widespread in urban waters; sul3 is less prevalent	[21]
21	Case report	Observational case study	2012	*In vitro* resistance to sulfonamides; testing variability	Documenting and analyzing sulfonamide resistance in the clinical setting, with attempts at understanding the discordance between laboratory resistance findings and successful clinical outcomes from TMP-SMX (Trimethoprim-Sulphamethoxuzoe) treatment.	Successful TMP-SMX treatment despite resistance; highlights lab-clinic discordance	[22]
22	Metagenomics Study	Observational study	2011	sul4 gene: 69% amino acid identity to DHPS; confers high resistance to sulfamethoxazole	To discover and characterize the new sul4 gene in metagenomic datasets, analyze geographic prevalence of sul4, and assess its possible contribution to high sulfamethoxazole resistance.	Discovered a new sul4 gene, widespread in Asia and Europe	[34]

activities [21]. The results showed that farming activities could act as a source of development of antimicrobial-resistant genes and pose a higher risks to the public health systems [12, 22]. Studies on the presence of wastewater contaminants have also shown that almost all sul genes are predominantly detected in cities, which is alarming as it indicates that such resistance genes located in water systems for the communities may be hard to eradicate [23].

From a clinical point of view, various publications advocate for the monitoring of genetic alterations and sul gene distribution in various environments since such changes pose difficulties in treatment. For instance, *Pseudomonas* isolates from clinical samples have shown that in the presence of gene mutations, efflux pumps may work together in enhancing resistance, which presents challenges for the treatment of patients [25]. In the same way, it has been documented through enzyme kinetics studies that some mutations in dihydropteroate synthase (DHPS) interfere with the binding of sulfa drugs [32]. The recent evidence corroborated that the generation of sulfonamide-resistant strains is caused by selective genetic mutations, sheep-like horizontal gene transfer, and environmental factors [35]. Several pieces of evidences indicated that amino acid substitutions in genes known as folP and DHPS are present in multiple bacteria (*e.g. E. coli* and *S. aureus*), where such mutations diminish the drug binding affinity and eventually efficacy of sulfonamide drugs. [35]. Moreover, the environmental research further indicated that certain farming practices, such as the application of manure, enhanced the dissemination of antibiotic resistance genes into the soil and water, since sul genes can disseminated through mobile genetic elements to wide bacterial populations [35]. Also, genomic surveying of the effluent discharged from hospitals, other public health facilities, fecal and febrile wastes has shown that sul1 and sul2 genes exist in high frequencies, suggesting a worrying expansion of resistance in natural and clinical environments [36]. On top of this, the studies showed the role of efflux pumps, which are commonly performed alongside sulfonamide-specific gene mutations as additional mechanisms of resistance [37]. These observations establish the necessity for effective management of containments from health care and agricultural systems by active surveillance and other environmental interventions [38].

Sulfonamide resistance is a major threat to antimicrobial therapy and its solution will require a multidisciplinary approach to understanding its evolution and management. Recently, the discovery of the fourth mobile sulfonamide resistance gene was identified and it gives alarm that how dynamic resistance evolution is occurring [17]. Due to the new identifcation of resistance gene, it was also further studied and new genomic features of antimicrobial resistance in *Escherichia coli* was noted [18]. Scientists also worked on wastewater in their studies and monitored sulfonamide resistance in different geographical regions [20]. The work was

also done on enzymatic engineering and whole-genome sequencing; the methodologies employed revealed cutting-edge tools for studying the sulfonamide resistance pathways and therapeutic targets [39]. These studies strongly indicate that the resistance to sulfonamide could be perceived as undergoing changes in nature and could be seen as a momentum towards precision in surveillance, genomic analyses, and therapy. The surveillance of resistance and combination therapy may lead to heightened success of the treatment. New treatment options including the new generation of folate antagonists, combinations of antibiotics, and bacteriophages are promising but still have to be further researched to be clinically useful.

CONCLUSION

The sulfonamide resistance presents a serious challenge to the healthcare systems; these resistances of organisms are due to mechanisms such as folP mutations, acquisition of sul genes, and efflux pump activities. Genomic understanding, environmental management, and new therapies may provide strategic management of resistance.

RECOMMENDATIONS

The agricultural phenomenon of manure spreader chains of resistance; therefore, better regulatory policies are warranted. Combination therapy may lead to the success of the treatment and a reduction in resistance. New treatment options are required by future research that interact with folate metabolism. This multifaceted strategy will be critical in the fight against sulfonamide resistance and for the protection of public health services.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

SAK supervised the whole review and finalized the manuscript; WM conceived the idea, collected and evaluated the data; MS validated the data and wrote the initial draft of manuscript.

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