Review Article

Interplay Between Microbial Pathogenesis and Pharmacological Management in Congenital Heart Disease: A Narrative Review of Mechanisms, Microbiome Dysbiosis, and Therapeutic Prospects

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Abstract

Cardiovascular diseases (CVDs) remain the foremost global cause of mortality, with congenital heart disease (CHD) representing the most prevalent birth defect and a major contributor to childhood morbidity and mortality. Beyond structural abnormalities, CHD pathophysiology involves dynamic interactions between host genetics, immune dysregulation, and microbial imbalance. Emerging evidence highlights the role of the gut and oral microbiota in modulating inflammation, metabolism, and therapeutic responses, particularly in neonates with critical CHD (CCHD). This review explores the mechanistic links between microbial pathogenesis and pharmacological management in CHD, emphasizing microbiome-mediated effects on cardiovascular pathology and drug efficacy. A narrative literature of eligible studies addressed microbial alterations, infection risks, or pharmacological interventions in CHD or CVD. Data were synthesized thematically into microbial pathogenesis, early-life microbiome dysbiosis, and drug–microbiota interactions. Microbial agents including Chlamydia pneumoniae, Helicobacter pylori, and cytomegalovirus—are implicated in atherogenesis and endothelial dysfunction. In neonates with CCHD, gut dysbiosis is characterized by Enterococcus and Clostridium overgrowth, depletion of Bifidobacterium and Lactobacillus, and enrichment of temperate phages. These microbial shifts correlate with suppressed amino acid and vitamin metabolism, elevated arachidonic acid derivatives, and systemic inflammation, contributing to poor surgical outcomes. Pharmacologically, several cardiovascular drugs such as statins, ACE inhibitors, ARBs, and beta-blockers modulate microbial composition, influencing drug absorption, metabolism, and therapeutic response. Conversely, microbial enzymes can inactivate key drugs like digoxin and alter warfarin efficacy, underscoring the bidirectional interplay between pharmacotherapy and the microbiome. CHD represents a complex intersection of developmental, microbial, and pharmacological determinants. Targeting microbiome imbalance through precision pharmacotherapy, probiotics, and prebiotic interventions offers a promising avenue to improve clinical outcomes. Future work integrating genomics, metabolomics, and microbiome profiling will be essential to achieve personalized cardiovascular medicine and restore host–microbe homeostasis in CHD patients.

Keyword: Cardiovascular diseases, congenital heart disease, ACE inhibitors, pharmacotherapy, microbiome

Introduction

Cardiovascular diseases (CVDs) represent a broad spectrum of disorders affecting the heart and blood vessels, and they remain the leading cause of death globally. According to the World Health Organization (WHO), CVDs accounted for 17.9 million deaths worldwide in 2019, representing approximately 32% of all fatalities [1]. The pathogenesis of these diseases involves complex interactions between genetic, metabolic, environmental, and lifestyle factors [2]. Among the various forms of CVD, congenital heart dise ase (CHD) is unique in its early onset and developmental origins. CHD encompasses a range of structural cardiac malformations arising from aberrations in embryonic organogenesis [3]

It is recognized as the most common birth defect and the leading cause of mortality from congenital anomalies [4]. Globally, CHD affects approximately 10% of all births, with 20–25% classified as critical congenital heart disease (CCHD) requiring early surgical or pharmacological intervention for survival [5].

Despite advancements in neonatal and pediatric cardiology that have improved CHD survival rates to nearly 90% in developed countries [6], mortality and morbidity remain high in low- and middle-income regions [7]. In addition to structural and hemodynamic abnormalities, patients with CHD are at elevated risk of infection, inflammation, and metabolic disturbances that complicate disease management [8]. These complications are often linked to interactions between the cardiovascular system, the immune system, and the host microbiome a relationship increasingly recognized as a determinant of both disease pathogenesis and pharmacological outcomes [9]. The human microbiome the collective genome of microorganisms inhabiting the body plays a vital role in maintaining physiological homeostasis [10]. It is estimated that the gut alone harbors over 1000 species of bacteria, contributing to nutrient metabolism, immune regulation, and the synthesis of essential compounds such as short-chain fatty acids and vitamins [11]. Similarly, the oral microbiome, composed of diverse bacterial, fungal, and viral communities, contributes to mucosal defense and systemic health [12]. Disruptions in microbial balance, or dysbiosis, have been implicated in inflammatory and metabolic disorders, including CVDs, obesity, type 2 diabetes, autoimmune diseases, and cancer [13]. Notably, alterations in gut microbial composition have been associated with the production of pro-atherogenic metabolites, such as trimethylamine-N-oxide (TMAO), which promotes endothelial dysfunction, vascular inflammation, and thrombosis [14]. Emerging evidence indicates that the gut microbiome may be particularly significant in CHD, especially during early life, when microbial colonization influences immune development and metabolic programming [15]. The early-life gut microbiota supports nutrient acquisition, immune tolerance, and epithelial integrity [16]. In neonates with CHD particularly those with cyanotic or critical forms prolonged hypoxemia, altered perfusion, and repeated antibiotic exposure contribute to intestinal dysbiosis and impaired barrier function [17]. Such microbial alterations are thought to exacerbate systemic inflammation and nutritional deficiencies, contributing to perioperative complications and poor postoperative outcomes [18]. Understanding these host–microbe interactions is essential to improving management strategies for CHD patients. Beyond pathogenesis, the microbiome has profound implications for pharmacological therapy. Many cardiovascular drugs including statins, beta-blockers, and antiplatelet agents interact with or are metabolized by gut microorganisms, which can influence drug bioavailability, efficacy, and toxicity [19]. Conversely, pharmacological interventions can alter microbial diversity and function, potentially aggravating or mitigating disease risk. This bidirectional relationship forms the basis of pharmacomicrobiomics, a field exploring how microbial variability contributes to personalized drug responses [20]. In CHD, where pharmacotherapy is often empirical and long-term, elucidating microbiome-mediated drug interactions may enable more precise and effective therapeutic approaches. Overall, the interplay between microbial pathogenesis and pharmacological management in CHD represents a novel frontier in cardiovascular medicine. Deciphering these complex interactions could

advance personalized treatment strategies, optimize perioperative outcomes, and reduce systemic complications in this vulnerable patient population.

Literature Search Strategy

This narrative review was conducted to explore the relationship between microbial pathogenesis and pharmacological management in congenital heart disease (CHD). A systematic literature search was performed across PubMed, Scopus, Web of Science, and Google Scholar databases for studies published between 2000 and 2025. The search terms included combinations of congenital heart disease, microbiome, gut dysbiosis, oral microbiota, pharmacology, cardiovascular drugs, and pharmacomicrobiomics. Relevant studies were identified using Boolean operators (AND, OR) to refine search results [21]. Inclusion criteria encompassed peer-reviewed original articles, reviews, and clinical trials addressing microbial alterations, infection risks, or pharmacological interventions in CHD patients. Studies involving animal models or in vitro experiments were also considered if they contributed to understanding host–microbe–drug interactions. Exclusion criteria included non-English papers, case reports, and studies lacking microbiological or pharmacological data [22]. All retrieved articles were screened by title, abstract, and full text to assess eligibility. Data were extracted on microbiome composition, pharmacological impacts, and clinical outcomes. Key findings were synthesized under thematic categories—microbial pathogenesis, early-life microbiome effects, and drug–microbiota interactions—to identify emerging trends and research gaps [23–25].

Overview of Cardiovascular Pathology and Risk Factors

Cardiovascular diseases (CVDs) remain the predominant cause of global mortality, imposing a significant burden on both developed and developing nations [26]. Atheromatous vascular disease constitutes the primary underlying pathology, manifesting as coronary artery disease (CAD), peripheral vascular disease, and cerebrovascular disease, which often progress to arrhythmias and heart failure [27]. Key risk factors include hypertension, diabetes mellitus, hyperlipidemia, obesity, and smoking [28–30]. Moreover, low cardiorespiratory fitness has been independently linked to cardiovascular and metabolic disorders [31]. Atherosclerosis, a chronic inflammatory condition, represents the central mechanism underlying CVDs such as stroke, myocardial infarction (MI), and heart failure. The process begins with endothelial activation, lipid deposition, and immune cell recruitment, leading to fibrous plaque formation and luminal narrowing [32]. Progressive cholesterol crystal accumulation and smooth muscle proliferation culminate in fibrosis and calcium deposition, resulting in vascular stiffness and occlusion [33].

Calcific Aortic Valve Disease and Endothelial Inflammation

Calcific aortic valve disease (CAVD) is another common cardiovascular pathology characterized by progressive valve mineralization and hemodynamic obstruction [34]. Once viewed as a degenerative condition, CAVD is now recognized as a chronic, cell-mediated inflammatory process driven by endothelial dysfunction, oxidative stress, and lipoprotein infiltration [35,36].

Hemodynamic stress and shear forces initiate endothelial injury, promoting the expression of adhesion molecules such as VCAM-1 and ICAM-1, which mediate immune cell recruitment and fibroblast activation [37,38].

In early stages, aortic sclerosis manifests as microcalcification and valve thickening, whereas

advanced disease leads to calcific nodules and leaflet rigidity, resulting in impaired blood flow [39-41].

Infective and Rheumatic Cardiac Diseases

Infective endocarditis (IE) remains a life threatening cardiovascular condition, commonly associated with prosthetic valves and implantable cardiac devices [42]. Epidemiological data show increasing incidence due to aging populations and device-related infections [43]. IE typically involves the left-sided heart valves and manifests as acute or subacute forms depending on pathogen virulence [44,45]. Staphylococcus aureus is now the leading etiological agent, followed by Streptococcus viridans and Enterococcus spp. [46,47]. Rheumatic heart disease (RHD) persists as a major cause of mortality in low-income countries, where Group A Streptococcus infections remain endemic [48]. The autoimmune sequelae of acute rheumatic fever lead to chronic valvular fibrosis and dysfunction, primarily affecting the mitral valve [49,50]. RHD continues to affect more than 20 million people globally, representing a preventable burden in cardiovascular health [51].

Microbial Pathogenesis in Atherosclerosis and Cardiovascular Disease

Mounting evidence links microbial infections to atherogenesis and cardiovascular pathology [52]. Chlamydia pneumoniae and Cytomegalovirus (CMV) have been identified within atherosclerotic plaques, suggesting a causative role in endothelial activation, lipid oxidation, and immune-mediated plaque instability [53]. Chlamydophila pneumoniae phospholipase D (CpPLD) specifically drives Th17 cytokine-mediated inflammation, enhancing lesion vulnerability [54].

Similarly, Helicobacter pylori infection has been correlated with coronary heart disease (CHD) and ischemic heart disease (IHD), owing to systemic inflammation, elevated triglycerides, and decreased HDL levels [55]. Collectively, these infections foster vascular dysfunction and promote the development of prothrombotic states [56].

Viral and Circulating Microbiota Contributions

Cardiotropic viruses such as human cytomegalovirus (HCMV) and Coxsackie B virus (CVB) are increasingly implicated in cardiovascular pathology [57,58]. HCMV-infected endothelial cells upregulate prion-flammatory and calcification-related genes, accelerating aortic stenosis and coronary atherosclerosis, whereas CVB infection can result in viral myocarditis and chronic cardiomyopathy [59,60]. Furthermore, advanced sequencing techniques have revealed the presence of microbial DNA and metabolites in the bloodstream of patients with cardiovascular disease, contradicting the traditional concept of sterile blood [61]. Blood microbiota dysbiosis, marked by elevated Firmicutes and Bacteroidetes and decreased microbial diversity, correlates with systemic inflammation, gut permeability, and endothelial dysfunction [62–64].

Gut Microbiome Alterations in Congenital Heart Disease

Recent studies demonstrate that neonates with critical congenital heart disease (CCHD) exhibit marked gut dysbiosis compared with healthy infants. CCHD patients display increased microbial α-diversity but disrupted ecological balance, characterized by the overgrowth of Enterococcus, Klebsiella, and Clostridium and depletion of Bifidobacterium and Lactobacillus

[65,66]. Parallel analysis of the gut virome shows enrichment of temperate phages, including Siphoviridae and Myoviridae, which harbor virulence and antibiotic resistance genes, modulating bacterial adaptation and persistence [67,68]. Metabolomic profiling reveals suppressed amino acid, fatty acid, and vitamin metabolism, with upregulation of arachidonic acid derivatives hallmarks of oxidative stress and inflammation [69]. Elevated Enterococcus faecium abundance correlates with increased gut permeability markers (zonulin, D-lactate, LPS) and proinflammatory cytokines (IL-1β, IL-6, TNF-α), serving as an independent predictor of adverse surgical outcomes in CCHD [70].

Pharmacological Interactions with the Microbiome

Pharmacological therapies for CVD and CHD can profoundly influence the microbiome, altering drug bioavailability and therapeutic efficacy [71]. Statins have been shown to reduce Faecalibacterium prausnitzii while increasing Bacteroides species, potentially modifying lipid metabolism and anti-inflammatory responses [72]. Conversely, angiotensin receptor blockers (ARBs) promote Akkermansia muciniphila proliferation, improving intestinal barrier function and blood pressure regulation [73]. Warfarin disrupts vitamin K-producing bacterial populations, affecting coagulation homeostasis [74]. Microbial metabolism also modifies drug potency: Eggerthella lenta inactivates digoxin, while Bacteroides species alter statin absorption, and oral pathogens such as Porphyromonas gingivalis interfere with antiplatelet drug efficacy [75]. These findings underscore the bidirectional interaction between microbiota and cardiovascular pharmacology, highlighting the need for microbiome-informed therapy [76,77].

Discussion

This review underscores the multifaceted interplay between microbial pathogenesis, pharmacological interventions, and host–microbiome homeostasis in congenital and acquired heart diseases. Accumulating evidence suggests that cardiovascular medications themselves can alter the composition, diversity, and metabolic activity of the gut microbiome, potentially modulating therapeutic efficacy and adverse outcomes [78]. Medication-induced dysbiosis affects drug metabolism, absorption, and bioavailability through microbial enzymatic pathways, indicating a bidirectional interaction wherein drugs reshape microbial ecology, and in turn, microbial metabolites influence drug performance [79,80]. Despite these insights, this field remains in its infancy. Only a limited number of cardiovascular drugs—such as statins, ACE inhibitors, ARBs, and antiplatelet agents—have been systematically studied for microbiome interactions [81]. There is a clear need for large-scale, multi-omic investigations encompassing diverse populations and a broader drug spectrum. Expanding this knowledge base will be pivotal for developing personalized pharmacomicrobiomic frameworks, enabling individualized treatment strategies that consider each patient's unique microbial and metabolic profile [82,83]. Such integration promises to revolutionize cardiovascular care by optimizing drug response, minimizing adverse effects, and restoring microbiome-mediated homeostasis. However, current research faces critical limitations. Much of the existing evidence derives from small-scale or preclinical studies, which limits generalizability to clinical practice [84]. Furthermore, inter-individual microbiome variability complicates the establishment of standardized therapeutic models. Ethical, technical, and methodological challenges also

hinder comprehensive human trials in this domain. Many investigations focus narrowly on specific drugs or microbial taxa, overlooking the broader microbial networks and inter-drug interactions that influence systemic pharmacology [85,86]. To overcome these constraints, future work must involve multi-center, longitudinal clinical trials integrating metagenomic, metabolomic, and pharmacokinetic data from heterogeneous cohorts [87]. Critical congenital heart disease (CCHD) exemplifies the intersection between host genetics, immune physiology, and microbial ecology. The findings from recent metagenomic studies reveal that CCHD neonates harbor profound gut microbial dysbiosis, characterized by depletion of beneficial Bifidobacterium and Lactobacillus and an overrepresentation of opportunistic taxa such as Enterococcus and Clostridium [88]. This imbalance disrupts the metabolic production of short-chain fatty acids (SCFAs), aromatic lactic acids, and B vitamins key molecules in maintaining epithelial integrity and immune regulation. Mechanistically, the loss of Bifidobacterium-associated genes involved in human milk oligosaccharide (HMO) utilization leads to impaired fermentation and reduced SCFA output, weakening mucosal immunity and predisposing to inflammation [89]. In contrast, the overgrowth of Enterococcus species enhances inflammatory cascades via arachidonic acid metabolism, elevating serum cytokines (IL-1β, IL-6, TNF-α) and biomarkers of gut permeability (zonulin, D-lactate, LPS). These findings collectively link microbial imbalance to systemic inflammation and adverse surgical outcomes in CCHD infants [90]. The gut virome further contributes to this pathological ecology. Enrichment of temperate bacteriophages particularly Siphoviridae supports bacterial adaptation and persistence through horizontal gene transfer and virulence enhancement [91]. Such phage–bacteria mutualism fosters Enterococcus dominance and sustains inflammatory signaling, revealing a cross-kingdom mechanism of microbial-host coevolution that may shape disease trajectory [92]. Understanding these dynamics opens avenues for microbiome-targeted interventions ranging from phage therapy to probiotic supplementation to restore homeostasis in neonatal CHD. The integration of pharmacomicrobiomics into CHD management represents a promising frontier. As the gut microbiome modulates drug absorption, metabolism, and signaling, individualized profiling could inform the dosing and selection of ACE inhibitors, ARBs, statins, or endothelin antagonists to optimize outcomes [93,94]. In addition, microbiome modulation through Bifidobacterium supplementation, prebiotics, or non-digestible oligosaccharides may enhance immune resilience and reduce perioperative inflammation in vulnerable infants [95]. Despite the expanding therapeutic landscape, clinical research in CHD remains disproportionately underrepresented. Less than 10% of all cardiovascular trials focus on congenital conditions, and fewer than 1% target pediatric populations [96]. Existing trials such as those assessing bosentan, macitentan, or riociguat in pulmonary arterial hypertension secondary to CHD—demonstrate therapeutic benefit, yet the evidence base remains fragmented [97–99]. To bridge this gap, novel trial designs employing digital simulations, global registries, and AI-assisted analytics could facilitate patient recruitment and real-time data harmonization across centers [100]. Furthermore, identifying genomic polymorphisms within the renin–angiotensin–aldosterone system (RAAS) and adrenergic pathways may enable precision pharmacogenomic approaches, ultimately

improveing ventricular function and survival [101].

Conclusion

Congenital heart disease remains a complex, multifactorial disorder that demands multidisciplinary and personalized management strategies. The integration of microbiome science into cardiovascular pharmacology offers unprecedented potential to refine therapy and prognosis. Current evidence highlights a reciprocal relationship between microbial communities and cardiovascular pathophysiology whereby dysbiosis not only drives inflammation and metabolic dysfunction but also modifies drug efficacy and toxicity Future directions should emphasize systematic, large-scale clinical investigations that incorporate genomic, microbial, and pharmacological parameters into cohesive predictive models. By aligning microbiome modulation with optimized pharmacotherapy, clinicians can move toward precision cardiology enhancing efficacy, minimizing harm, and promoting sustainable health outcomes for patients with CHD. Ultimately, restoring the delicate equilibrium between microbial ecosystems and the cardiovascular system may represent one of the most promising frontiers in next-generation cardiovascular medicine.

Conflict of interest

None

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