# *Salmonella* Myocarditis: Suspecting and Estimating the Associated Clinical Complications

Sandeep Satapathy[1,*], Kashyap Bhuyan[2,*] and Smruti Ranjan Nayak[2]

[1]Department of Biological Science, Indian Institute of Science Education and Research, Bhopal, India. [2]Department of Microbiology, Orissa University of Agricultural Technology, Bhubaneswar, India. *These authors contributed equally to this work.

**ABSTRACT:** *Salmonella* myocarditis has been a case of medical underestimation in terms of the occurrence, identification, and treatment decision for most patients. One prominent reason is the lack of significant scientific literature or reports highlighting the same. In addition, most often the complications associated are not exclusively limited to myocardiac infection and thus end up being neglected or undiagnosed. Cases of virus-induced myocardiac infection and the virus-mediated exacerbation are well realized in our scientific community, but the case is not same for bacteria-related myocardiac infection. Rarity of bacteriological myocardiac infection and the lack of prompt and first hand medical suspicion have led to this consistent medical negligence, ultimately resulting in further complications. In this review, we discuss about the case histories of *Salmonella* myocarditis and the existing treatment options. This review also tries to summarize the most common observed electrocardiographic and functional changes noted in cases of *Salmonella* myocarditis, to enable clinicians be updated with various markers for suspicion of *Salmonella*-triggered infection and ultimately resulting in improved clinical diagnosis and treatment.

**KEYWORDS:** *Salmonella*, ST-T segment, Q waves, chest pain, myocardiac infarctions, rhabdomyolysis, multidrug resistance

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**CORRESPONDENCE:** satapathys@live.in

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## Introduction

With a worldwide prevalence accounting for 16–33 million of cases per year, *Salmonella* myocarditis still remains a victim of neglected clinical estimation and diagnosis along with infrequent or delayed suspicion by clinicians. One of the obvious reasons is the inconsistent and heterogeneous disease manifestation and the unusual resemblance of symptoms with other forms of inferior myocardiac infarctions or myocardiac injury.[1]

*Salmonella* myocarditis has witnessed global prevalence with higher cases during seasonal fluctuations. Most commonly reported cases belong to developing countries such as Nepal, Pakistan, India, Turkey, and Greece, and few cases report of the incidence among travelers from UK and USA who have had recent trips to the developing countries.[1] The geographical bias of higher disease prevalence among developing countries is due to the lack of proper sanitation and hygiene and food- and water-based contamination that lead to frequent exposure and attack by *Salmonella* spp.[2]

*Salmonella* spp. most commonly associated with typhoid and other gastroenteritis infections present a noncomplicated and nonfatal clinical case, which most often leads to delayed treatment, leading to further fatality and medical complications. In these cases of immunocompetent persons, bacteriological myocarditis involves secondary infection of the myocardium[1,3] (Fig. 1). Typhoid, an otherwise water- and foodborne gastrointestinal infection, can led to life-threatening situations, where reports exist of cases involving cardiac arrest, multiorgan failure,[2] and incidences of mycotic aneurysms, acute congestive heart failure, and osteomyelitis. These incidences range from viable to latent forms of clinical manifestations[3] (Fig. 1).

*Salmonella* myocarditis is often reported to be a case of complicated salmonellosis or *Salmonella* sepsis with occurrence both among adults and young children[4] (Fig. 1). Growing evidence indicates that the case gets complicated even for immunocompetent patients with a sound health profile and no earlier history of medical complications. Rafid Al-aqeedi et al had presented a case of healthy young adult man from Qatar with no previous clinical history to have multiple-organ failure due to *Salmonella* myocarditis.[4] However, the existing bias for diagnosis and the incidental overlapping of the symptoms with other forms of inferior cardiac infarctions have led to reports of morbidity and mortality associated with *Salmonella* infections.[4]

## The Biology of Myocarditis and *Salmonella* Infection

Myocarditis is commonly caused by viral infections such as Coxsackie viruses and adenoviruses (rarely by bacterial infection like *Salmonella*), thereby severally implicating virus in its etiology.[2,4] In addition, immune-mediated inflammation and

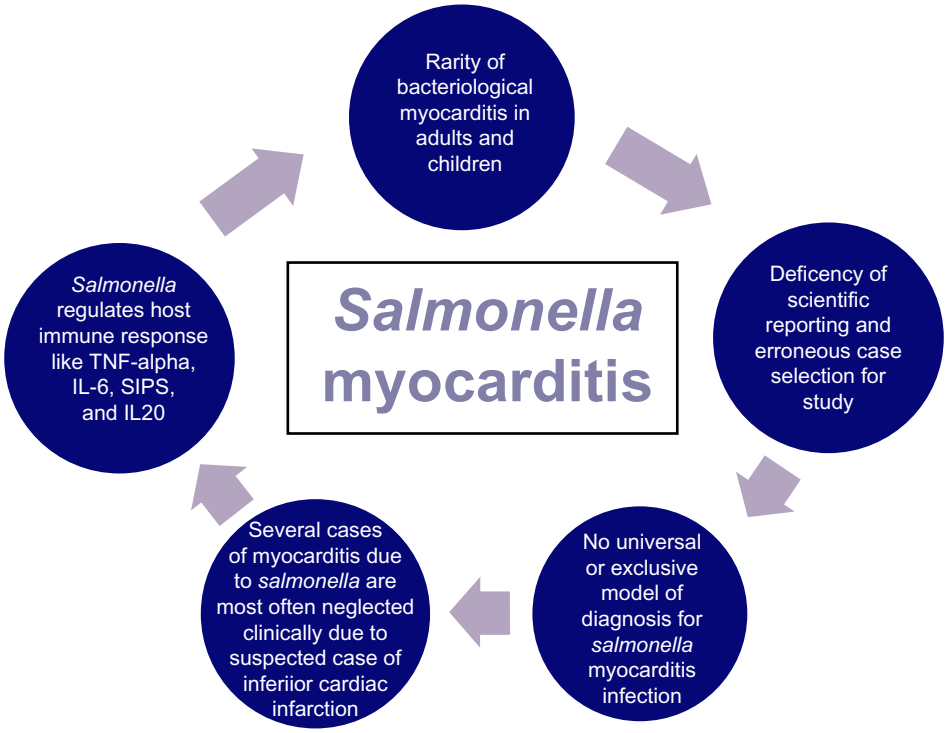


**Figure 1.** The realms of *Salmonella* myocarditis and major causes for the clinical underestimation of the disease.

toxic accumulation and exposure of the myocardium can lead to myocarditis.[5] It is a form of myocardial sepsis with the most common option of treatment being antibiotic prophylaxis.[6] Thorough clinical investigations have revealed infrequent or rare reports of bacteriological association of myocarditis, and thereby we aim to present a landscape report of the "what and how of the disease." Typhoidal gastroenteritis has been related to cases of further complication resulting from subsequent myocarditis. However, nontyphoidal gastroenteritis presents a case of a self-limiting foodborne disease and has not been much discussed from the perspective of myocarditis.[6] The pathological confirmation of *Salmonella* comes from the blood culture, and this is facilitated due to bacteremia in the otherwise sterile blood environment.[7]

The commonly reported species of *Salmonella* causing myocarditis are

- *Salmonella choleraesuis* (associated clinical complications – chest pain, shortness of breath, ventricular rupture, and sudden death).[8]
- *Salmonella typhimurium* (associated clinical complications – tachycardia and palpitation, cardiogenic shock, and sudden death).[9]
- *Salmonella hiedelberg* (associated clinical complications – cardiac arrest).[10]
- *Salmonella virchow* (associated clinical complications – sudden infant death).[10]
- *Salmonella enteritidis* (associated clinical complications – gastroenteritis).[9,10]

## Pathogenicity of *Salmonella* and the Possible Role in Myocarditis

*Salmonella typhi*, the commonly known gram-negative bacteria that cause typhoid fever in human beings, have very specific pathogenic expression pattern of genes and this distinguishes them from their nonpathogenic counterparts.[9] The specific pathogenic genes that render infectivity are found in a particular order within the bacteria and these are called Pathogenicity Islands (PIs).[10] *Salmonella* PIs code for a specific protein called Type III secretion system,[11] which regulates the molecular virulence and the bacterial propagation both in case of usual typhoidal fever and in case of life-threatening associated complications such as myocarditis, cardiogenic shock, and congestive heart failure.[11]

One of the strategies adopted by the bacteria include induction of apoptosis of macrophages to evade the host immune system, and this feat is achieved by secretion of *Salmonella* invasion proteins (SIPs), namely Sip A, B, C, D, and E.[12] In addition, the lipopolysaccharide-binding protein along with CD14 helps in macrophage-mediated cell signaling.[12] Since *Salmonella* invades macrophages and directs it for apoptosis, the most important defense system for *Salmonella* infection includes neutrophils followed by nuclear cells.[13] These neutrophils produce a wide range of cytokines such as interleukin (IL)-2, IL-6, IL-8, IL-1, interferon-γ, and tumor necrosis factor-alpha.[12]

The clearance of bacteria from the liver cells requires CD28-dependent activation of T-helper cells.[11,12] In addition, T-cell receptors (such as alpha and beta T cell), major

histocompatibility complex class II genes, dendritic cells, and B cells are active players modulating the T-cell immune response to *Salmonella*.[13]

Therefore, one of the ideas we propose is to understand how these molecular effectors of *Salmonella* propagation and host immune response regulate the cardiac damage of myocytes or in other words cause myocarditis. It is crucial to explore the pattern of expression for these molecular effectors among a cohort of myocarditis patients consisting of those with and without *Salmonella* infection.

## Biomarkers

The specific molecules that are differentially either upregulated or downregulated add to the charecterization of the disease and help in both the diagnosis and prognosis for the same. However, the science of biomarker identification and validation mostly targets spatiotemporally upregulated molecules during the diseased state. So, understanding the known biomarkers for *Salmonella*-associated myocarditis will add further to the scope of this review[13–17] (Table 1). We have summarized the list of identified and potential biomarkers in a tabular form.

## Diagnosis and Detection Modalities

Clinical diagnosis of *Salmonella* myocarditis involves electrocardiographic monitoring for change of pattern (change in Q waves, ST-T segment changes, etc.)[14] and physical symptoms of stiffness or difficulty of breathing,[15] chest pain,[16] sweating,[16] palpitation, shortness of breath, ventricular rupture, and tachycardia).[16] In addition to electrocardiogram (ECG) reports, sample biopsy and troponin detection (detection of cardiac enzyme level) confirm for possible myocardial infection post-salmonellosis.[17]

*Echocardiography* is one such powerful technique, which helps in distinguishing the cardiac abnormalities in case of myocarditis (*Salmonella*-infected cases will have inflammatory-associated responses) in comparison to those with non-inflammatory cardiac changes.[18] Most reported cases of myocarditis exhibit regional wall abnormalities along with the dysfunction of ventricular and diastolic functions.[16] *Salmonella*-associated exacerbation of cardiac dysfunction results in thickened, nondilated with lesser contractile ability of the left ventricle, resulting from the sudden and hyperactivation of inflammatory immune response.[17] The points of distinction for such a comparison encompass ventricular function, chamber size, wall thickness, and effusion of pericardial fluid.[17]

*Endomyocardial biopsy (EMB)* along with the Dallas criteria is one of the most commonly used standards for determining myocarditis. But several of these reports have indicated a lower sensitivity 10%–22%,[18] arising from error in sampling, subjectivity in interpretation of samples, and absence of

**Table 1.** Summary of known biomarkers and the details on their usage and reliability for myocarditis detection and clinical management of treatment.

| BIOMARKER TYPE | BIOMARKER | DIAGNOSTIC RELIABILITY | OVERLAP WITH OTHER CARDIAC ABNORMALITIES |
|---|---|---|---|
| Inflammatory biomarkers | Erythrocyte Sedimentation Rate (ESR) Reactive C protein levels | Low to average | Similar with cases of acute pericarditis |
| Cardiotropic viruses | Polyclonal antibodies secreted in response to viral infection (IgG and IgM) | No-direct correlation established | The elevated levels of IgG are also exhibited in cases of non-viral heart diseases thus the validation of raised IgG levels in viral infected cases becomes ambiguous. |
| Non-cardiotropic viruses | Polyclonal antibodies secreted in response to viral infection | Mahfoud et.al (2011) report the lack of any correlation between the viral sera and the electromyocardial biopsy reports. | Similar to the cardiotropic viral abnormalities. |
| Cardiac hormones, enzymes and proteins | Troponin<br>Creatinine Kinase<br>Brain natriuretic peptides<br>Cytokines<br>Extracellular matrix degradation markers Galectin3<br>Pentraxin 3<br>Growth differentiation factor 15 | High sensitivity<br>Low sensitivity<br>Non-specific<br>Non-specific<br>Non-specific<br>Non-specific<br>Non-specific | Most of these hormones/proteins/enzyme based biomarkers are also measured in non-salmonella associated myocarditis and even in normal cases. |
| Cardiac autoantibodies detected in serum | Autoantibodies specific to cardiac and muscle derived autoantigens (IgG class of antibodies) | Specific autoimmune biomarkers useful for analyzing the familial risk and the role of immuno-modulation in non-infected myocarditis cases. However, lacks commercially available test kit for cardiac autoantibodies. | Not reported |

prognostic approach in this method. Most of the cases of positive EMB however have been reported from necrotomies.[19]

The sensitivity and specificity of *troponin* have been the best for detection of myocarditis in comparison to other known biomarkers of mycotic injury.[19] Nevertheless, with a restricted sensitivity of only 34%, the diagnosis myocarditis becomes not so easy with troponin level measurement.[19] Reports recommend use of troponin for detection in gastroenteritis patients with complications such as chest pain, cardiac shock, and tachycardia.[18] But in several existing medical case reports, either biopsy or troponin detection has failed or has not been performed, so the generalized applicability of these detection methods is still subjective and debatable.

*Nuclear imaging* is another technique for evaluation of myocarditis but the usage has been least recommended due to the risk of exposure to radioactive substances as well as the lower sensitivity and availability of the radionuclide/antimyosin antibody for a valid detection.[19]

Modern imaging techniques such as *contrast-enhanced magnetic resonance imaging* (MRI)[19] have been instrumental in efficient detection of myocarditis. These have facilitated the existing conventional detection methods. The use of MRI should be considered especially in circumstances where both conventional imaging methods and other diagnostic tools fail to detect myocardial dysfunction.[20]

## Case Studies and Disease Pattern

**ECG signatures of *Salmonella* myocarditis.** Adhikari et al (1995)[21] studied the electrocardiographic changes of 100 patients suffering from enteric fever. Only 2 out of 100 had symptoms such as hypotension, congestive heart failure, and persistent tachycardia.[18] The ECG data over a time series revealed sporadic and ambiguous data, which could not confirm the incidence of myocarditis.

Notably, the common abnormalities reported in the ECG report of these patients with enteric fever and myocarditis involved[18–20]:

- Q-Tc prolongation in 29% of cases.
- ST-T changes in 20% of cases.
- Bundle branch block in 7% of cases.
- First degree A-V block in few cases.

***Salmonella* myocarditis in otherwise healthy patients.** Pangiotis et al (2011)[22] reported a case of 18-year-old healthy male patient from Greece who had developed myocarditis after *Salmonella* infection.[18] Previous medical report clarified no cardiac risk factors (eg, coronary artery risk factors, valvular abnormality, etc.). The reports indicated increased blood pressure, raised temperature, and heartbeat of 100 per minute, with a respiration rate of 25 per minute. From the literature survey, it reveals that such cases of infective endocarditis and myocytic injury in myocarditis due to *Salmonella* only account for 1.3%–4.8% of such cases reported annually.[18]

***Salmonella* myocarditis in patient with Wolf–Parkinson–White syndrome.** An 18-year-old male with Wolf–Parkinson–White (WPW) syndrome had symptoms of 9 days of fatigue and shaking chills, accompanied with sweating, chills and palpitations.[19] The patient was initially confused for inferior myocardial infarction as the electrocardiographic signatures suggested similar patterns. However, subsequent pathological diagnosis confirmed the patient to be suffering from myocarditis due to *Salmonella* infection. The electrocardiographic data revealed flat to inverted T waves and ST-segment changes. The report mentions that these specific electrocardiographic changes worked as timely alert for diagnosis of myocarditis due to *Salmonella* infection.[20]

The report uniquely identified WPW syndrome as two distinct types:

- *Type* 1 *WPW with* delta waves of approximately 30° with Q wave changes similar to inferior myocardial infarctions (on derivations LII, LIII, and a VF).[20]
- *Type* 2 *WPW with* ST segment depression suggesting *Salmonella* myocarditis (anterior derivations on $V_1$–$V_5$).[20]

***Salmonella* gastroenteritis causing Myocarditis and Rhabdomyolysis.** *Salmonella* gastroenteritis which otherwise is known to be a common food borne disorder rarely complicates the disease into a life-threatening situation. However, Al-Shamkhani et al.[23] reported a case (28-year-old male with no prior medical history) where *Salmonella*-induced enteritidis led to incidence of both myocarditis and rhabdomyolysis.[24] As already mentioned, bacterial cause for myocarditis is 1.3%–4.8% of all the known cases, similar figure exists for rhabdomyolysis (5% of all such known cases).[24] Notably an early detection and efficient chemotherapy resulted in successful recovery of the patient from both the rare and life threatening complications.

***Salmonella* myocarditis in travelers.** Shah S (2013)[25] reported a case of 25-year-old male from UK who returned from a trip reported with sudden pain in chest. The ECG data revealed infero-lateral ischemic changes with increased troponin and inflammatory biomarkers and salmonellosis (blood culture data).[24] However, the detection was diluted preliminarily due to other healthy markers such as normal sized left ventricle (ECG data), active systolic function, stable valves, and normal coronary arteries (angiography data).[26]

***Salmonella* myocarditis with multidrug resistance.** *Salmonella typhi* infection in children was reported to be associated with multidrug resistance. The study involved 48 children who had *Salmonella* infection and among these 30 patients confirmed for myocarditis.[26] The common complications noted were cardiac shock, myocarditis, encephalopathy and paralytic ileus.[27] The multidrug-resistant *Salmonella* myocarditis, however, could be successfully treated with combination of gentamicin and cephalexin (antibiotic prophylactic treatment).[28]

**Salmonella myocarditis among pediatric patients.** With the commonly reported cases involving immunocompetent and compromised adults suffering from *Salmonella* myocarditis, it is essential to discuss about its prevalence among pediatric patients.[29] The case being reported is from Turkey in which 66 pediatric patients within 14 years old (confirmed with *Salmonella* infection) were found to be positive for secondary involvement of myocardiocytes. Even two other patients confirmed more severe case of both myocarditis and pericarditis.[30]

In addition to the commonly used antibiotic prophylactic treatment, pericardiodentesis and pericardiectomy have also been used for recovering the patients.

## Future Perspectives

As an augmentation to our efforts to cure *Salmonella* myocarditis, it is imperative to understand the molecular signaling crosstalks that involve this bacterial mediated myocardiac infection and the expression patterns of the key immune molecules and the bacterial propagation mode.

The commonly reported symptoms such as sudden cardiogenic shock, cardiac arrest palpitation, and chest pain must be noted in patients with immediate history or simultaneous *Salmonella* infection. The change in Q waves and depression and flattening of ST-T segments are some of the electrocardiographic markers of myocarditis, which can be helpful in confirming the disease along with biopsy and troponin detection. The common modality of treatment involves a combinatorial antibiotic-based prophylactic treatment aided by blood culture and bacterial strain analysis. Therefore, *Salmonella* myocarditis needs more scientific and clinical attention with focus on recording, analyzing, and evaluating medical cases of disease initiation and propagation.

## Conclusion

In most cases of myocarditis post *Salmonella* infection, the real incidence largely remains neglected and underestimated. The exact incidence of *Salmonella* myocarditis is very hazy as various authors quote differing rates of prevalence, and this is mostly due to lack of clear rules for case selection and nonstandard diagnostic criteria. The deficiency in prompt and proper clinical suspicion along with the rarity of bacteriological myocarditis has limited our approach and understanding of how *Salmonella* results in myocarditis and further cardiac complications in healthy patients. At one point this indicates that there is no dearth of scientific experiments that can be performed to unravel this mystery of co-infection or cardiac damage triggered by bacterial infection. However, the fact that there is a major gap in the scientific reports and case studies of *Salmonella* myocarditis limits our understanding of the disease etiology and the propagation pattern.

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## Author Contributions

Concept conception and draft preparation: SS. Manuscript preparation and valuable content editing: KB. Graphic presentation, manuscript editing, and preparation: SRN. All authors reviewed and approved the final manuscript.

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