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Review Article

An Umbrella Literature Review on Aortopathy and Fluoroquinolone Use

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ABSTRACT

Background: Mortality from sepsis continues to remain high in hospitalized patients worldwide. Previously, the conceptual model of sepsis was based on the systemic inflammatory immune response syndrome, an *adaptive* model. In 2016, a new definition of sepsis was proposed as a *dysregulated* host response to infection. However, until now, no model has been proposed to elucidate what immunologic and metabolic mechanisms are dysregulated.

Aim: We sought to propose a new directional model of sepsis, from adaptive to dysregulated. This will help to elucidate evidence-based immunologic and metabolic mechanisms that are dysregulated in sepsis.

Methods: The literature was reviewed for themes comparing and contrasting sepsis before and after the 2016 consensus definition of sepsis. Themes from research published after 2016 were described, connecting immunologic and metabolic mechanisms in sepsis. This information further informs the results of earlier research published by the primary author.

Results: In recent years, evidence of dysregulation in innate immune signaling and cellular respiration has been uncovered. The authors constructed a new conceptual model of sepsis to elucidate the current definition of sepsis as a dysregulated host response. Themes uncovered in sepsis research post-2016 were used to guide the construction of the model.

Conclusion: The model proposed here supports clinicians in applying the current definition of sepsis to a physiological model. This can benefit clinicians by offering new ways of recognizing sepsis and researchers by recommending a physiologic model to advance sepsis research.

Keywords: Aortopathy, aortic aneurysm, aortic dissection, aortic rupture, fluoroquinolones

INTRODUCTION

Aortopathy and Fluoroquinolones

The aorta is the largest artery in the body, and the vascular outflow tract from the left ventricle is responsible for delivering oxygenated and nutrient-rich blood from the heart to the body. An aortopathy involves impaired remodeling of the aortic wall with

resultant aneurysmal dilation, weakening, dissection, or rupture (Wu et al., 2013). Aortopathies can be inherited or acquired. Inherited aortopathies are frequently associated with Marfan's syndrome, Loeys-Dietz syndrome, bicuspid aortic valve, or Ehlers-Danlos syndrome (Lucchese & Bilkhu, 2022). Acquired aortopathies can occur from syphilis, giant cell arteritis, Takayasu's arteritis, smoking, or even trauma (Salameh et al., 2018). An aortic aneurysm implies an irreversible focal dilation of the aorta to more than 1.5 times its original size (Kent, 2014). It can affect different regions of the aorta. When the aneurysm affects the aorta above the diaphragm it is referred to as thoracic aortic aneurysm (TAA). Aortic aneurysms below the level of the diaphragm are referred to as abdominal aortic aneurysms (AAA). Aortic aneurysm can be asymptomatic and can culminate in sudden death from dissection or rupture. An aortic dissection ensues when the inner layer of the aorta splits apart, with a resultant filling of blood through the defect occupying the space between the inner and outer layers of the aorta. When a dissected aorta is ruptured, the intravascular components, including the blood, are extravasated. The rupture of an aortic aneurysm or aortic dissection is a rare, but represents an emergent condition, even more critical when associated with an aortopathy (Harris et al., 2019). Annual mortality related to aortic aneurysms is estimated to be approximately 200,000 globally (Liu et al., 2020). The annual mortality rate associated with acute aortic events has increased in the United States, with noticeable increases in those of Black race and women (Nazir et al., 2022).

Pharmacological treatment has a limited role in the clinical management of aortic aneurysms. Surgical correction (either open or endovascular) remains the only option for definitive treatment (Liu et al., 2020). Acute type A aortic dissection (dissection involving the ascending aorta) is a surgical emergency, and the mortality rate is up to 30%. Surgical repair at the earliest possible time is the recommended treatment for this scenario (Sabe et al., 2021). A median sternotomy with replacement of the aortic arch is the usual approach for Type A aneurysmal dissection or rupture. Endovascular techniques for Type A aneurysmal repair (such as Endo Bentall procedure) are technically difficult and are employed less frequently. Endovascular techniques are becoming more popular for the treatment of type B (aneurysm of the descending thoracic aorta) dissections (Fukui, 2018). Some patients may not be ideal candidates for aortic interventions because of complications of aortic dissection/rupture

including stroke, cardiogenic shock, or visceral malperfusion (Sabe et al., 2021).

Significance of Fluoroquinolone Use in Aortopathy

How a commonly used antibiotic, fluoroquinolone (FQ) can become the culprit in aortopathy is a relatively novel and unfrequented topic in clinical practice. Fluoroquinolones are one of the commonly prescribed antibiotics for respiratory infections, urinary infections, and certain sexually transmitted infections. Common FQs include ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, and delafloxacin. Fluoroquinolones work as a bactericidal agent by directly inhibiting bacterial deoxyribonucleic acid (DNA) synthesis. They possess high oral bioavailability and exhibit activity against common respiratory pathogens, gram-negative bacilli, and aerobes. Some FQs are antipseudomonal and are effective against certain gram-positive organisms, anaerobes, and mycobacteria (Hooper, 2023).

While considering the use of FQs, prescribers are often concerned about the risk of musculoskeletal injuries and tendinopathies associated with its use. Although the Food and Drug Administration (FDA) issued a warning about the risk of aortic dissection and rupture with FQ use in 2018 (Buehrle et al., 2021), the extent to which this warning is considered is unclear. Despite FDA warnings and cautions on FQ use, studies have reported inadvertent use of FQs in patients with known aortopathy and those with a genetic predisposition for aortopathy, such as Marfan syndrome, even in inpatient settings (Frankel et al., 2019). Frankel et al. (2019) reported that 19% of patients with aortopathy admitted for aortic repair received FQ during a hospitalization before the repair. Although the number of FQ prescriptions by different specialties had decreased sufficiently following multiple safety warnings by FDA, infectious disease specialists and nurse practitioners account for increasing use of FQs (Buehrle et al., 2021).

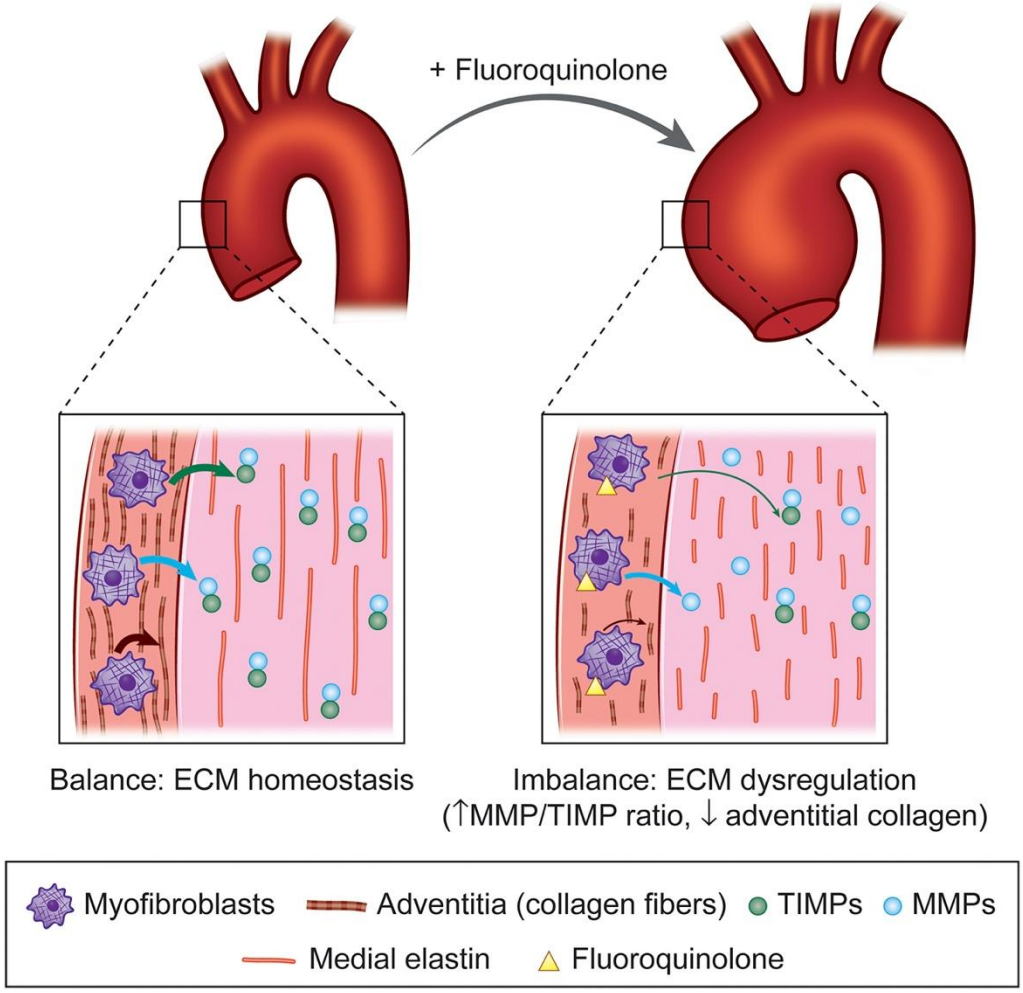
Effects of Fluoroquinolones on Aorta

A review of the structure of the aorta is essential before understanding the effects of FQs on the aortic wall. The wall of the aorta is a three-layered wall comprised of a complex arrangement of smooth muscle cells, endothelial cells, fibroblasts, and extracellular matrix (ECM). The ECM is a key component of the aortic wall synthesized by the smooth muscle cells and fibroblasts (Jana et al. 2019). The ECM and cellular components of the aorta are closely regulated by a variety of interacting pathways that include tissue

inhibitors of metalloproteinases and matrix metalloproteinases (MMPs) (Ibrahim & Szeto, 2022). Fluoroquinolones can produce ECM dysregulation in the aorta, causing accelerated degradation of collagen that, in turn, causes impaired deposition of collagen. Fluoroquinolones alter the equilibrium of matrix metalloproteinase (MMP) and tissue inhibitors of MMP (TIMP) in the aortic myofibroblasts with resultant increased activity of MMP protease that, in turn, causes degeneration of collagen fibers. These, along with decreased collagen synthesis by aortic myofibroblasts secondary to FQ exposure, predispose the aorta to dissection and rupture from increased aortic wall fragility (Guzzardi et al., 2019). Please refer to

Figure 1

Effects of Fluoroquinolones on Aorta



Note. Fluoroquinolone induces aortic myofibroblast-mediated extracellular matrix dysregulation. ECM (extracellular matrix), MMP (matrix metalloproteinase), TIMP (tissue inhibitor of matrix metalloproteinase). Figure reproduced with permission from Elsevier. License # 5627791270545

METHODS

Literature review

An umbrella review was utilized to find evidence for the research question for this manuscript. The research question was coined using the PICO (Population, Intervention, Comparator, Outcome) strategy and is as follows: In patients with known aortopathy or with a known risk of aortopathy, what are the risks of an acute aortic event from taking FQs as compared to other antibiotics. A PRISMA flow diagram (Page et al., 2021) was used as the guide to find the relevant articles on the topic of interest based on the key search terms and the major databases. The electronic databases searched were the Cochrane Library, UptoDate, ProQuest, Google Scholar, and Medical Literature On-Line. Key search terms used included fluoroquinolone-induced aortopathy, aortopathy, acute aortic events, fluoroquinolones and aortic aneurysms, fluoroquinolones, and aortopathy, risks of aortopathy with fluoroquinolone use, and fluoroquinolone use in patients with a genetic predisposition for aortopathy.

The search criteria were refined to full-text and peer-reviewed articles. The search criteria involved only publications in English. The search criteria included all the relevant available articles to date. Among the studies that met the inclusion criteria, the ones that utilized systematic review and meta-analysis were listed in the literature review matrix for analysis (Table 1). Data were synthesized by a review of the selected studies to arrive at the conclusions in the matrix. Points of interest were highlighted in from all the included studies in the manuscript. In addition, the selected studies were grouped together, and the data of the studies that reported the findings as relative risk (RR) were used to produce a forest plot to arrive at conclusions. The studies that reported RR were chosen to make a forest plot as the majority of the selected studies for this umbrella review reported the findings as relative risk.

The data from the studies that used relative risk were utilized for the forest plot (Figure 2). A meta-analysis was then performed using a random effects model (utilizing Statsdirect software).

RESULTS

A Taiwanese nested case-controlled study that analyzed the risk of aortopathy with FQ use revealed that FQ use was associated with an increased risk of aortic aneurysm or dissection (AAD) (RR = 2.43, 95%CI, 1.83-3.22)(Lee et al., 2015). A Swedish cohort study that investigated the

association between two commonly prescribed antibiotics in aortopathy revealed that when compared to patients getting penicillin, antimicrobial therapy with FQs was associated with a 66% increased risk (HR, 95%CI, 1.12-2.46) of AAD within 8 weeks of therapy (Pasternak et al., 2018). Meng et al. (2019) used data mining from the FDA Adverse Event Reporting System (FAERS) from January 2004 through December 2016 to evaluate FQ-induced aortopathy. A review of 3721 adverse events revealed that FQs (specifically ciprofloxacin, levofloxacin, and moxifloxacin) were associated with aortic aneurysm while levofloxacin alone was associated with aortic dissection. A cohort study in the United States by Newton et al. (2021) involving more than 2.7 million adults with commercial insurance who were prescribed antibiotics showed that when compared to other antibiotics, FQ fills were associated with an increased risk of aortic aneurysm (HR, 1.20; 95% CI, 1.17-1.24). This study also concluded that the prescription of FQs for adults should be done with caution, even in individuals with no known risk factors for aortopathy (Newton et al., 2021).

A systematic review and metanalysis by Rawla et al. (2019) has reported that FQ administration within the previous two months has been associated with more than doubled the risk of developing aortic aneurysm and eventual dissection (RR = 2.14, 95% CI, 1.93-2.36; I^2= 15.8%). Another systematic review and meta-analysis from Latif et al. (2020) concluded an increased combined risk of AAD with FQ use when compared to controls (RR = 2.11; 95% CI, 1.62-2.75; I^2 = 83.700). A different metanalysis by Dai et al. (2020) involving observational studies that had more than 2.8 million reported cases of FQ use confirmed a significantly increased risk of aortopathy in FQ users versus non-users (adjusted OR, 2.10; 95% CI, 1.65–2.68; P = .000, I^2 = 16.4%). A systematic review and meta-analysis by Ribiero et al. (2021) showed a higher risk of aortopathy associated with the use of FQs when compared to non-treatment intervention (OR = 2.26; 95% CI, 1.93-2.65; I^2 = 30%). This study also showed a higher aortopathy risk with FQ use versus the use of beta-lactams (OR = 1.56; 95% CI, 1.37-1.79; I^2 = 0%). The significant findings of the aforementioned studies that utilized systematic review and meta-analysis are summarized in Table 1.

Animal studies have demonstrated the potential mechanisms for increased AAD risk with the use of FQs in high-risk patients. LeMaire and colleagues (2022) reported accelerated aortic enlargement and increased

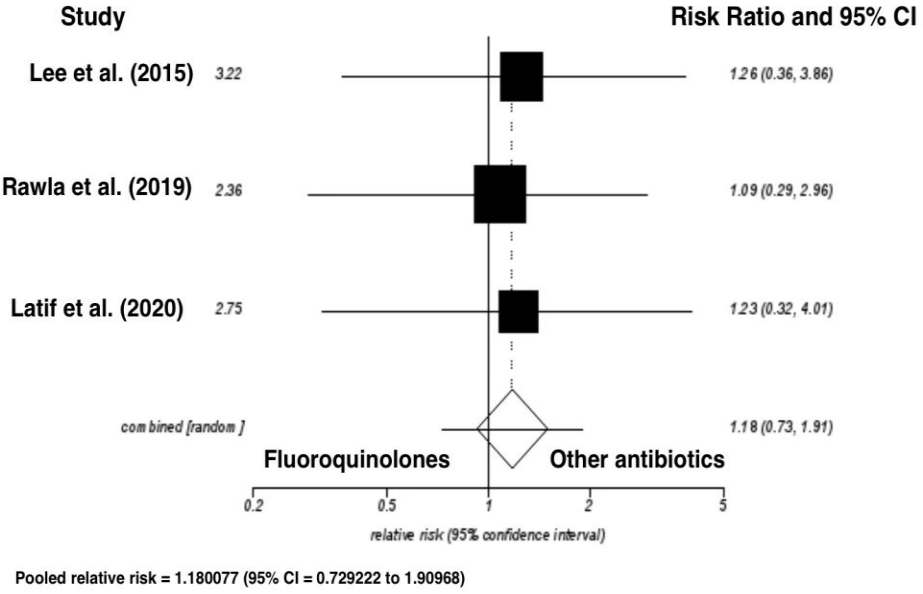
incidence of aortic dissection (25% vs 47%, p = .03) and rupture (5% vs 25%, p = 0.005) in Marfan mice treated with ciprofloxacin. In addition, increased levels of MMP expression, elastic fiber fragmentation, and apoptosis were evident in ciprofloxacin-treated Marfan mice versus the vehicle-treated Marfan mice (LeMaire, 2022). The findings of this study restate the importance of avoiding ciprofloxacin in patients with known aortopathy and risk for developing aorptopathy. However, the transferability of this study findings to humans remains unclear.

Interestingly, a case-controlled study from Taiwan by Dong et al. (2020), which examined the use of antibiotics two months prior to the incidence of aortopathy showed that FQs did not increase the risk of aortopathy when compared to penicillin (OR, 1.01; 95% CI, 0.82-1.24) and cephalosporins (OR, 0.88; 95% CI, 0.70-1.11). This finding was supported by another Taiwanese study by Chen et al. (2022) that concluded no significant difference in aortopathy incidence in individuals exposed to FQs and second or first-generation cephalosporins ([aHR], 0.86 [95% CI, 0.59–1.27]).

Three studies were included in the meta-analysis as reflected in the forest plot (Figure 2) resulting in a pooled relative risk of 1.18 (95% CI; 0.73-1.91). (Lee, 2015; Faula, 2019; Latif, 2020).

Figure 2

Forest Plot of Studies Reporting Relative Risk



Implications for Clinical Practice

Acute aortic dissection syndromes are associated with high mortality rates despite improvements in the management of these critical events (Nazir et al., 2022). As such, FQs should be reserved for use in situations where its benefits clearly outweigh the risks. Fluoroquinolones must be avoided in patients with known aortopathy and in patients with high risk for developing aortopahty. In addition to FDA warnings, hospital pharmacies should activate warnings for FQ use, especially in tertiary centers with aortic centers and those centers that serve a large volume of patients with aortopathies. Pharmacies in tertiary centers with aortic centers should add patient information on any history of aortopathy or genetic risk for aortopathy along with the allergy list. Critical Care providers who are often involved in the care of patients with aortic aneurysm and/or aortic dissection need to be proactive in avoiding the use of FQs during hospitalization unless it is absolutely necessary and if the benefits of FQ use outweigh the risks. Enthusiastic involvement of critical care providers in antibiotic stewardship programs addressing FQ use in patients who have known aortopathy or patients who are predisposed to aortopathy is imperative. Patients with known aortopathy or individuals with high risk for aortopathy should have medical alert bracelets or appropriate identifiers to remind the providers involved in the patient's care to avoid prescribing FQs. Last but not least, it is vital for community pharmacies to inquire about patients' prior history of any aortopathy or genetic predisposition to aortopathy to alert the prescribers while dispensing any prescription FQs.

This review article included a meta-analysis of relevant peer-reviewed studies related to the topic. Studies from different geographical locations and thus involving multiple ethnicities were used in this review, increasing the generalizability of the conclusions from this review. Shortcomings of this review may include selection bias in the studies, as the studies selected for the review were done by a single author. In addition, studies were not graded for bias and only included publications in English, potentially affecting the generalizability of the conclusions.

CONCLUSION

Acute aortic events from underlying aortopathy are associated with increased mortality and morbidity. FQs possess broad spectrum

antimicrobial activity and high oral bioavailability that makes them an ideal antibiotic for many common illnesses. Evidence of FQ-induced aortopathy has been reported multiple times in the literature. FQ use potentiates the risk of developing aortic aneurysm and aortic dissection. Despite published evidence and warnings from manufacturers and regulatory bodies, FQ use continues to be a covert contributor to the development of aortopathy. Stringent measures backed up by regulatory bodies need to be instituted in the prescription and disposition of FQs not only in tertiary centers and academic settings but also in outpatient settings.

Table 1
Literature Review Matrix

Author & Year	Purpose	Sample	Design	Data Analysis	Findings	Strengths & Weaknesses
Rawla et al., 2019	Evaluate the risk of aortic aneurysm and aortic dissection following FQ administration.	4 controlled observational studies	Systematic review and meta-analysis.	When the statistical heterogeneity was low, a fixed-effect model was employed, while a random-effects model was utilized when the statistical heterogeneity was moderate. Neyeloff et al. method employing spreadsheet was used for meta-analysis.	FQ use within the previous 60 days, more than doubled the risk of developing aortic aneurysm and eventual dissection (RR = 2.14, 95% CI, 1.93 - 2.36; I^2= 15.8%).	This was a systematic review and meta-analysis conducted using Cochrane grade criteria for quality of evidence. However, the studies included in this meta-analysis are observational studies and the study sample was relatively small.
Dai et al., 2020	The purpose of the study was to find the risk of aortic	Meta-analysis of 5 observational studies.	Meta-analysis.	The random effects model with inverse variance method was utilized to	The study reported a significantly increased risk of aortopathy	This was a meta-analysis with two authors independently conducting the original research.

	diseases with the use of FQs.			compound the adjusted odds ratio (OR), hazard ratio (HR), and relative risk (RR) of the studies. ORs were calculated with 95% confidence interval (CI). P<.05 was considered statistically significant. Statistical analyses were done utilizing STATA software.	in FQ users versus non-users (adjusted OR, 2.10; 95% CI, 1.65–2.68; *P* = .000).	The authors reported adherence to Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. However, the studies included in this meta-analysis are observational studies and the study sample was realtively small.
Latif et al., 2020	To investigate the association between FQ use and the increased risk of aortopathy, including aortic	The meta-analysis utilized 6 studies, 1 FDA database study, 1 longitudinal	Systematic review and meta-analysis.	Random effect model was used for meta-analysis using STATA software. Heterogeneity was calculated using I^2 and Q	The study showed an increased combined risk of aortic dissection and aortic aneurysm	This was a systematic review and meta-analysis including a longitudinal cohort study, a nationwide study and a FDA database study. Nevertheless, study sample was relatively small and did

	aneurysm without or with dissection.	cohort study, 1 nationwide cohort study, 1 case crossover study, 1 nested case-control study, and 1 case time control study.		statistic. A 2-sided confidence interval (CI) of 95% was considered statistically significant.	with FQ use, when compared to controls (RR = 2.11; 95% CI, 1.62 - 2.75; I^2 = 83.700).	not include randomized studies.
Ribeiro et al., 2021	To investigate the association between FQ use and aortic disease including aneurysm, dissection and/or rupture.	Meta-analysis of 7 observational studies involving 2,851,646 subjects.	Systematic review and meta-analysis.	Random effect model was used for meta-analysis and heterogeneity was calculated using I^2.	The study showed a higher risk of aortopathy associated with the use of FQs when compared to non-treatment (OR = 2.26; 95% CI, 1.93-2.65; I^2 = 30%)	This was a systematic review and meta-analysis involving 7 observational studies. The study sample was relatively small and did not include randomized studies.

					and beta-lactam interventions (OR = 1.56; 95% CI, 1.37-1.79; I^2 = 0%).	

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