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Review

The cardiovascular manifestations of influenza: A systematic review

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ABSTRACT

Influenza accounts for 3 to 5 million cases of severe illness and up to 300,000 deaths annually, presenting a considerable burden to healthcare services. A spectrum of cardiovascular complications has been reported in association with influenza infection. This can occur through direct effects of the virus on the myocardium or through exacerbation of existing cardiovascular disease. Direct myocardial involvement presenting as myocarditis is not uncommon during influenza infection. Clinical presentation may vary from asymptomatic to fulminant myocarditis resulting in cardiogenic shock and death. Cardiovascular mortality is also increased during influenza epidemics in patients with pre-existing coronary artery disease. Rates of myocardial infarction have been shown to increase following influenza outbreaks, whilst decreases in cardiovascular mortality have been demonstrated following influenza vaccination in high risk patients. The purpose of this review is to provide an overview of cardiovascular complications, their presentation, clinical course and the management options available following influenza infection.

1. Introduction and aim

Influenza is the most important viral respiratory infection. Influenza epidemics and pandemics present a considerable burden to healthcare services. In the UK there is an average of 1.1 million extra consultations for acute respiratory infections during epidemic season and over 3000 excess respiratory admissions [1]. An average of 12,554 deaths occurs in England and Wales during annual influenza epidemics [1]. Influenza pandemics occur every 10–20 years. The most fatal pandemic to date is the Spanish influenza pandemic of 1918–1919, which caused 50 million deaths worldwide [2]. The most recent pandemic was in 2009, caused by a novel strain of swine-origin H1N1 [3]. An estimated 540,000 people in England had symptomatic H1N1 infection with a case fatality rate of 26 deaths per 100,000 cases [4].

Influenza infection has predominantly respiratory manifestations; however multi-organ involvement is not uncommon. We have previously provided an oversight regarding the spectrum of cardiovascular manifestations associated with influenza infection [5]. Since the publication of our original work, many further studies have been published that provide further insight into both the pathophysiological mechanisms and clinical presentation of cardiovascular manifestations of influenza infection. The aim of the current work is to provide an update and systematically review and appraise literature focussing on the cardiovascular complications of influenza infection.

2. Methods

Electronic databases (Ovid MEDLINE, Ovid EMBASE, SciVerse Scopus) were searched using relevant MeSH (Medical Subject Headings) terms for literature published between January 1946 and April 2012 (Fig. 1). The Cochrane library was searched for relevant review articles. The titles and abstracts of all results were reviewed and studies were selected for full text analysis according to the eligibility criteria (Table 1). Further studies were identified by cross-referencing from relevant papers. Final study selection was based on fulfilment of eligibility criteria and relevancy. Critical review of selected studies was undertaken with the aid of CASP (Critical Appraisal Skills Programme) appraisal tools [6].

3. Results

Our search yielded 325 results. 145 papers were selected for full text analysis, of these 40 were selected for inclusion in the review (Table 2). We have discussed related studies under suitable subheadings.

3.1. Acute myocardial infarction (AMI)

There is strong evidence supporting the role of influenza as a trigger for cardio-vascular events. The precise mechanism is unclear; however, coagulopathy and inflammation are key factors [7].

Studies have demonstrated increased risk of both arterial and venous thromboses after acute infection [8–10]. Animal studies have demonstrated a coagulopathic state during influenza infection. Thrombin generation, fibrin deposition and fibrinolysis increased in influenza infected mice compared to controls [11]. Coagulation abnormalities such as excess clotting and consumptive coagulopathy occurred in chickens infected with H5N1 influenza virus [12]. Inflammation is implicated throughout the atherosclerotic process.

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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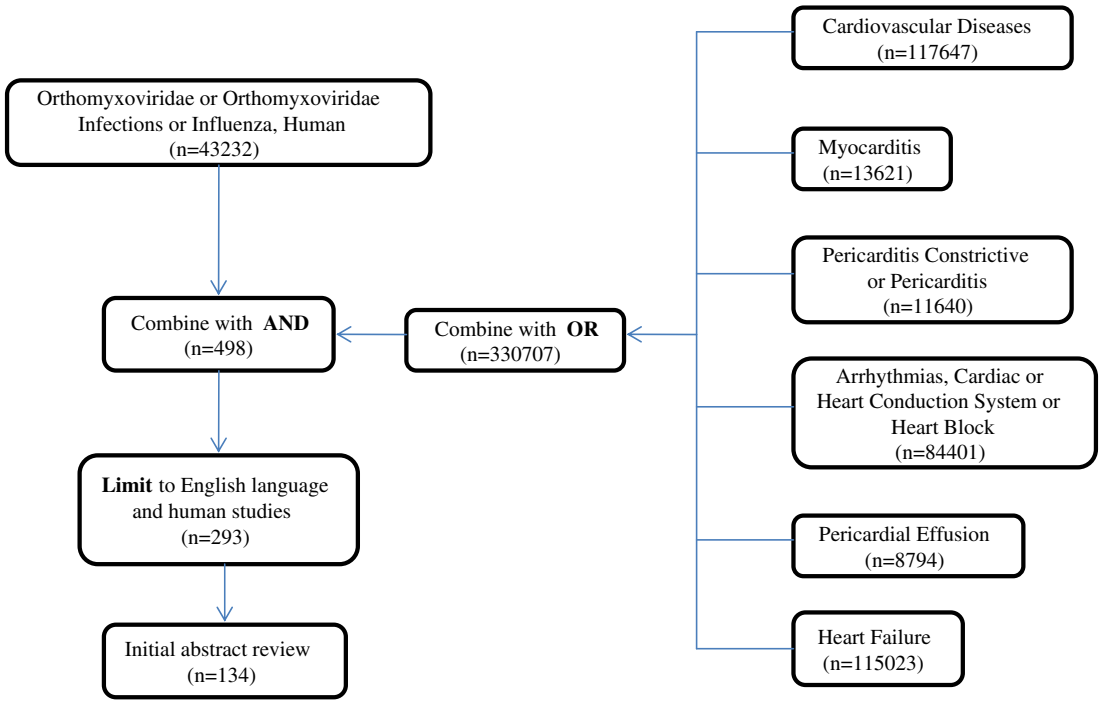

Fig. 1. Summary of search strategy for Ovid MEDLINE database.

Markers of systemic inflammation such as C-reactive protein are associated with increased cardio-vascular risk [13]. A study of inflammatory markers in AMI demonstrated significantly higher levels of cytokines such as IL-6 in patients with STEMI (ST elevated myocardial infarction) compared with NSTEMI (non-ST elevated myocardial infarction) patients [14]. Mice studies have demonstrated increased inflammatory cytokines such as TNF-α and IL-6 in the context of influenza infection [15]. Experimental studies in healthy individuals demonstrate a significant transient endothelial dysfunction mediated by a range of inflammatory cytokines, whose circulating levels surge during acute inflammation [16].

3.1.1. Studies of general practice data

Several studies have used primary care data to examine the relationship between influenza-like illnesses and AMI (Table 3). Meier et al. [8] retrospectively reviewed GP consultation records from the United Kingdom General Practice Research Database (GPRD). In the five days before AMI, cases (n = 1922) had significantly more visits for "acute respiratory infection" than controls (n = 7649) (OR = 3.6, CI = 2.2 − 5.7, p < 0.01). Cross-over analysis yielded similar results (RR = 2.7 CI = 1.6–4.7). Smeeth et al. [9] conducted a self-controlled case series using the same database. They selected influenza episodes based on records of "systemic respiratory tract infection". Clayton et al. [17] conducted a similar study using the IMS Disease Analyzer Mediplus general practice database. Both report an increased risk of AMI following acute respiratory infection, which is highest in the first 5 − 7 days post-infection and reduces over time.

These studies, by the nature of their study designs have their limitations. Patients who experienced, but did not attend their GP for symptoms of respiratory infection, have been excluded. There is no differentiation between repeated attendance for the same episode and distinct episodes. Additionally, there is no guarantee that a recorded episode is an actual influenza episode, as there was no laboratory verification of the diagnosis.

3.1.2. Questionnaire-based studies

Pesonen et al. [18] randomly selected 110 AMI admissions and 323 matched controls to complete a questionnaire designed to identify symptoms of infection in the preceding month. The risk of AMI increased with the number of symptoms reported (≥4 symptoms vs ≤1 symptom) (OR = 16.0, CI = 1.75–146.31, p = 0.014). Clayton et al. [19] used a similar study design to look more specifically for symptoms of acute respiratory infection, which they defined based on the presence of a syndrome of symptoms. They report no evidence of association based on this definition (OR = 1, CI = 0.5 − 1.9, p = 0.98). However, strong associations were noted for isolated fever (OR = 5.9, CI = 2.0 − 16.8, p = 0.0004) and pleuritic chest pain (OR = 17.5, CI = 3.6 − 85.6, p = 0.0001). In another questionnaire study, Pentinnen et al. [20] report more visits to a physician for acute upper respiratory tract infection in cases of AMI compared to matched controls (OR = 1.4, CI = 0.8 − 2.3, p = 0.01) (Table 4).

3.1.3. Studies using antibody titres

Mattila et al. [21] present a prospective case − control study comparing 40 consecutive AMI admissions with 41 random controls and 30 chronic coronary heart disease (CCHD) patients. Paired antibody titres were taken on admission and at four weeks. A clinical history was obtained to screen for symptoms of recent infection. Based on

Table 1
Eligibility criteria used for study selection.

Inclusion criteria	Exclusion criteria
Study involving adults or children	Animal studies
Valid method for diagnosing influenza	Non-English studies
Clearly defined cardiovascular endpoints	

Table 2
Summary of hits obtained from electronic database searches.

Database	Number of unique hits	Selected after review of abstract
Ovid Medline	293	134
Ovide EMBASE	9	3
SciVerse Scopus	23	8
The Cochrane Library	0	0
Total	325	145