Editorial



# Pneumonia as a cause of chronic cardiac disease

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Traditionally clinicians who treat patients with pneumonia generally consider their job well done when the patient is safely discharged from hospital.

In recent years, there has been an increasing awareness that survivors of pneumonia have significantly worse long term health outcomes than population controls (1-8). The explanation for the adverse health outcomes in pneumonia survivors remains to be fully elucidated, but a significant excess of cardiovascular disease is a major factor (3,9-11).

Adding to the weight of literature about adverse cardiac consequences of pneumonia is a recent study published in the British Medical Journal by Eurich and colleagues (12). In this Canadian study of a prospectively collected database of adults with community acquired pneumonia, 4,988 patients with no prior history of heart failure were matched to between one and five controls based on age (5-year bands) and gender. Controls were obtained from patients presenting to hospital for other reasons at the same time of year as the pneumonia case. The principal finding of the study was that survivors of pneumonia had, over a median of 9.9 years of follow up, an incident rate of heart failure of 11.9% compared to 7.4% in controls [hazard ratio 1.61, 95% confidence interval (CI): 1.44–1.81]. Unsurprisingly older patients developed more heart failure. In keeping with other published data overall mortality was also higher in pneumonia survivors than controls (38.4% *vs.* 23.9%, P<0.001). Of clinical importance the difference between cases and controls was established within 90-day of discharge and appears to be maximal by one year. Unfortunately due to the nature of the database additional data on severity and cause of pneumonia as well as the severity of the subsequent heart failure could not be assessed.

The findings of Eurich and colleagues are not surprising. Analysis of the Cardiovascular Health Study (CHS), a large prospective population cohort study initiated in the 1990's, by Corrales-Medina and colleagues (13) also found that an episode of pneumonia predicted a subsequent significantly greater risk of a new diagnosis of cardiac failure. In this study the hazard ratio for new onset heart failure was maximal at 31–90 days (6.9, 95% CI: 4.46–10.63) and declined slowly to 2.6 (95% CI: 1.64–4.04) at 1-year but was still 2.0 (95% CI: 1.56–2.58) after 5 years.

What then explains the greater incidence of heart failure in pneumonia survivors? There is abundant evidence that acute myocardial infarction is a common complication in patients with pneumonia (14-18), increasing with severity of the pneumonia to as high as 15% in the most severe disease (15). This is not just observation of elevation of cardiac enzymes as is seen commonly in severe sepsis, but also abnormalities consistent with myocardial ischaemia on electrocardiographs. While the majority of myocardial ischaemia is not ST-elevation myocardial infarction, in one series these were as much as 16% of all events (16). A reasonable hypothesis is therefore that myocardial infarction precipitated by the acute pneumonia, both recognized and unrecognized, causes cardiac damage sufficient to lead to early cardiac failure.

Why are acute coronary events higher in pneumonia survivors? The persistence of radiological infiltrates for

months in some patients suggests a continued low-level inflammatory response (19,20). Even small elevations of systemic inflammatory markers such as c-reactive protein have been associated with substantial increases in subsequent cardiac events (21,22), and patients with the highest level of inflammatory markers at discharge from hospital with CAP have the worst 1-year outcomes (23).

A less recognized but also clearly established cause of cardiac damage is direct myocardial invasion by the pneumonic pathogen(s). In the case of *Streptococcus pneumoniae*, the most common cause of community-acquired pneumonia, it has recently been documented in mice that direct translocation into the heart can occur but is associated with minimal inflammatory response and results in significant fibrosis (24). Disease severity correlated with levels of serum troponin and the number and size of cardiac microlesions. Similar microlesions were also demonstrated in cardiac samples from human patients who had died from invasive pneumococcal disease. In a murine model of burn trauma, *S. pneumoniae* inoculation led to a significant further depression of cardiac function (25) (Sheeran *et al.*, *J Surg Research*, 1998). Myocarditis has also been described in the setting of pneumonia with a variety of other common bacterial pathogens (26-29). In the case of viral disease myocarditis may be even more common, especially with influenza (30,31).

In the case of both coronary artery occlusion and direct myocardial invasion the extent that subclinical disease is present during pneumonia and contributes to subsequent adverse cardiac outcomes is unknown. Two lines of evidence suggest subclinical involvement may be substantial. The first is the high rate of arrhythmias in acute pneumonia (10,11,14,17,32), and especially atrial fibrillation, and that the onset of a new arrhythmia during admission predicts worse subsequent outcomes (10,32). While a variety of problems may contribute to a higher risk of arrhythmia including hypoxia and electrolyte disturbance, subclinical myocarditis may also contribute. The second suggestive evidence is that significant elevations of cardiac enzymes are common in patients with pneumonia and predict a worse prognosis in the short term (16,33-35), and after discharge (35). Similar results have been observe for b-type natriuretic peptide (4,36-38), but these studies are complicated by premorbid cardiac disease.

The evidence is therefore extremely strong that pneumonia causes cardiac disease and that when it does, outcomes are significantly worse. Furthermore the evidence is also strong that pneumonia survivors have significantly more cardiac disease over the subsequent months to years. Antibiotics may rapidly clear bacteria from cardiac tissue, but this does not appear to be sufficient to prevent the adverse development of cardiac fibrosis (24). Can we do anything else about the increased cardiovascular risk? There is some evidence to suggest anti-platelet agents may reduce coronary artery occlusion in acute pneumonia (39-43), but further studies are needed. Longer-term interventions now standard in patients who have had myocardial ischaemia like anti-platelet agents, statins, angiotensin-converting enzyme inhibitors and beta-blockers have not been studied in pneumonia survivors. It is likely that therapies in development to improve 'healthy' recovery from brain and cardiac injury may also be important in the setting of pneumonia, especially severe disease. We do not need any more studies like that of Eurich and colleagues (12) to tell us that the whole area of short and long term cardiac disease precipitated by pneumonia is now urgently in need of significant research investment.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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