Acute pneumonia and the cardiovascular system

Vicente F Corrales-Medina, Daniel M Musher, Svetlana Shachkina, Julio A Chirinos

Although traditionally regarded as a disease confined to the lungs, acute pneumonia has important effects on the cardiovascular system at all severities of infection. Pneumonia tends to affect individuals who are also at high cardiovascular risk. Results of recent studies show that about a quarter of adults admitted to hospital with pneumonia develop a major acute cardiac complication during their hospital stay, which is associated with a 60% increase in short-term mortality. These findings suggest that outcomes of patients with pneumonia can be improved by prevention of the development and progression of associated cardiac complications. Before this hypothesis can be tested, however, an adequate mechanistic understanding of the cardiovascular changes that occur during pneumonia, and their role in the trigger of various cardiac complications, is needed. In this Review, we summarise knowledge about the burden of cardiac complications in adults with acute pneumonia, the cardiovascular response to this infection, the potential effects of commonly used cardiovascular and anti-infective drugs on these associations, and possible directions for future research.

Introduction

Pneumonia and cardiac disease are leading causes of morbidity and mortality worldwide.[1–5] Community-acquired pneumonia affects more than 5 million adults, and causes 1·1 million hospital admissions and more than 60000 deaths every year in the USA.[1,2] Cardiac disease affects more than 30 million US adults and leads to 5 million hospital admissions and more than 300000 deaths every year.[3,6] Disease burdens in Europe are similar.[4,5,7] Pneumonia and cardiac disease often coexist in the same patients.[8] For example, more than half of elderly patients admitted to hospital with pneumonia also have a chronic cardiac disorder—an association that will become more prevalent as the population continues to age.[8]

Investigators have reported a high incidence of cardiac complications during the course of community-acquired pneumonia, and have shown that these events are independently associated with increased short-term mortality.[9] In view of this association, full appreciation of the magnitude of this problem and an understanding of the cardiovascular consequences of this infection are important. In this Review, we summarise the present knowledge about the burden of cardiac complications in adult patients with pneumonia, the cardiovascular response to acute pneumonia, and the potential effects of commonly used cardiovascular and anti-infective drugs on these associations. We also discuss potential areas for future research.

Burden of cardiac complications in patients with pneumonia

For several decades, investigators have noted that acute respiratory infections, including pneumonia, often precede the development of acute cardiac events, and a causal relation has been proposed.[10,11] For acute coronary syndromes specifically, this association satisfies most of Bradford Hill's criteria for causality and is discussed elsewhere.[11,12] The high prevalence of cardiac arrhythmias after an episode of pneumonia and the temporality of this association also suggest a causal role for pneumonia in

cases of pneumonia-associated arrhythmias.[9] Although a similar argument can be made for the association between pneumonia and heart failure, this relation is probably more complex. Results of clinical studies suggest that patients with heart failure have reduced immunological responses, and experimental evidence indicates that pulmonary congestion can promote the growth of common bacteria such as *Streptococcus pneumoniae* (pneumococcus) and *Staphylococcus aureus* in the lungs.[13–15] Epidemiological data also suggest that pre-existing heart failure is a risk factor for the development of pneumonia.[16] Therefore, the cause–effect relation between pneumonia and heart failure might be bidirectional. A causal relation between infections in other organs, such as the urinary or gastrointestinal tracts, and acute cardiac events has also been suggested, but has not yet been characterised.[17,18]

Although acute cardiac events have been recognised as important complications in patients with pneumonia

**Department of Medicine,
University of Ottawa, ON,
Canada** (V F Corrales-Medina MD,
S Shachkina MD); **Ottawa
Hospital Research Institute,
ON, Canada**
(V F Corrales-Medina,
S Shachkina); **Departments of
Medicine and Molecular
Virology and Microbiology,
Baylor College of Medicine,
Houston, TX, USA**
(Prof D M Musher MD); **Medical
Care Line, Infectious Disease
Section, Michael E DeBakey VA
Medical Center, Houston, TX,
USA** (D M Musher); **Division of
Cardiology, University of
Pennsylvania, PA, USA**
(J A Chirinos MD); **and
Philadelphia VA Medical Center,
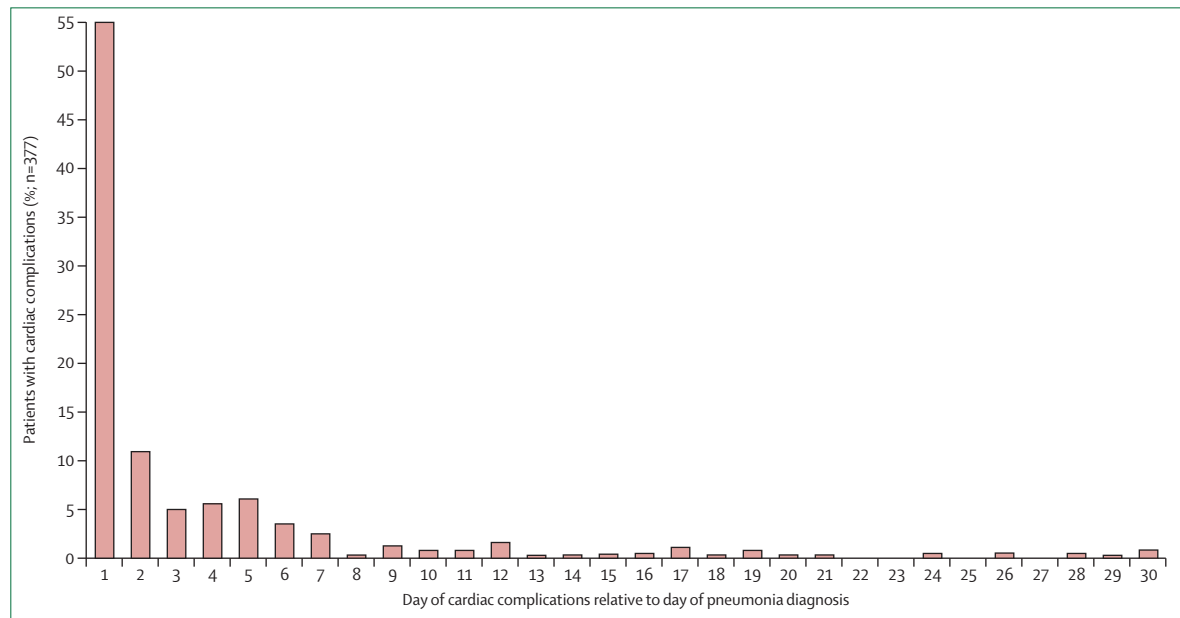PA, USA** (J A Chirinos)

Correspondence to:
Dr Vicente F Corrales-Medina,
Department of Medicine,
University of Ottawa,
1053 Carling Avenue, CPC 470,
Ottawa, ON, K1Y 4E9, Canada
vcorrales@toh.on.ca

See **Online** for appendix

Search strategy and selection criteria

We searched Medline (from 1946 to May 15, 2012), Scopus (from 1950 to May 15, 2012), and Embase (from 1947 to May 15, 2012) databases, using detailed search strategies (appendix). We developed search methods to capture clinical and experimental evidence of cardiac complications in patients with pneumonia, and the effects of pneumonia on the human cardiovascular system, the consequences of commonly used cardiovascular drugs on the outcomes of patients with pneumonia, and the effects of available antibiotics on the cardiovascular system. Only articles in English, Spanish, Russian, German, French, and Chinese were included. Articles in languages other than English were translated by medical doctors proficient in those languages. Then, relevant articles were reviewed in their entirety and discussed by the investigators to establish their relevance to this Review. When appropriate, we preferred to cite comprehensive reviews of the literature rather than many individual reports. Similarly, our Review focuses on conceptual syntheses of data, rather than detailed descriptions of original research.

***Figure* 1: Timing of cardiac complications in patients with community-acquired pneumonia**
Cardiac complications included any of the following cardiac events: new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction. Data from the Pneumonia Patient Outcomes Research Team cohort study. Adapted from Corrales-Medina et al,[9] with permission of Wolters Kluwer Health.

since the early 20th century, the magnitude of this problem has only recently begun to be appreciated fully.[19] A meta-analysis of 25 studies reporting the incidence of cardiac events within 30 days of pneumonia diagnosis reported cumulative rates of new or worsening heart failure (14%, range 7–33%), new or worsening arrhythmias (5%, range 1–11%), and the acute coronary syndromes myocardial infarction or unstable angina (5%, range 1–11%) in patients admitted to hospital with pneumonia.[20] Most studies, however, did not use clear definitions for the outcomes investigated, relied on retrospective chart review for their ascertainment, or were restricted to high-risk populations (eg, veterans, patients with diabetes, and elderly patients). In their 2012 analysis of a prospective multicentre cohort of 2344 unselected patients with community-acquired pneumonia (1343 inpatients and 944 outpatients), Corrales-Medina and colleagues reported the 30-day incidence of well-defined cardiac complications.[9] In this cohort, new or worsening heart failure, new or worsening arrhythmias, and myocardial infarction occurred in, respectively, 21%, 10%, and 3% of inpatients, and 1·4%, 1·0%, and 0·1% of outpatients. Overall, cardiac complications (defined as any of the aforementioned events) occurred in 27% of in-patients and 2% of outpatients.[9] Cardiac arrest occurs in up to 3% of patients admitted to hospital with community-acquired pneumonia.[21]

The occurrence of two or more types of cardiac event in a patient with pneumonia is not uncommon and has been reported in 20–40% of patients who develop cardiac complications.[9,19] In this setting, the recognition of myocardial infarction is usually preceded by the diagnosis of other cardiac events (69% of patients).[9] Conversely, new or worsening heart failure and arrhythmias are the first recognised, or only, pneumonia-associated cardiac event in most cases (85% and 69%, respectively).[9]

Risk for cardiac complications is higher in the first few days after a pneumonia diagnosis, with about 90% of these events recognised within 7 days of diagnosis, and more than half identified within the first 24 h (figure 1).[9,22] Risk factors for cardiac complications include older age (about 86% of cardiac complications occur in people aged ≥60 years), nursing home residence, pre-existing cardiovascular disease, and greater severity of pneumonia at presentation.[9,22,23] Nonetheless, about a third of pneumonia-associated cardiac complications occur in patients with no history of clinical cardiac disease, a quarter of cases are in patients considered to be at low risk on the basis of their pneumonia severity index score, and about three-quarters of cases arise in patients thought not to need intensive care after their first assessment.[9,19,21,24]

Cardiac complications have an important effect on the clinical course of patients with pneumonia. In patients admitted to hospital with pneumonia who experience clinical failure to treatment, about a third do so because of cardiac complications.[25] Diagnostic criteria for myocardial infarction are present in as many as 50% of patients with pneumonia who need intensive care unit treatment within 24 h of admission to hospital.[23] Cardiac complications are also the direct or underlying cause of death in 27% of pneumonia-associated deaths.[26] Death within 30 days of pneumonia diagnosis is five times more common in patients who develop cardiac complications than in those who do not.[9] Even after adjustment for baseline risk, cardiac complications are associated with a

60% increase in pneumonia-associated short-term mortality,[9] and lead to one in four readmissions after hospitalisation for pneumonia.[27]

Effects of pneumonia on the cardiovascular system

The present understanding of the human cardiovascular response to infections, including pneumonia, is derived mainly from studies of critically ill patients with septic shock. This disorder is characterised by inability of the peripheral vasculature to constrict despite increased concentrations of catecholamines and increased activity of the renin–angiotensin–aldosterone system;[28] myocardial systolic and diastolic dysfunction, mainly of the left ventricle, with some myocardial injury manifested by increased serum troponin concentrations in the absence of recognisable acute coronary syndromes;[29,30] cardiac autonomic dysfunction;[31] substantial changes in haemostasis, mainly driven by activation of the extrinsic coagulation pathway and suppression of fibrinolysis;[32] impairment of the haemostatic functions of the vascular endothelium;[28,29] and renal dysfunction, which presumably arises from many of the preceding processes or other primary insults to the kidneys.[33] Comprehensive discussions about the cardiovascular system in septic shock are published elsewhere and are not the focus of this Review.[28,29,33] Although septic shock occurs in a minority of patients with pneumonia (complicating the disease in about 4% of those requiring hospital admission),[34] in this Review we will concentrate on evidence from studies of patients with pneumonia who are not necessarily critically ill. The table presents a summary of this evidence.

Vascular endothelium and peripheral vessels

Patients with pneumonia have transiently raised serum concentrations of endothelin-1, an endothelium-specific vasoconstricting peptide.[40] Circulating concentrations of endothelin-1 at hospital admission are associated with severity and prognosis of pneumonia, a finding also reported for adrenomedullin, another peptide produced by endothelial cells but with vasodilatory effects.[41] Transient disturbances of vascular responses to restoration of blood flow (ie, reactive hyperaemia) and to nitric oxide during the acute phase of pneumonia also suggest some vascular dysfunction associated with this infection.[35]

A decrease in peripheral vascular resistance is the norm during the acute phase of pneumonia in young and middle-aged people.[36–39] However, increased peripheral vascular resistance only partly responsive to volume expansion can occur in up to a third of middle-aged patients.[37,38] This finding suggests that vasoactive responses leading to increased cardiac afterload (ie, increased peripheral vascular resistance) can also present in elderly individuals with pneumonia, which is potentially counterproductive in patients with chronic impairment of myocardial function.[6] Further studies are

	Effect of pneumonia
Vascular endothelium and peripheral vessels	Impaired reactive hyperaemia response and response to nitric oxide;[35] decreased peripheral vascular resistance in most young adults, but increased peripheral vascular resistance in up to a third of middle-aged adults (no data available for elderly patients);[36–39] increased concentrations of endothelin-1 and adrenomedullin[40,41]
Myocardium	Depression of left ventricular function;[37,38,42] myocarditis;[43] increased concentrations of troponins, BNP, and ANP[44–47]
Cardiac rhythm	Acute cardiac arrhythmias[20,48,49]
Coronary arteries	Possible acute inflammatory changes in atherosclerotic plaques;[50–52] possible coronary vasoconstriction[53]
Pulmonary circulation	Increased pulmonary artery pressures[54]
Cardiac autonomic function	Impairment of cardiovascular autonomic reflexes[55]
Coagulation	Increased procoagulant activity[56–58]
Renal function and fluid and sodium balance	Increased production of vasopressin;[41,59,60] decreased ACE activity;[61–63] water retention;[59] acute kidney injury[64,65]

BNP=B-type natriuretic peptide. ANP=atrial natriuretic peptide. ACE=angiotensin-converting enzyme.

Table: Effects of pneumonia on the cardiovascular system

needed to characterise the systemic vascular response to acute pneumonia in elderly patients.

Myocardium

A transient decrease in left ventricular function occurs in up to a third of middle-aged people with pneumonia, even without a history of cardiac, renal, hepatic, or chronic pulmonary diseases, and has also been described in young, otherwise healthy, populations.[37,38,42] Serum concentrations of B-type natriuretic peptide and atrial natriuretic peptide increase during the acute phase of pneumonia, and the magnitude of this increase is associated with the severity and outcome of the infection.[44–46] The extent to which left ventricular dysfunction during pneumonia is secondary to direct depressant effects of circulating inflammatory mediators (ie, cytokines, endotoxins, or both), with or without vascular responses affecting cardiac afterload or preload, is unclear. Increased resistive afterload occurs in some patients with pneumonia,[37,38] whereas pulsatile afterload, which can change unfavourably in response to other acute inflammatory stimuli and is highly relevant for ventricular–arterial interactions,[66–68] has not been assessed in this setting.

Increased serum troponin concentrations without recognisable acute coronary syndromes are also well described across the range of pneumonia severity.[47] Whether these raised concentrations represent a manifestation of otherwise unrecognised myocardial infarctions or non-ischaemic myocardial injury is unknown. Myocardial ischaemia can result from coronary occlusion, focal spasm, severe diffuse microvascular dysfunction, or hypoxaemia, with or without increased metabolic demands in patients with pre-existing coronary stenosis.[11] However, the low incidence of clinically apparent myocardial ischaemic events compared with that of heart failure in patients with pneumonia suggests that non-ischaemic mechanisms (ie, load changes, neurohormonal

hyperactivity, or non-ischaemic myocardial injury) are more often the cause.[9]

Non-ischaemic myocardial injury can result from acute myocarditis. Many agents that cause pneumonia also cause myocarditis—mainly viruses such as influenza virus, respiratory syncytial virus, adenovirus, and enteroviruses, but also bacteria including *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Staphylococcus aureus*, pneumococcus, and *Legionella* spp—have also been implicated.[69–73] Studies using PCR-based diagnostic tests suggest a viral cause in about a third of adults with community-acquired pneumonia.[69] A detailed autopsy study of 67 patients with lobar pneumonia showed pathological evidence of myocarditis in 39% of patients.[43] Because of the difficulties in the non-invasive diagnosis of myocardial inflammation, the precise incidence of myocarditis in non-fatal pneumonia is unknown. Techniques such as T2-weighted and post-gadolinium delayed-enhancement cardiac MRI, however, are promising for non-invasive diagnosis.[74]

Cardiac rhythm

New or worsening cardiac arrhythmias, especially atrial fibrillation, are well-characterised complications of acute pneumonia.[20] The fact that acute pneumonia can cause a wide range of acute changes in the surface electrocardiogram of patients has also long been recognised.[48,49] Whether these changes result mainly from a direct effect of pneumonia on the cardiac conduction system, concomitant myocardial disorders such as ischaemia or myocarditis, or pericardial involvement by pneumonia-producing organisms is unknown.

Coronary arteries

Animal models have shown that *C pneumoniae* can initiate and accelerate atherosclerosis in mice.[75] This organism has also been identified in atherosclerotic plaques of human beings, but no causal association has been shown.[75] A comprehensive discussion of the possible role of *C pneumoniae* in the pathogenesis of human atherosclerosis is beyond the scope of this Review and can be found elsewhere.[75] However, the possibility that *C pneumoniae* can trigger acute coronary syndromes in the short term after causing pneumonia has not yet been investigated. Studies of apolipoprotein E-deficient mice have shown that influenza can promote acute inflammation, smooth muscle cell proliferation, and fibrin deposition in atherosclerotic plaques of these animals.[50,51] A small post-mortem study of patients with sepsis of various causes suggested increased inflammatory infiltrates in their coronary atherosclerotic plaques and adventitia compared with patients dying from non-infectious causes.[52] On the basis of these results, investigators have proposed that acute infections can affect the stability of coronary atherosclerotic plaques in human beings.[11] Animals infected with *C pneumoniae* and influenza virus show increased coronary vasoconstricting responses.[53]

Pulmonary circulation

Hypoxaemia, the consolidated lung parenchyma, and the adaptive local regulatory mechanisms to reduce pulmonary ventilation–perfusion mismatches (ie, shunts) can affect resistance to blood flow through the pulmonary vasculature in patients with acute pneumonia.[76] Studies of young and middle-aged patients have shown that pneumonia can increase pulmonary artery pressures proportional to the degree of ventilatory restriction and hypoxaemia.[54]
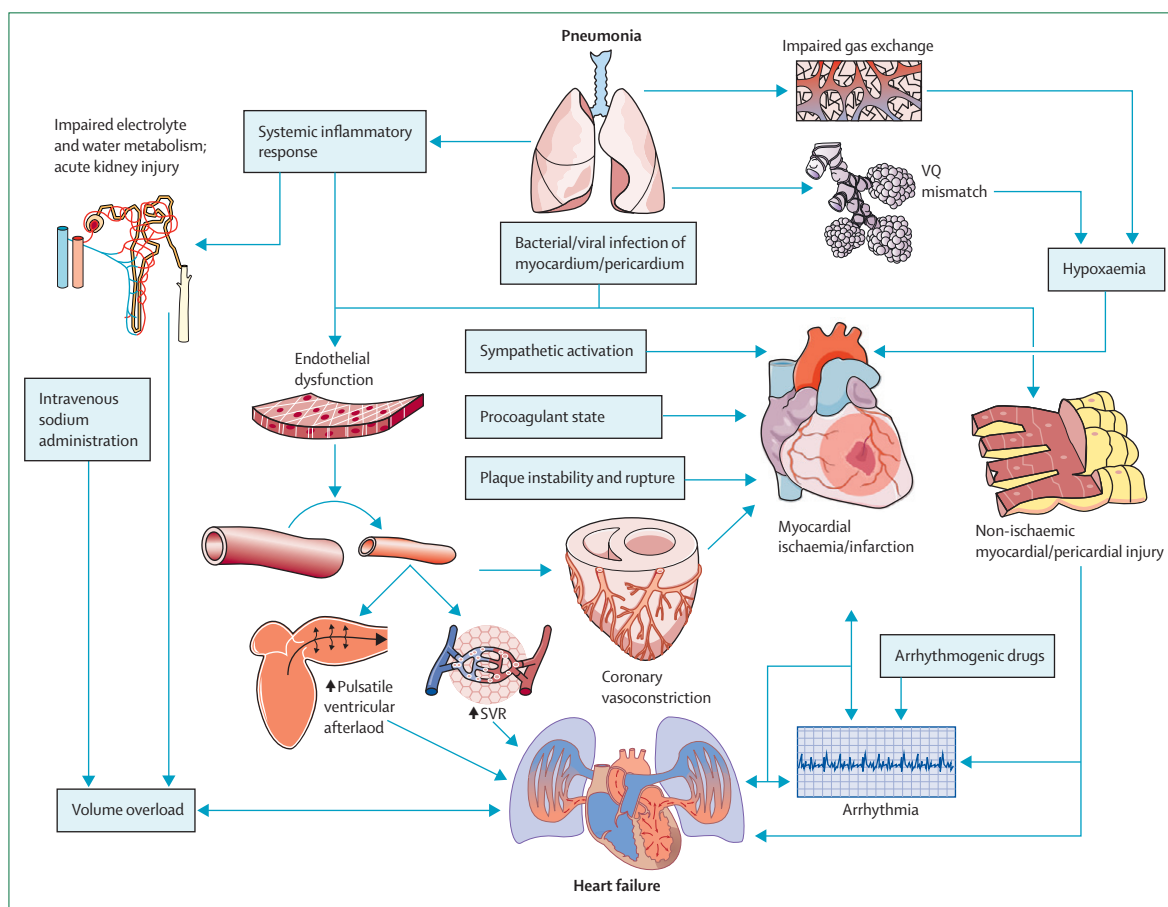
Cardiac autonomic function

Elderly patients with acute pneumonia show transient impairments of their cardiovascular autonomic reflexes, as shown by a reduced heart rate response to the Valsalva manoeuvre, a more pronounced fall of systolic blood pressure on standing, and impaired rise in diastolic blood pressure on sustained hand grip.[55]

Coagulation

Almost 90% of patients who are admitted to hospital for pneumonia have increased coagulation activation, as manifested by at least one of the following: increased antithrombin activity, decreased factor IX activity, increased thrombin–antithrombin complex concentrations, increased D-dimer concentrations, or increased plasminogen activator inhibitor concentrations.[56] Patients with acute coronary syndromes complicated by pneumonia have higher platelet-aggregating activity and non-responsiveness to aspirin than do patients with acute coronary syndromes not complicated by the infection, suggesting that acute pneumonia also results in pro-aggregant platelet dysfunction.[77] When plasma from patients with pneumonia is injected into mice, the plasma induces lethal thrombosis-inducing activity, which has also been described in patients with advanced lung cancer.[57,58] This effect, however, disappears if plasma is taken from patients after treatment for pneumonia.[57] The endothelial dysfunction of pneumonia probably also encompasses impairment of endothelial anti-coagulant properties, contributing further to a pro-coagulant state.[78]

Renal function and fluid and sodium balance

Pneumonia is a well-recognised cause of the syndrome of inappropriate antidiuretic hormone secretion.[79] Pneumonia-induced increases in serum vasopressin with impairment of renal water excretion occur even in euvolaemic patients with normal plasma sodium concentrations in the absence of recognised clinical cardiac, liver, renal, or chronic lung disease.[59] Both extreme hyponatraemia and amounts of copeptin on admission to hospital (copeptin is the C-terminal fragment of the vasopressin precursor, which indicates vasopressin production) are strong predictors of disease severity and mortality in patients with community-acquired pneumonia.[41,60,80] The lungs are a major site for expression of angiotensin-converting enzyme (ACE).[61,81]

Figure 2: Proposed pathophysiological mechanisms contributing to cardiac complications in patients with acute pneumonia
VQ=ventilation–perfusion mismatch. SVR=systemic vascular resistance. Image of heart and lungs at the bottom of the figure reproduced with permission from Peter Gardiner at clinicalskills.net.

During pneumonia, serum ACE activity decreases transiently, but the extent of change does not seem to predict high disease severity or poor outcomes, even with consideration of the variance associated with the genetic ACE insertion/deletion polymorphism.[61–63] The specific activity of aldosterone during acute pneumonia, however, has not been characterised. Acute kidney injury develops in as many as 34% of patients with pneumonia during their hospital stay, and is associated with high short-term mortality.[64] Although sodium and water retention from renal dysfunction probably contribute to new or worsening heart failure in some patients with pneumonia, this possibility has not yet been investigated.

Integrated mechanistic model for cardiac complications in patients with pneumonia
Introduction
On the basis of present knowledge already discussed, the following pathophysiological model for cardiac complications in patients with pneumonia can be proposed (figure 2).

New or worsening heart failure
Several mechanisms can contribute to myocardial dysfunction in patients with pneumonia. Circulating inflammatory mediators (ie, cytokines and/or endo-toxins) or direct infection of cardiomyocytes with pneumonia-causing organisms, or both these mechanisms, can lead to non-ischaemic myocardial injury. Acute myocardial ischaemia secondary to acute coronary syndromes or demand ischaemia can also occur. Transient disturbances of endothelial function and vascular tone, driven by the systemic response to infection, can increase left ventricular afterload by increasing the peripheral microvascular resistance (ie, systemic vascular resistance) or the pulse wave reflections from medium and large arteries (the pulsatile component of left ventricular afterload). The systemic inflammatory response to pneumonia can also result in acute kidney injury and impaired sodium and water metabolism, leading to volume overload. This effect can be exacerbated by the administration of antibiotics or other drugs with high sodium content or large infusion volumes. Patients with impaired cardiac

function at baseline are especially sensitive to these effects. Cardiac arrhythmias can also trigger new or worsening heart failure by interfering with the effective synchronisation of the cardiac cycle and the coordinated contraction of cardiomyocytes.

Myocardial ischaemia or infarction

Pneumonia results in impaired gas exchange across the alveoli of inflamed lung parenchyma and ventilation–perfusion mismatching, which can lead to hypoxaemia. The systemic response to pneumonia also increases sympathetic activity, causing sinus tachycardia. An increased heart rate not only increases myocardial oxygen requirements but also shortens the diastolic period, during which coronary perfusion occurs. The net result is a decrease in the ratio of myocardial metabolic supply to demand, which can lead to demand ischaemia, especially in the presence of pre-existing coronary artery disease. The metabolic consequences of cardiac tachyarrhythmias and the compensatory sympathetic hyperactivity of heart failure can contribute to this effect. The systemic inflammatory response to pneumonia can also increase the inflammatory activity within coronary atherosclerotic plaques, making them unstable and prone to rupture. This same pneumonia-driven systemic inflammatory response causes endothelial dysfunction and increases the procoagulant activity of the blood, which can contribute to the formation of an occlusive thrombus over a ruptured coronary plaque. Endothelial dysfunction can also change the coronary vascular tone (ie, vasoconstriction), contributing further to myocardial ischaemia and infarction.

New or worsening cardiac arrhythmias

In patients with pneumonia, new or worsening cardiac arrhythmias can result from myocardial or pericardial injury, or both, from ischaemic (acute coronary syndromes, demand ischaemia, or both) and non-ischaemic causes (direct bacterial or viral infection with or without systemic inflammatory mechanisms). Cardiac arrhythmias can also result from strain-induced changes in the electrical properties of cardiomyocytes and the compensatory sympathetic hyperactivity recorded in heart failure. Some antibiotics, such as macrolides and fluoroquinolones, also have arrhythmogenic potential (see later).

Effects of commonly used cardiovascular drugs on the course of pneumonia

Aspirin

In a large retrospective cohort study (n=1007) of unselected patients with pneumonia admitted to hospital, investigators reported a non-statistically significant 37% reduction in short-term mortality in those patients using aspirin,[82] whereas in a smaller (n=127) study of elderly patients with severe community-acquired pneumonia, the investigators showed a significant association between use of antiplatelet drugs (84% low-dose aspirin) and reduced need for intensive care and shorter hospital stays.[83] Only one prospective, blinded controlled study has assessed the effect of aspirin in patients with pneumococcal pneumonia.[84] However, this study was too underpowered to show any meaningful difference in its relatively young population (67 patients, 54% of whom were <40 years old).[84] Relevant large contemporary randomised trials investigating the potential effect of aspirin in patients with pneumonia are not available.

Statins

Although theoretical considerations and the results of numerous observational studies suggest that statins might affect the outcomes of pneumonia with their pleotropic anti-inflammatory effects,[85] no prospective study has yet specifically addressed this question. Nevertheless, a recent meta-analysis of retrospective observational studies estimated a pooled reduction in pneumonia-related mortality of 47% in patients who were taking a statin when their pneumonia developed.[86] Although some investigators have questioned whether unrecognised bias associated with a so-called healthy user effect might have contributed to these results,[87,88] a beneficial effect of statins was also reported in studies that used propensity-matched analyses,[89,90] those in which investigators contrasted the effect of statins against that of other cardiovascular medications in their cohorts,[82] or when investigators analysed populations in which the use of statins was actively and uniformly emphasised and widely accessible.[91]

The value of continuing statin treatment during the acute phase of community-acquired pneumonia is also undefined. A large retrospective study suggested that this strategy might only be beneficial in patients with less severe pneumonia not needing intensive care, in whom continued statin treatment was associated with a 21% reduction in in-hospital mortality.[92] No studies have assessed a potential benefit of statins in reduction of the incidence of cardiac complications in patients with pneumonia.

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

The results of observational studies assessing the effect of previous use of ACE inhibitors on the outcomes of patients with community-acquired pneumonia are conflicting. Although some investigators reported increased survival of such patients,[89,93,94] others did not find an effect, but demonstrated an increased risk of acute kidney injury during the course of the infection.[65] Dissimilar pharmacological characteristics of lipophilic and hydrophilic ACE inhibitors might partly explain these differences.[95] Conflicting results have also been reported for users of angiotensin II receptor blockers.[81,96] Randomised trials addressing the effect of ACE inhibitors or angiotensin II receptor blockers in patients with acute pneumonia are not available.

Beta-blockers

A large observational cohort study showed that previous use of beta-blockers was associated with increased 30-day mortality and need for mechanical ventilation in patients with community-acquired pneumonia.[82] Randomised trials of the effect of beta-blockers on the incidence of cardiac complications in patients with pneumonia are not available.

Diuretics, calcium channel blockers, and other vasodilators

No studies have reported on the effect of diuretics, calcium channel blockers, or other vasodilators on the outcomes of patients with pneumonia.

Cardiovascular effects of common antibiotics

Intravenous formulations of some beta-lactam antibiotics contain substantial amounts of sodium and need frequent dosing, which might be a relevant consideration in patients with pre-existing heart failure. Typical regimens of aqueous benzylpenicillin (5 million units intravenously every 6 h) or piperacillin–tazobactam (3·375 g intravenously every 6 h), for example, can provide daily sodium loads equivalent to 1·3 g and 0·8 g, respectively; however, when sodium from the normal saline used for infusion of these drugs is considered, daily sodium loads can be as high as 3·3 g and 1·4 g, respectively. Macrolides have anti-inflammatory activity, and a beneficial reduction of inflammation-driven effects of pneumonia on the cardiovascular system has been hypothesised.[85] However, macrolides can also induce QT prolongation and, rarely, polymorphic ventricular tachyarrhythmia (ie, torsades de pointes)—an effect also attributed to fluoroquinolones.[97] A large retrospective study suggested that, when compared with patients taking amoxicillin, patients receiving azithromycin have a small but statistically significant increase in their short-term risk of cardiovascular death (47 additional events per 1 million courses of azithromycin treatment), especially in patients with high baseline cardiovascular risk.[97] A similar trend was also noted for levofloxacin, but was not statistically significant in this analysis.[97] Vancomycin, when infused rapidly, induces antigen–antibody-independent release of histamine from mast cells and basophils, causing peripheral vasodilation that results in pruritus and an erythematous rash over the face, neck, upper chest, and arms (red man syndrome) and, occasionally, severe hypotension.[98] This reaction can be mostly prevented with longer infusion times (≥1 h) and, if needed, prophylactic administration of antihistamines.[98,99] Although experimental studies have suggested potential cardiovascular actions of several other antibiotics, these findings have not translated into clinically meaningful effects.[100]

Implications for clinical practice

Clinicians and public health officials should optimise rates of influenzal and pneumococcal vaccination, especially in elderly patients and individuals with chronic cardiac disorders. Because more than 50% of cardiac complications are recognised at or within 24 h of presentation with acute pneumonia, a thorough investigation for the presence of cardiac complications should be part of the initial assessment of patients presenting with this infection. Clinicians should specifically investigate pre-existing cardiovascular disease and symptoms or signs of decompensated heart failure, cardiac arrhythmias, and acute coronary syndromes. A 12-lead electrocardiogram should be considered seriously, both for the assessment of prevalent abnormalities and for comparison purposes, in case cardiac complications are suspected later. Measurement of serum B-type natriuretic peptide concentrations can be considered when the presence of new or worsening heart failure cannot be established on clinical grounds alone. Further cardiac testing (ie, echocardiogram, or measurement of serum cardiac troponin concentrations) should be guided by clinical suspicion, and is not recommended routinely or as a screening tool to detect early subclinical abnormalities in this setting. Special attention should be paid to patients with clustering of risk factors for cardiac complications. These investigations should complement assessment of pneumonia severity (using validated methods such as the pneumonia severity index or CURB-65 scores), as recommended by existing guidelines, in site-of-care decisions for these patients (inpatient *vs* outpatient, and general medical ward *vs* intensive care unit).[17] In patients with prolonged QTc interval, alternative antibiotic regimens that do not include macrolides or fluoroquinolones should be considered, especially when pharmacokinetic or pharmacodynamic interactions with other medications known to prolong the QT interval (class Ia and class III antiarrhythmics, cisapride, antipsychotics, and tricyclic antidepressants) are likely, or when uncorrected hypokalaemia or hypomagnesaemia is present. In hospital inpatients, daily clinical assessment of cardiovascular status, including weight measurement and careful assessment of fluid balance, should be done. In patients with signs of volume overload, especially in those with a history of pre-existing heart failure, antibiotic alternatives with low sodium contents and infusion volumes should be chosen. In view of the high incidence of cardiac complications in patients admitted to hospital with pneumonia, a high index of suspicion for these events should be applied, especially for patients with a suboptimal clinical response. In patients who develop cardiac complications, the investigation and management of these events should follow standard clinical practice and procedures, but should also be informed by the pathophysiological considerations discussed earlier (figure 2). For example, physicians should be aware that increased serum concentrations of cardiac troponins without recognisable acute coronary syndrome are not infrequent in the setting of pneumonia. At hospital discharge, the patient's immunisation status against

influenza and pneumococcus, cardiovascular risk profile, and cardiovascular medications should be reviewed and updated as appropriate.

Areas for future research

The panel lists some suggested goals for future research. Previous investigations have focused mainly on characterisation of pneumonia-associated temporal changes in distinct elements of the cardiovascular system (ie, left ventricular function, peripheral vascular resistance, neuroendocrine system, and water and sodium balance) without consideration of potential interactions between them or their role in triggering cardiac complications in patients with this infection; therefore, more integrative mechanistic studies are needed. For example, although several pathophysiological processes might lead to new or worsening heart failure in patients with pneumonia (figure 2), distinction between non-ischaemic myocardial injury, metabolic supply–demand mismatch, changes in ventricular afterload, excessive neurohormonal activation, or a combination of these factors as the main mechanism driving the development of this complication will be of great importance in the design of strategies to prevent its occurrence. This rationale also applies to other pneumonia-associated cardiac complications. Because most pneumonia-associated cardiac complications occur in non-critically ill and elderly patients, these mechanistic studies should include these populations. Future investigations should also improve our ability to risk stratify patients with pneumonia for the occurrence of cardiac complications with the development of validated prediction algorithms, which should be applicable in research and clinical settings. This new information should guide interventions aimed at prevention of pneumonia-associated cardiac complications in high-risk groups, while characterising their effect on all-cause morbidity, mortality, health-care utilisation, and cost. Finally, methods to promote the synthesis and dissemination of this knowledge in a manner that translates effectively into positive changes in clinical practice are also essential.

Conclusions

Pneumonia is usually considered to be an acute process confined to the lungs, unless the disease is complicated by severe sepsis. However, pneumonia affects essential parts of the cardiovascular system, which is probably responsible for the substantial burden of acute cardiac complications that has been documented thoroughly in large cohorts. In view of the high incidence of cardiac complications in patients with pneumonia and the effect on mortality, the possibility of improving the outcomes of these patients by prevention, early detection, and early treatment of these events should be pursued. However, before targeted interventions can be designed and tested adequately, a better understanding of the mechanistic pathways underlying this association is needed. Meanwhile, awareness of this association should inform clinical practice in the provision of care for patients with pneumonia.

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