Cardiovascular sequelae of pneumonia

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Purpose of review
In this brief review, we discuss the current epidemiological data and latest results from basic research on the cardiovascular sequelae after lower respiratory tract infection.

Recent findings
Novel epidemiological evidence substantiates the association between pneumonia and subsequent cardiovascular events (CVEs) in the short- and long-term after viral or bacterial acute infection. Biomarkers such as cardiac troponin or coronary artery calcium may represent useful predictive tools for the detection of cardiac involvement during and after pneumonia. Particularly, *Streptococcus pneumoniae* directly cause cardiac damage by invasion into the myocardium and formation of microscopic lesions finally leading to the development of cardiac scarring in rodents and nonhuman primates. In addition, a causal relationship between pulmonary inflammation and atherosclerotic plaque formation in systemic arteries has emerged that appears to involve a mechanistic role for neutrophil granulocytes. However, many key pathomechanisms by which pneumonia may trigger or promote subsequent CVEs still remain unclear.

Summary
Pneumonia may deleteriously impact cardiovascular function. Direct cardiomyocyte destruction by pathogens as well as host inflammatory response associated effects including atherosclerotic plaque development and/or rupture have been observed. Details of underlying mechanisms need to be further investigated to deliver future perspectives for the prevention of CVEs subsequent to pneumonia.

Keywords
cardiovascular events, pneumonia, streptococcus pneumoniae

INTRODUCTION

Pneumonia is the most frequent infectious disease and has for decades been among the four leading causes of death worldwide. Even patients who survive the acute episode of pneumonia remain at an increased risk for morbidity and mortality in the postinfection period. Yet, the underlying causes for these long-term effects remain elusive. A growing number of epidemiological studies suggest associations between acute respiratory tract infections and increased risk for subsequent cardiovascular events (CVEs), including acute heart failure, acute coronary artery syndrome or ischemic stroke within days and weeks to years after pneumonia [1–3].

PATHOPHYSIOLOGY

Pneumonia affects the entire organism and involves many organ systems. Replication of pathogens such as *Streptococcus pneumoniae* or influenza virus inside the alveolar space causes tissue damage by release of virulence factors (e.g. the pore-forming toxin pneumolysin) and leads to activation of innate immunity. Pro-inflammatory cytokines [such as tumor necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1 beta) or IL-6] mediate an inflammatory response increasing the body's energy demand and oxygen consumption. In parallel, inflammation of the lung parenchyma and oedema formation disturb alveolar gas exchange and cause ventilation-perfusion-mismatch with subsequent hypoxemia, aggravating this critical state. In parallel, pulmonary vascular resistance increases in response to pro-inflammatory mediators such as platelet-

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KEY POINTS

- Epidemiological evidence suggests that pneumonia contributes to cardiovascular events within days and weeks to years after pulmonary infection.
- Discussed mechanisms include direct invasion of *S. pneumoniae* into the myocardium with formation of microscopic lesions as well as inflammation-driven destabilization of atherosclerotic plaques.
- In-depth understanding of underlying mechanisms is lacking but required to develop appropriate preventive and therapeutic strategies.

activating factor, resulting in an increased right ventricular afterload and a reduced left ventricular preload. Simultaneously, systemic vascular resistance may decrease causing hypotension, and in turn secretion of catecholamines. As a consequence, a hyperdynamic state manifests with persistent hypotension and tachycardia eventually requiring fluid resuscitation. However, administration of larger amounts of fluids may further affect the already compromised function of the right ventricle, and in combination with infection-associated anaemia lead to increased oxygen demand, and promote oedema formation in lungs with leaky capillaries due to pneumonia-induced endothelial barrier dysfunction, which further compromises oxygenation. Moreover, the increased heart rate primes the myocardium for the development of arrhythmias. In combination, these factors frequently impair left ventricular function in acute infection, as reflected by elevated levels of cardiac biomarkers such as B-type natriuretic peptide (BNP) or atrial natriuretic peptide (ANP). As such, a dangerous scenario of several positive feedback loops emerges by which acute respiratory infections negatively impact on the cardiovascular system (Fig. 1). Although otherwise healthy individuals are able to cope with these challenges, this situation may easily become critical in patients with preexisting coronary artery or heart disease [4].

CLINICAL DATA

Consistently, previous studies have demonstrated the close association between an acute infection and the onset of cardiovascular sequelae, with occurrence of CVEs in about 18% of pneumonia patients [3]. Most complications not only arise within the short-term period after infection (30 days) with about 90% occurring within the first week [5], but also events that occur later (several months up to years) are likely associated with previous lung infection [6].

Bornheimer *et al.* [7] studied the effects of pneumonia on the course of preexisting heart failure in a retrospective trial and described an increase in risk by 47.2% (17.8 vs. 12.1% in controls without pneumonia) for hospitalization due to aggravated heart failure in a follow-up period of 30 days up to 1 year. In a prospective study, the long-term effects of community-acquired pneumonia (CAP) or acute exacerbated COPD (AECOPD) on the occurrence of ischemic heart events in patients with preexisting peripheral artery disease were investigated over a period of 1.5 years [8]. Patients had a higher risk for CVEs (29.0 vs. 7.1% in controls) after acute respiratory infections, with a mean latency of 59.5 days. No differences between the effects of CAP or AECOPD on CVEs were detected. Eurich *et al.* [9▪▪] investigated the first-ever occurrence of congestive heart disease in a 10-year period after CAP. Previously, healthy patients had an increased risk for developing congestive heart disease [adjusted hazard ratio (HR) = 1.61] that was still increased 90 days after CAP (HR = 1.52) and even higher 1 year (HR = 1.86) after CAP. Interestingly, patients younger than 65 years showed a higher relative risk for the development of congestive heart disease than controls without infection, while older patients showed a higher absolute but a lower relative risk (HR = 1.98 and 1.55, respectively). These results were found for both inpatients and outpatients and are in line with previous studies showing that the risk of CVEs after CAP is highest shortly after infection, decreases after the first week, but remains elevated for years compared with controls [2,6].

Data from studies elucidating the effects of acute respiratory infections on the cardiovascular system are mostly derived from patients with pneumococcal CAP. However, cardiovascular sequelae of respiratory infections do not seem to be exclusively limited to bacterial pneumonia, as viral respiratory infections (especially influenza infections) are similarly associated with subsequent CVEs, specifically acute myocardial infarction (AMI) and stroke. In a recent population study from England, weekly occurrence of new AMI or stroke was documented and correlated with positive laboratory testing for several viral pathogens (including influenza, parainfluenza, RSV, human metapneumovirus, rhinovirus and adenovirus). The association between viral infections and AMI/stroke was specifically prominent at advanced age (> 65 years) [10]. A second study from Scotland investigated the effects of influenza infection or pneumococcal pneumonia on the incidence ratio for AMI/stroke in a case–control study. They observed an increased incidence ratio for AMI especially in the first 3 days after admission for pneumococcal pneumonia (incidence ratio = 5.41) as well as for influenza

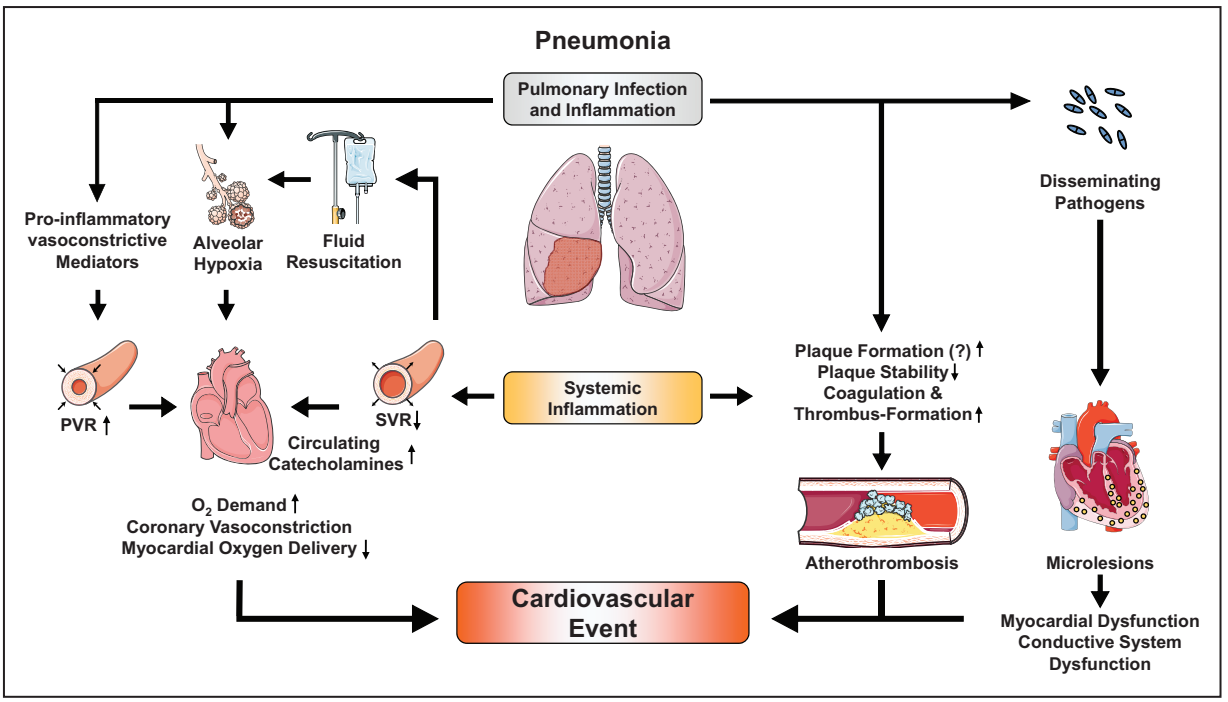

FIGURE 1. Illustration of the interrelation between acute pneumonia and cardiovascular events. PVR, pulmonary vascular resistance; SVR, systemic vascular resistance. Figure was produced using Smart Servier Medical Art (http://smart.servier.com/).

infection (incidence ratio = 5.59). Similar associations were evident in stroke for both influenza (incidence ratio = 6.79) and – with an even higher ratio – for pneumococci (incidence ratio = 12.3), and remained elevated throughout the follow-up period of over 28 days [11▪]. Comparable findings have been reported by Kwong *et al.* [12▪▪] from a population in Canada. They found an increased incidence ratio especially within a determined risk interval of days 1–7 after influenza infection, but no significant increase after day 8. Again, the risk was highest for patients aged more than 65 years. [12▪▪]. The notion that influenza infections may trigger subsequent CVEs is also in line with several studies showing a close association between vaccination against influenza virus and a reduced incidence of CVEs [13▪,14]. However, the question arises whether the influenza infection alone causes CVEs or rather paves the way for superinfection (e.g. with pneumococci), which then leads to CVEs. As potential direct mechanism by which influenza may promote CVEs, alterations in lipid metabolism affecting the course of atherosclerosis have been discussed [15,16]. At present, however, further research is warranted to confirm direct causal links.

Notably, the effects described above are not unique to respiratory infections. A series of studies have identified a link between various kinds of infections such as gastroenteritis, urinary tract infection or bacteraemia/sepsis and the occurrence of CVEs [17]. For patients hospitalized with sepsis, Wang *et al.* [18] described the risk to develop acute and fatal myocardial infarction (MI) over 10 years. As compared to controls, patients surviving sepsis had a significantly increased risk for the development of an MI over a 10-year follow-up period, with the highest risk in the first year (HR = 4.38) and a gradually decreasing, yet persistent risk over the following years. In addition, the risk for fatal MI was elevated, in particular in the first 4 years after hospitalization (HR = 3.29).

Many of the cited studies identified risk factors for patients with pulmonary infections to develop CVEs. An often reported risk factor was advanced age, which can be explained in part by the higher prevalence of cardiac comorbidities, including atherosclerosis, congestive heart disease or atrial fibrillation in elderly patients. The aforementioned results by Eurich *et al.* [9▪▪], however, were contradictory to this general trend, as CAP increased the risk for developing congestive heart disease relatively more in younger as compared to older patients. The authors suggested that lower vaccination rates against influenza and pneumococci in younger patients than older ones may account for this counterintuitive effect. In a recent study, Cilli *et al.* [19] analysed additional risk factors for the development of CVEs in patients with severe CAP. For AMI, they identified not only advanced age but also the presence of hypoalbuminemia, use of diuretics, vasopressors and haloperidol as significant

risk factors. Severity of disease, preexisting conditions and medications also seem to increase the risk for developing CVEs. Vasopressors may be correlated with a higher overall burden of disease and overstrain the cardiovascular system of critically ill patients leading to CVEs. The effects of diuretics, on the contrary, may be in part attributable to side effects of hypokalaemia, causing arrhythmias, which are also a common adverse effect of haloperidol due to elongation of the QT-interval. Along similar lines, it remains controversial whether the use of certain antibiotics, particularly macrolides, correlates with the occurrence of CVEs [20], as macrolide antibiotics can cause fatal arrhythmias by prolonging the QT-interval [21]. Accordingly, the previously mentioned study by Cilli *et al*. [19] also investigated whether different antibiotic combinations are associated with an increased risk for arrhythmias and mortality in CAP patients [19], and detected a significantly increased risk for arrhythmias for patients treated with a beta-lactam/macrolide combination. A study by Berni *et al*. [22], on the contrary, compared the outcomes for different antibiotic monotherapies in patients with upper and lower respiratory tract infections over a 37-day period, and presented seemingly opposing results, in that clarithromycin monotherapy was not associated with an increased risk for CVEs. However, the population studied by Berni *et al*. [22] was an outpatient cohort of younger patients with minor preexisting cardiac conditions. Thus, preexisting cardiovascular disease might play an important role, as Ray *et al*. showed in 2012: they demonstrated a higher risk for CVEs in patients with a higher baseline risk score for cardiovascular disease when treated with azithromycin [23]. In line with these findings, a recent study also highlighted the importance of adjustment for patient comorbidities finding a lower risk for CVEs following azithromycin therapy due to adjustment for patient characteristics and comorbidities [odds ratio (OR) = 1.35 without and 1.01 with adjustment] [24▪].

Although the works summarized here have established a generally increased risk for CVEs subsequent to pneumonia, prediction of CVEs on an individual level is at present still impossible, and specific strategies to abrogate or minimize the risk-enhancing effects of pneumonia are lacking. Thus, means for prediction and secondary prevention are urgently needed. Of the potential biomarkers that could aid in predicting individual risks for CVEs after pneumonia, cardiac troponins T and I (cTnT and cTnI) seem particularly promising. Troponins are filament proteins that are released from the cardiomyocyte upon myocardial damage and are used as state-of-the-art diagnostic tool for AMI with high sensitivity and specificity. Importantly, troponin levels have been shown to be elevated in patients with severe pneumonia and correlated with mortality [25]. Similarly, levels of cTnT were significantly associated with both short-term and long-term mortality after pneumonia and improved prognostic accuracy of the pneumonia severity index (PSI) [26▪]. Using noninvasive quantification of coronary artery calcium (CAC, an objective marker of coronary atherosclerotic burden) by MRI in hospitalized patients before and after pneumonia, Corrales-Medina *et al*. [27▪▪] identified patients at a high risk for CVEs to have higher baseline CAC levels and an additional significant increase in CAC after CAP, while patients at a low risk presented with lower CAC baseline levels, which did not increase after CAP. Moreover, among patients with high baseline burden of atherosclerotic cardiovascular disease, patients with pneumonia showed more pronounced increases in CAC than those without pneumonia, providing important evidence that increased risk for CVEs after pneumonia is not solely due to a higher baseline burden of atherosclerotic cardiovascular disease (ASCVD) in pneumonia patients, but triggered by pneumonia [27▪▪].

Although these findings identify troponin and CAC as promising prognostic candidates, discovery of meaningful biomarkers and development of effective prevention strategies are largely hampered by our limited mechanistic insight into the causal link between pneumonia and subsequent CVEs. In recent years, however, a number of experimental studies have started to address this critical knowledge gap.

EXPERIMENTAL DATA

Apart from the pathophysiological impact of preexisting cardiac disease (e.g. via demand ischemia), our understanding of the mechanisms contributing to CVEs in pneumonia patients is still in its infancy. Of late, however, a direct interaction between the most frequent pathogen of CAP, *S. pneumoniae*, and the heart is being discussed (Fig. 1).

In 2014, Brown *et al*. [28] described the ability of *S. pneumoniae* to invade and damage murine heart tissue during invasive pneumococcal disease (IPD), forming microscopic lesions (microlesions). Recent studies in mice show that bacterial invasion starts continuously as early as 12 h after infection, long before the first microlesions become visible. Moreover, immune cell infiltrations are only visible in an intermediate stage of lesion formation. In both early and late stages, immune cells are frequently absent, suggesting a local immunodeficiency. This may be explained by the fact that recruited macrophages are getting killed by pneumolysin via necroptosis and

the reduced number of macrophages within the heart in turn attenuates the inflammatory response [29]. The appearance of these microlesions, however, seems to be serotype- and strain-dependent. Strains need to reach high-grade bacteraemia first in order to form microlesions, and thus not all strains of pneumococci are capable of cardiac invasion. The spectrum of patterns of cardiac damage between strains varies from diffuse hydropic degeneration to demarked microlesions filled with bacteria and myocytolysis [30]. Further characterization of the invading pneumococci revealed that bacteria within the myocardium formed biofilms, had decreased sensitivity to antibiotics and produced large amounts of pneumolysin [31▪]. Although it has been proposed that in the heart bacteria are mainly found extracellularly, Brissac *et al.* [32] described the ability of *S. pneumoniae* to directly invade and replicate inside cardiomyocytes. They also identified Streptococcus pyruvate oxidase, an enzyme with key metabolic functions that also mediates reactive oxygen species (ROS) production. Deletion of the pneumolysin gene in serotype 4 pneumococci did not prevent cardiac microlesion formation, but application of antioxidants was efficient suggesting that ROS may act as an alternative virulence factor enabling heart tissue destruction [32]. To confirm the results in an experimental model that better reflects human disease, Reyes *et al.* [33▪] developed a nonhuman primate (NHP) model of severe pneumococcal pneumonia. In NHP with severe pneumonia, noninvasive cardiac monitoring revealed transient aberrations in the normal heart function shown by ECG abnormalities and ventricular motility disorders. Further, pneumococci were shown to invade the hearts of NHP, noteworthy in a more disseminated manner compared with the demarked microlesions in mice. When rescued with antibiotic therapy, NHP developed cardiac scarring as a result of collagen synthesis in damaged myocardium suggesting that scarring might contribute to the long-term consequences of CAP by promoting arrhythmias and/or impairing left ventricular function leading to CVEs.

Apart from affecting the myocardium, acute respiratory infection might also affect the course of atherosclerosis: Jaw *et al.* [34] investigated the effects of sterile inflammation following the intratracheal application of lipopolysaccharide (LPS) in atheroprone mice and showed that LPS-induced pulmonary inflammation led to destabilization of atherosclerotic plaques as demonstrated by increased cell content and signs of haemorrhage. LPS activates toll-like receptor 4 leading to recruitment of polymorphonuclear leukocytes (PMNs) as main effector cells. As depletion of PMNs was efficient to prevent plaque destabilization, PMNs were suggested to play a crucial role in the pathogenesis of plaque vulnerability induced by lung injury. Interestingly, intraperitoneal application of LPS did not cause plaque destabilization suggesting that pulmonary localization of the focus of inflammation might be important in the pathogenesis [34,35]. Although infection with *Chlamydophila pneumoniae* had previously been proposed as an underlying cause of atherosclerosis, convincing clinical evidence supporting this hypothesis could not be produced so far, as antibiotic treatment did not turn out to be beneficial against atherosclerosis progression [36].

CONCLUSION

Numerous epidemiological studies have convincingly shown a link between acute lung infection and subsequent cardiovascular disease, but the underlying mechanisms are not yet understood. Occurrence of CVEs in the long-term period after infection implies that long-lasting pathomechanisms are initiated in the acute stages of pneumonia. In experimental studies, some possible mechanisms, such as invasion of bacteria into the myocardium with subsequent scarring, and destabilization of atherosclerotic plaques in the context of pulmonary inflammation have been identified, but further validation and systematic expansion of these findings is warranted. Systems medicine approaches may help to unravel the complex relationship between lung infection and cardiovascular diseases by generating mathematical models that may enhance our mechanistic understanding, identify patient populations at risk for pneumonia-driven CVEs and create personalized therapeutic strategies.

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Figure 1 was created by modifying SMART Servier Medical Art illustrations by LES LABORATOIRES SERVIER SAS and licensed under a Creative Commons Attribution 3.0 Unported License.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Corrales-Medina VF, Musher DM, Wells GA, *et al.* Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. Circulation 2012; 125:773–781.
2. Corrales-Medina VF, Alvarez KN, Weissfeld LA, *et al.* Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA 2015; 313:264–274.
3. Corrales-Medina VF, Suh KN, Rose G, *et al.* Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. PLoS Med 2011; 8:e1001048.
4. Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA. Acute pneumonia and the cardiovascular system. Lancet 2013; 381:496–505.
5. Violi F, Cangemi R, Falcone M, *et al.* Cardiovascular complications and short-term mortality risk in community-acquired pneumonia. Clin Infect Dis 2017; 64:1486–1493.
6. Mortensen EM, Kapoor WN, Chang CC, Fine MJ. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. Clin Infect Dis 2003; 37:1617–1624.
7. Bornheimer R, Shea KM, Sato R, *et al.* Risk of exacerbation following pneumonia in adults with heart failure or chronic obstructive pulmonary disease. PLoS One 2017; 12:e0184877.
8. McDermott MM, Tian L, Wunderink RG, *et al.* Pulmonary hospitalizations and ischemic heart disease events in patients with peripheral artery disease. Vasc Med 2017; 22:218–224.
9. ■■ Eurich DT, Marrie TJ, Minhas-Sandhu JK, Majumdar SR. Risk of heart failure after community acquired pneumonia: prospective controlled study with 10 years of follow-up. BMJ 2017; 356:j413.

The large prospective study shows that community-acquired pneumonia substantially increases the risk of heart failure across the age and severity range of cases over a 10-year period.

10. Blackburn R, Zhao H, Pebody R, *et al.* Laboratory-confirmed respiratory infections as predictors of hospital admission for myocardial infarction and stroke: time-series analysis of English data for 2004-2015. Clin Infect Dis 2018; 67:8–17.
11. ■ Warren-Gash C, Blackburn R, Whitaker H, *et al.* Laboratory-confirmed respiratory infections as triggers for acute myocardial infarction and stroke: a self-controlled case series analysis of national linked datasets from Scotland. Eur Respir J 2018; 51:pii: 1701794.

A self-controlled case series based on national surveillance data reporting a pronounced triggering effect of both *S. pneumoniae* and influenza virus in AMI and stroke.

12. ■■ Kwong JC, Schwartz KL, Campitelli MA, *et al.* Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 2018; 378:345–353.

This work describes the association between laboratory-confirmed influenza infection and AMI. Further, the authors identified the first 7 days after detection of influenza as high-risk interval.

13. ■ Chiang MH, Wu HH, Shih CJ, *et al.* Association between influenza vaccination and reduced risks of major adverse cardiovascular events in elderly patients. Am Heart J 2017; 193:1–7.

A large, population-based case–control study demonstrating a protective effect of influenza vaccination against major CVEs in elderly patients.

14. Udell JA, Zawi R, Bhatt DL, *et al.* Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. JAMA 2013; 310:1711–1720.
15. Hebsur S, Vakil E, Oetgen WJ, *et al.* Influenza and coronary artery disease: exploring a clinical association with myocardial infarction and analyzing the utility of vaccination in prevention of myocardial infarction. Rev Cardiovasc Med 2014; 15:168–175.
16. Naghavi M, Wyde P, Litovsky S, *et al.* Influenza infection exerts prominent inflammatory and thrombotic effects on the atherosclerotic plaques of apolipoprotein E-deficient mice. Circulation 2003; 107:762–768.
17. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. Lancet Infect Dis 2010; 10:83–92.
18. Wang HE, Moore JX, Donnelly JP, *et al.* Risk of acute coronary heart disease after sepsis hospitalization in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. Clin Infect Dis 2017; 65:29–36.
19. Cilli A, Cakin O, Aksoy E, *et al.* Acute cardiac events in severe community-acquired pneumonia: a multicenter study. Clin Respir J 2018; 12: 2212–2219.
20. Svanstrom H, Pasternak B, Hviid A. Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study. BMJ 2014; 349:g4930.
21. Antzelevitch C, Sun ZQ, Zhang ZQ, Yan GX. Cellular and ionic mechanisms underlying erythromycin-induced long QT intervals and torsade de pointes. J Am Coll Cardiol 1996; 28:1836–1848.
22. Berni E, de Voogd H, Halcox JP, *et al.* Risk of cardiovascular events, arrhythmia and all-cause mortality associated with clarithromycin versus alternative antibiotics prescribed for respiratory tract infections: a retrospective cohort study. BMJ Open 2017; 7:e013398.
23. Ray WA, Murray KT, Hall K, *et al.* Azithromycin and the risk of cardiovascular death. N Engl J Med 2012; 366:1881–1890.
24. ■ Polgreen LA, Riedle BN, Cavanaugh JE, *et al.* Estimated cardiac risk associated with macrolides and fluoroquinolones decreases substantially when adjusting for patient characteristics and comorbidities. J Am Heart Assoc 2018; 7:pii: e008074.

This article highlights the importance of adjustment for risk factors when assessing the risk of macrolide antibiotics concerning CVEs, leading to a paradigm shift: The individual patient majorly determines the risk of macrolides for CVEs.

25. Lee YJ, Lee H, Park JS, *et al.* Cardiac troponin I as a prognostic factor in critically ill pneumonia patients in the absence of acute coronary syndrome. J Crit Care 2015; 30:390–394.
26. ■ Vestjens SMT, Spoorenberg SMC, Rijkers GT, *et al.* High-sensitivity cardiac troponin T predicts mortality after hospitalization for community-acquired pneumonia. Respirology 2017; 22:1000–1006.

This study shows that increased cardiac troponins on admission in patients hospitalized for CAP can serve as a prognostic biomarker for short-term and long-term mortality.

27. ■■ Corrales-Medina VF, Dwivedi G, Taljaard M, *et al.* Coronary artery calcium before and after hospitalization with pneumonia: the MESA study. PLoS One 2018; 13:e0191750.

Assessing CAC in patients with high atherosclerotic cardiovascular disease (ASCVD) risk before and after pneumonia, and in comparable patients without pneumonia, the authors showed that pneumonia was followed by a larger increase in coronary atherosclerotic burden. This study provides important evidence that increased risk for CVEs after pneumonia is not solely due to a higher baseline burden of ASCVD in pneumonia patients.

28. Brown AO, Mann B, Gao G, *et al.* Streptococcus pneumoniae translocates into the myocardium and forms unique microlesions that disrupt cardiac function. PLoS Pathog 2014; 10:e1004383.
29. Gilley RP, Gonzalez-Juarbe N, Shenoy AT, *et al.* Infiltrated macrophages die of pneumolysin-mediated necroptosis following pneumococcal myocardial invasion. Infect Immun 2016; 84:1457–1469.
30. Shenoy AT, Beno SM, Brissac T, *et al.* Severity and properties of cardiac damage caused by Streptococcus pneumoniae are strain dependent. PLoS One 2018; 13:e0204032.
31. ■ Shenoy AT, Brissac T, Gilley RP, *et al.* Streptococcus pneumoniae in the heart subvert the host response through biofilm-mediated resident macrophage killing. PLoS Pathog 2017; 13:e1006582.

An experimental study highlighting that formation of biofilm and switch to an altered bacterial phenotype contribute to the pathogenesis of cardiac injury by *S. pneumoniae in vivo*.

32. Brissac T, Shenoy AT, Patterson LA, Orihuela CJ. Cell invasion and pyruvate oxidase derived H2O2 are critical for Streptococcus pneumoniae mediated cardiomyocyte killing. Infect Immun 2018; 86: e00569-17.
33. ■ Reyes LF, Restrepo MI, Hinojosa CA, *et al.* Severe pneumococcal pneumonia causes acute cardiac toxicity and subsequent cardiac remodeling. Am J Respir Crit Care Med 2017; 196:609–620.

This translational in-vivo study demonstrates cardiac injury with necroptosis and apoptosis in NHPs with pneumococcal pneumonia. Demonstrating cardiac scarring after antibiotic therapy, the authors also provide an explanation for increased frequency of CVEs after therapy of pneumonia.

34. Jaw JE, Tsuruta M, Oh Y, *et al.* Lung exposure to lipopolysaccharide causes atherosclerotic plaque destabilisation. Eur Respir J 2016; 48: 205–215.
35. Fuijkschot WW, Morrison MC, Zethof IPA, *et al.* LPS-induced systemic inflammation does not alter atherosclerotic plaque area or inflammation in APOE3*LEIDEN mice in the early phase up to 15 days. Shock 2018; 50:360–365.
36. Joshi R, Khandelwal B, Joshi D, Gupta OP. Chlamydophila pneumoniae infection and cardiovascular disease. N Am J Med Sci 2013; 5:169–181.