Interpretation of PCT and ANP in patients presenting with dyspnea in the emergency department – clinical cases

Practical Case Studies – Background and Interpretation

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What is Procalcitonin?

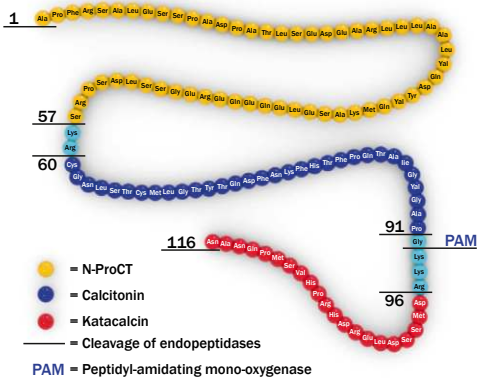


Fig. 1: Structure of PCT (Le Moullec et al. 1984)

- It is a precursor peptide of the hormone Calcitonin
- Levels increase particularly following bacterial infection and sepsis
- More rapid rise and fall in blood as compared to C-reactive protein
- Very strong signal with 10^5-fold increase as compared to other molecules showing only a 10 to 100-fold increase
- Half-life 24 hours
- Stable molecule

Why PCT instead of CRP, IL-6, lactate or clinical assessment (auscultation, temperature)?

Higher diagnostic accuracy for the diagnosis of sepsis

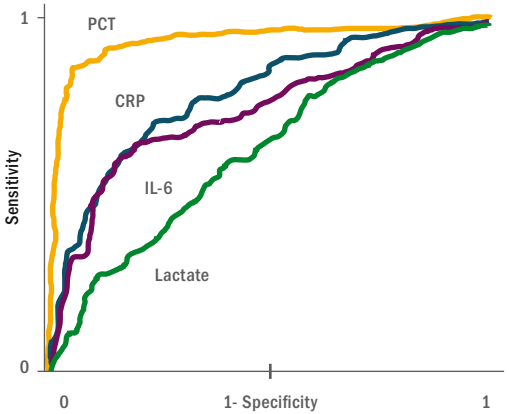


Fig. 2: Comparison of diagnostic performance of various markers for diagnosis of bacterial infection/sepsis (Mueller B, et al. Crit Care Med 2000)

Added value for diagnosis when PCT is used together with clinical assessment

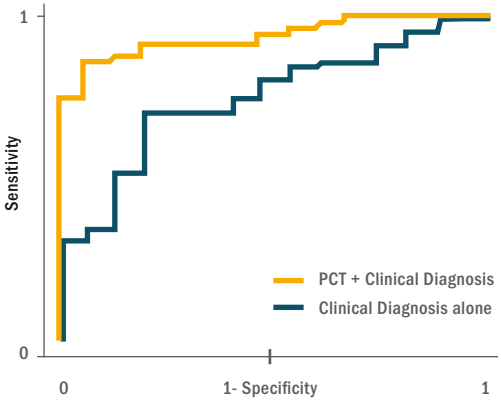


Fig. 3: Accuracy of sepsis diagnosis based on a clinical model with and without PCT(Harbarth S et al. Am J Respir Crit Care Med 2001, 164: 396-402)

Earlier increase compared to CRP and higher signal of PCT following a bacterial infection (marker time-concentration changes of PCT, IL-6 and CRP)

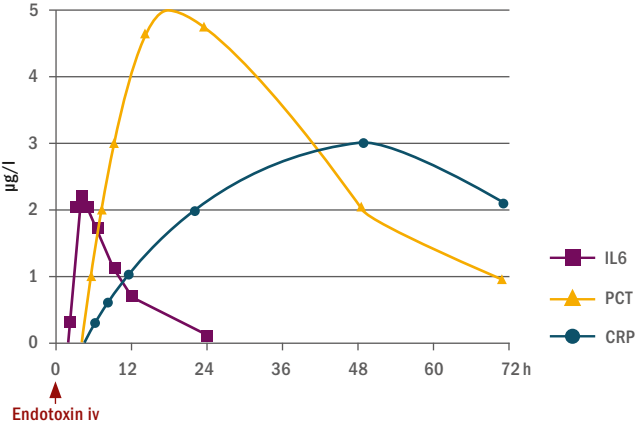


Fig. 4: Kinetics of PCT compared to other inflammatory markers upon infection
(Brunkhorst FM et al. Intensive Care Medicine 1998, 24: 888-892
Dandona P, J. Clin. Endocrinol. Metab. 1994, 79: 1605-1608
Harbarth S et al. Am J Respir Crit Care Med 2001, 164: 396-402
Meisner M, Procalcitonin – Biochemistry and Clinical Diagnosis, ISBN 978-3-8374-1241-3, UNI-MED, Bremen 2010)

Established use of PCT

PCT is used for early diagnosis of severe infection/sepsis and for guidance of antibiotic therapy

PCT is not only helpful for the decision to initiate antibiotic therapy early but also for identification of treatment success, and thus the need to stop or switch antibiotics during the course of treatment

Recommendations are based on findings from 14 randomized trials on 4,221 patients (Schuetz et al., Cochrane Database Syst Rev. 2012).

The recommended diagnostic PCT algorithm in patients presenting with acute symptoms of lower respiratory tract infection in an emergency:

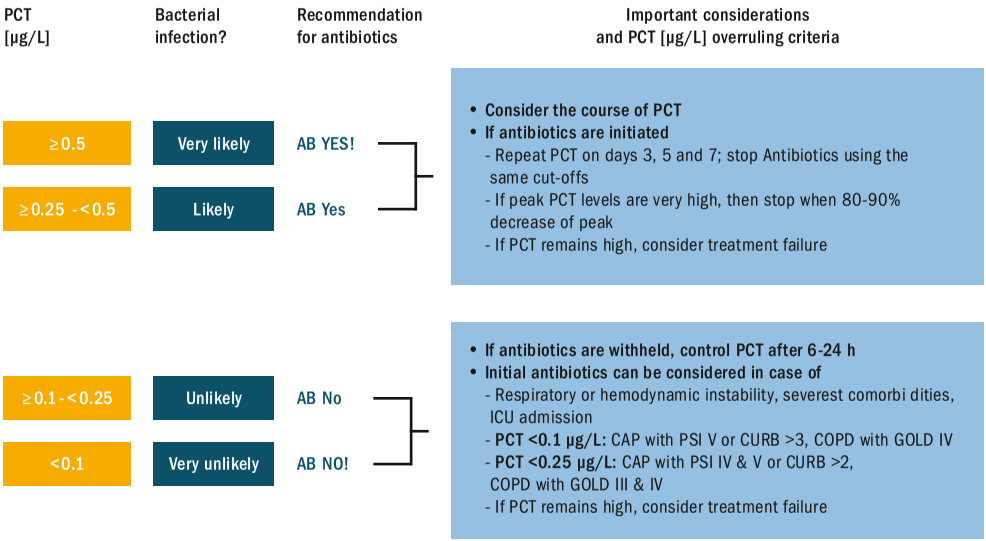


Fig. 5: Schuetz P, et al. Int J Cardiol 2016; 390-397.

Reduction of median time on antibiotic therapy

Use of PCT reduces median duration of antibiotic therapy from 8 days to 4 days without an increase of mortality or higher rates of treatment failures. One recent study shows reduced mortality (de Jong E et al., Lancet Infect Dis 2016)

High level of evidence supported by numerous clinical trials and a meta-analysis of 30 studies on 3,487 patients (Wacker et al., Lancet Infect Dis. 2013;13:426-35)

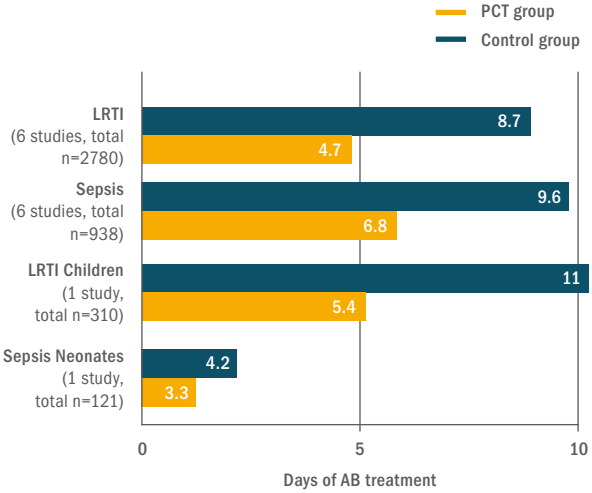


Fig. 6: Schuetz et al., Cochrane Database Syst Rev. 2012

Added value of PCT for dignosis of pneumonia in cases with clinical uncertainty (intermediate clinical pretest probability)

The highest diagnostic benefit from added measurement of PCT is observed among cases with diagnostic uncertainty (intermediate pretest probability between 21-80%) that can be expected in 50% of all cases.

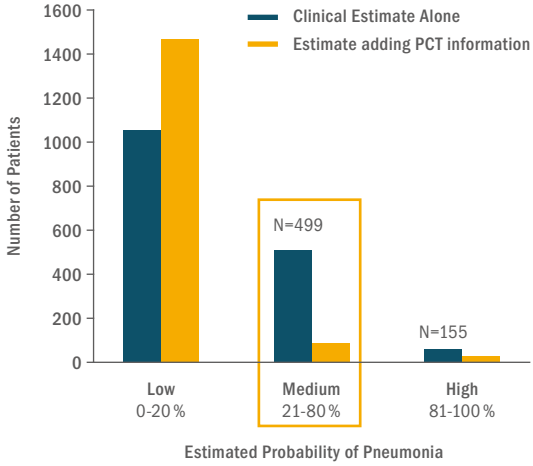


Fig. 7: Maisel A et al. Eur J Heart Fail 2012;14:278-286

PCT in the guidelines

For bacterial infections, sepsis, infections of lower respiratory tract (LRTI), community-acquired pneumonia (CAP), and for guidance of antibiotic therapy.

Established Guideline Recommendations of the most distinguished Medical Societies:


International

- Surviving Sepsis Campaign Guidelines 2016


Europe

- Guidelines for the management of adult lower respiratory tract infections
- EMA - Expert Meeting on Neonatal and Pediatric Sepsis


China

- Local guideline Xi'an province
- Guidelines for Quality Control in ED & ICU of Shanghai
- Expert Consensus: PCT in emergency clinical usage


France

- Practice guidelines for acute bacterial meningitides
- Management of lower respiratory tract infections in immunocompetent adults


Germany

- Prevention, diagnosis, therapy and follow-up care of sepsis
- Epidemiology, diagnosis, antimicrobial therapy and management of CAP and LRTI in adults
- Recommendations for calculated parenteral initial therapy of bacterial disease in adults
- Strategies securing rational antibiotic use in hospitals
- Epidemiology, diagnostic and therapy of adult patients with nosocomial pneumonia


Greece

- Definitions - Diagnostic Approach - Treatment Guidelines


Italy

- Tuscan Guidelines for Neonatal infections

Japan

- The Japanese Guidelines for the Management of Sepsis
- Guidelines for the management of acute pancreatitis
- Practical guideline of Febrile Neutropenia
- ICU Infection Prevention Guideline
- Guidelines for clinical testing

Spain

- Recommendations for the initial and multidisciplinary diagnostic management of severe sepsis in the hospital ED
- Consensus statement on management of severe sepsis and septic shock in pediatrics
- SEPAR Guidelines for nosocomial pneumonia
- Multidisciplinary guidelines for the management of community-acquired pneumonia

Sweden

- Swedish Medical Society: Severe sepsis and septic shock – early identification and initial management
- Swedish guidelines on the management of community-acquired pneumonia in immuncompetent adults

Switzerland

- Diagnosis and Management of Chronic Obstructive Pulmonary Disease

United States

- Guidelines for evaluation of new fever in critically ill adult patients
- The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age

Natriuretic peptides (NPs)

BNP or NT-proBNP or MR-proANP should be measured in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea. NPs have high sensitivity, and normal levels make the diagnosis unlikely in patients with suspected AHF.

What is MR-proANP?

MR-pro ANP, briefly proANP is a peptide hormone that is being secreted mostly from myocytes of the atria following stretch resulting in an increase in urine output coupled with depletion of sodium (called natriuretic effect). Increased levels indicate the presence of acute heart failure. Conversely, normal concentrations rule-out acute heart failure with a high negative predictive value of almost 100%. ProANP consists of 126 amino acids and is generated as a precursor of ANP after cleavage of a signal peptide from preproANP. ProANP is equimolar with ANP but is more stable and easier to measure in blood. It has no known hormonal activity.

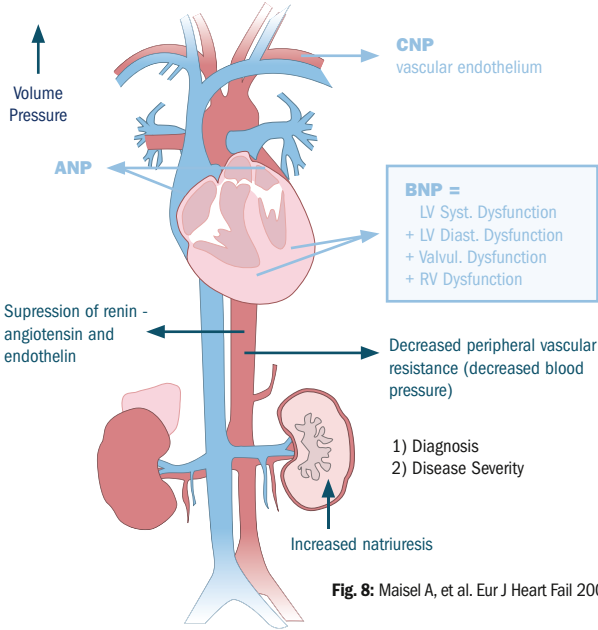


Fig. 8: Maisel A, et al. Eur J Heart Fail 2008; 10:824

How is proANP measured in blood?

ANP is measured using an automated immunofluorescent assay that measures MR-pro-ANP (midregional pro-atrial natriuretic peptide) in human serum, heparin- and EDTA plasma.

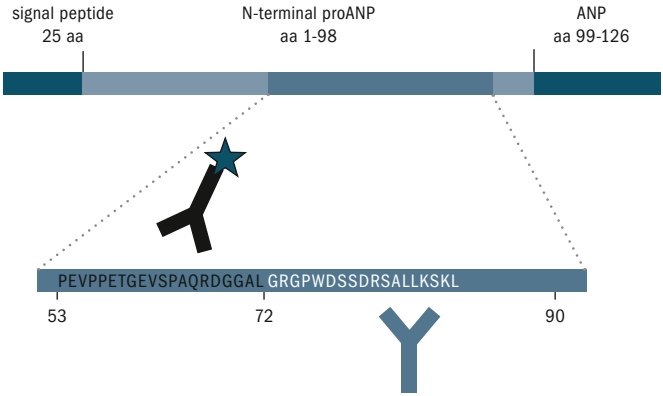


Fig. 9: Morgenthaler NG et al; Clin Chem 2004

- MR-proANP is the stable part of the prohormone
- A reliable surrogate marker of the active hormone
- Can be measured reliably and conveniently by standardized automatized sandwich immunoassay technology

Is proANP specific for acute heart failure?

Elevated levels of NPs, in general, do not automatically confirm the diagnosis of acute heart failure (AHF) as they may also be associated with a wide variety of cardiac and non-cardiac causes.

Causes of elevated concentrations of natriuretic peptides:

Cardiac	Heart failure Acute coronary syndromes Pulmonary embolism Myocarditis Left ventricular hypertrophy Hypertrophic or restrictive cardiomyopathy Valvular heart disease Congenital heart disease Atrial and ventricular tachyarrhythmias Heart contusion Cardioversion, ICD shock Surgical procedures involving the heart Pulmonary hypertension
Non-cardiac	Advanced age Ischaemic stroke Subarachnoid haemorrhage Renal dysfunction Liver dysfunction (mainly liver cirrhosis with ascites) Paraneoplastic syndrome Chronic obstructive pulmonary disease Severe infections (including pneumonia and sepsis) Severe burns Anaemia Severe metabolic and hormone abnormalities (e.g. thyrotoxicosis, diabetic ketosis)

Fig. 10: 2016 ESC - Heart Failure Guidelines
European Heart Journal (2016) 37, 2129–2200

Established clinical use

ProANP is a new diagnostic parameter for the diagnosis of AHF in patients presenting with acute dyspnoea.

- proANP is as effective for diagnosis of AHF as BNP and NT-proBNP
- proANP has advantages in particular subgroups such as patients with obesity (BMI >30), age>70 years, creatinine level > 1.6 mg/dl or BNP concentrations in the diagnostic grayzone (i.e. between rule-out and rule-in cutoffs).

ProANP possesses a similar performance for the diagnosis of AHF as BNP or NT-pro BNP (Findings from the BACH Trial)

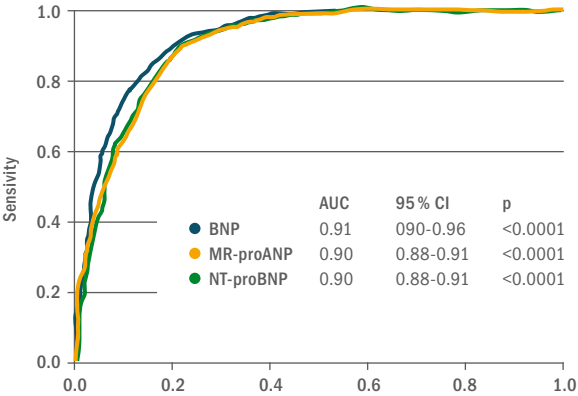


Fig. 11: Performance of various markers for diagnosis of AHF
Maisel A, et al. JACC 2010 European Journal of Heart Failure (2012) 14, 278–286

Diagnostic algorithm according to 2016 ESC Heart Failure Guidelines recommendations

Initial management of a patient with acute heart failure

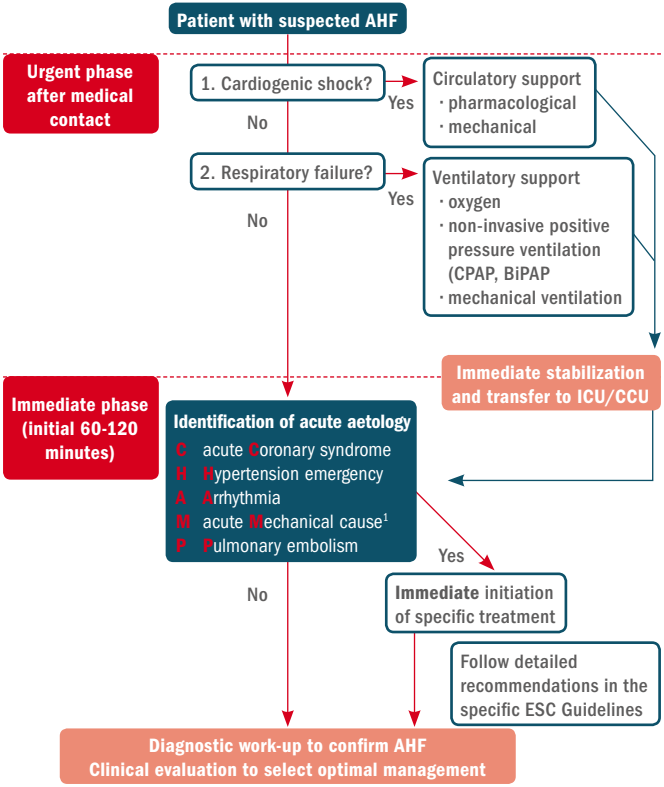


Fig. 12: 2016 ESC - Heart Failure Guidelines, European Heart Journal (2016) 37, 2129–2200

2016 ESC Heart Failure Guidelines recommendations for measurement of ANP and PCT in patients presenting with acute heart failure*

Biomarker measurements

- Upon presentation to the ED or CCU/ICU, a plasma natriuretic peptide (NP) level (BNP, NT-proBNP or MR-proANP) should be measured in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea.
- Assessment of procalcitonin levels may be considered in patients with AHF with suspected coexisting infection, particularly for the differential diagnosis of pneumonia and to guide antibiotic therapy, if considered.

Recommendations	Class	Level
Upon presentation a measurement of plasma natriuretic peptide level (BNP, NT-proBNP or MR-proANP) is recommended in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea.	I	A
At admission in all patients presenting with suspected AHF, the following diagnostic tests are recommended:		
a. 12-lead ECG;	I	C
b. chest X-ray to assess signs of pulmonary congestion and detect other cardiac or non-cardiac diseases that may cause or contribute to the patient's symptoms;	I	C
c. the following laboratory assessments in the blood: cardiac troponins, BUN (or urea), creatinine, electrolytes (sodium, potassium), glucose, complete blood count, liver function tests and TSH.	I	C

Optimal „rule-out" cutoff for NPs to rule-out acute heart failure:

- ≤300 ng/L NT-pro BNP
- ≤100 pg/ml BNP
- ≤120 pmol/l MR-pro ANP

* 2016 ESC Heart Failure Guidelines

Rationale for the combined measurement of proANP and PCT in the emergency department

1. Heart failure and pneumonia have a co-incidence of 10 to 15%
2. Infections of any kind complicate the course of acute heart failure in around 20% of cases
3. In-hospital mortality is about 20% among untreated patients with acute heart failure versus 5% in treated patients
4. The clinical diagnosis is challenging due to overlapping symptoms and pulmonary comorbidities such as COPD and asthma
5. The chest radiography is often difficult to interpret due to confounding effects of chronic congestion, pleural effusion, cardiomegaly and poor bedside image quality (inability to stand or for deep inspiration).

In many cases the diagnosis of either acute heart failure or pneumonia is straigth forward. However, often an exacerbation of acute heart failure triggered by infection or a dominating infection without relevant congestion cannot be excluded. The measurement of PCT in addition to clinical assessment allows identification of infection as a precipitant/ trigger of AHF and helps to “lable” the patient correctly.

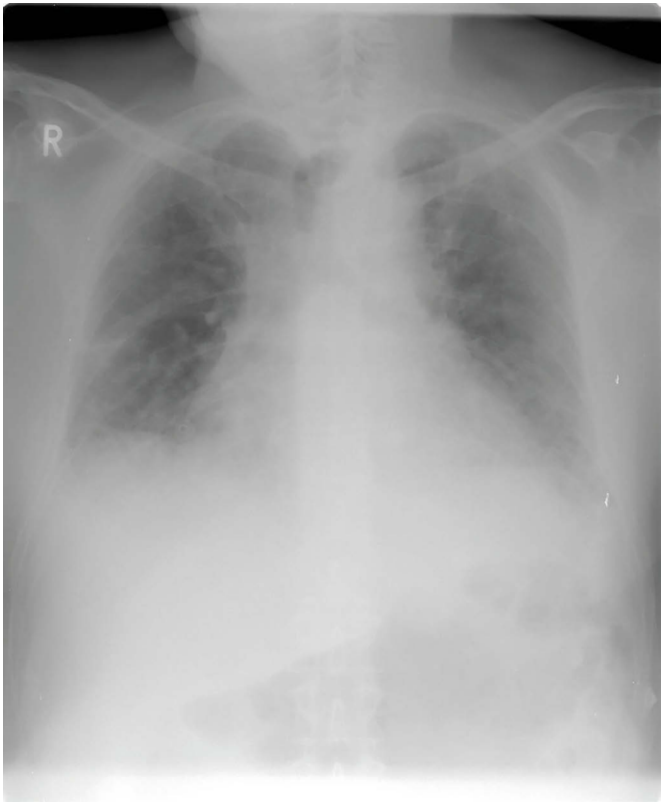


Fig. 13: Patient with AHF showing cardiomegaly and congestion. An infiltrate cannot be excluded reliably.

Added value of a combination of MR-proANP and PCT for diagnosis of AHF and/or pneumonia

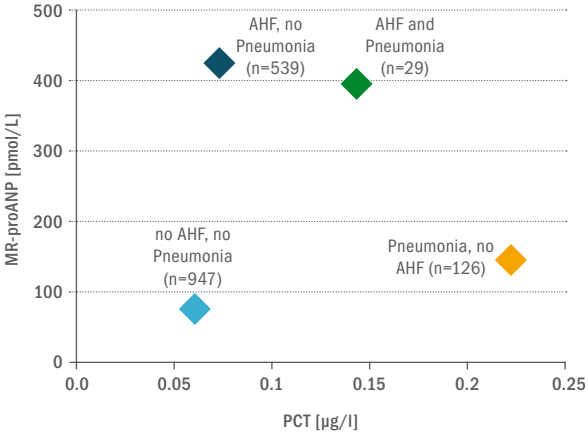
There are four different scenarios that should be distinguished:

A. Elevated MR-proANP and low PCT suggests AHF without pneumonia/infection

B. Elevated MR-proANP and elevated PCT suggests AHF with pneumonia/infection

C. Low MR-proANP and elevated PCT suggests pneumonia/infection

D. Low MR-proANP and low PCT suggests a differential diagnosis other than AHF or pneumonia/infection



Note: the figure shows median concentrations of Procalcitonin (PCT) and proANP.

Fig. 14: Median concentrations of PCT and proANP. Maisel A et al. Eur J Heart Fail 2012;14:278-286

Prognostic role of PCT in patients presenting with acute dyspnoea

BACH Study – Experience with PCT in patients presenting with acute dyspnea in the emergency department

Risk of 90-day mortality increases with increasing PCT concentration in patients with acute dyspnea (BACH trial)

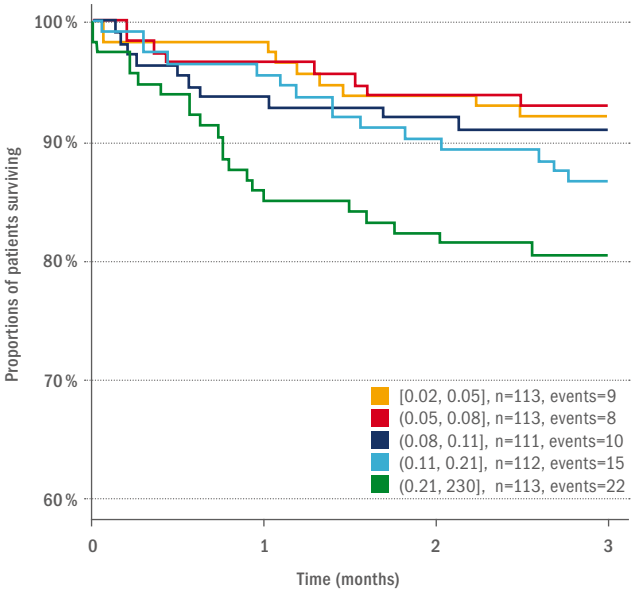


Fig. 15: PCT quintiles for patients diagnosed with AHF
Maisel A et al. Eur J Heart Fail 2012;14:278-286

Consequences of antibiotic treatment on 90-day survival by PCT concentration (Maisel A et al. Eur J Heart Fail 2012;14:278-286)

All patients

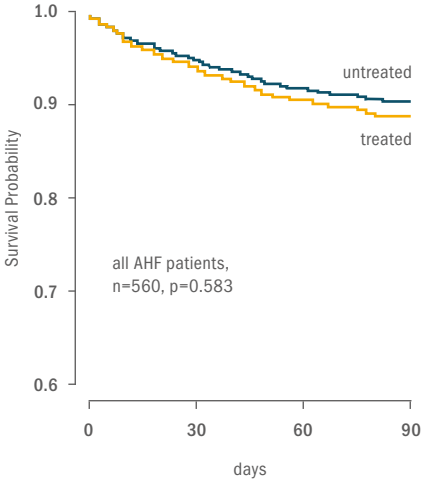


Fig. 16: antibiotic treatment and all-cause mortality within 90 days for patients with acute heart failure

Interpretation: No significant effect of antibiotic therapy on survival if not stratified by PCT level

Stratification by PCT level:

Possible scenarios

Scenario A: Patients with PCT values above the upper quintile (>0.21 µg/l who received antibiotic therapy demonstrated a significantly better survival.

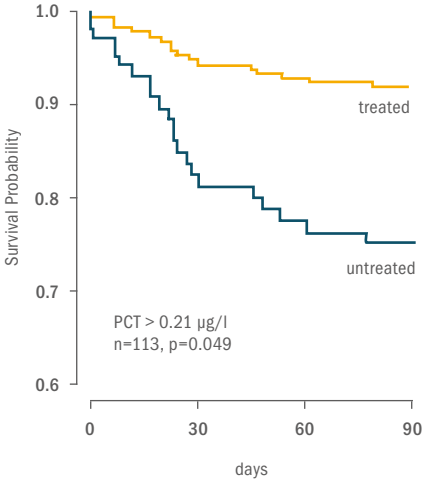


Fig. 17: antibiotic treatment and all-cause mortality within 90 days for patients with acute heart failure

Interpretation: correctly diagnosed and early treated patients with lower respiratory tract or other infection benefit from early administration of antibiotics

Scenario B Patients with PCT values <0.05 µg/l (lowest PCT quintile) who received antibiotic therapy had a significantly higher mortality at 30 days

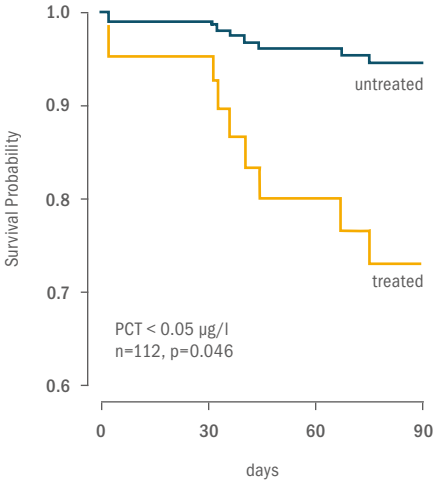


Fig. 18: antibiotic treatment and all-cause mortality within 90 days for patients with acute heart failure

Interpretation: Superfluous antibiotic treatment of suspected infection harms. Most probably the truly underlying acute decompensated heart failure is not treated optimally (delayed or no decongestion; eventually additional volume load) and/or potential toxic effects of antibiotic treatment, possible drug interactions occur.

Factors triggering acute heart failure

Acute coronary syndrome.
Tachyarrhythmia (e.g. atrial fibrillation, ventricular tachycardia).
Excessive rise in blood pressure.
Infection (e.g. pneumonia, infective endocarditis, sepsis).
Non-adherence with salt/fluid intake or medications
Bradyarrhythmia.
Toxic substances (alcohol, recreational drugs).
Drugs (e.g. NSAIDs, corticosteroids, negative inotropic substances, cardiotoxic chemotherapeutics).
Exacerbation of chronic obstructive pulmonary disease.
Pulmonary embolism.
Surgery and perioperative complications.
Increased sympathetic drive, stress-related cardiomyopathy.
Metabolic/hormonal derangements (e.g. thyroid dysfunction, diabetic ketosis, adrenal dysfunction, pregnancy and peripartum related abnormalities).
Cerebrovascular insult.
Acute mechanical cause: myocardial rupture complicating ACS (free wall rupture, ventricular septal defect, acute mitral regurgitation), chest trauma or cardiac intervention, acute native or prosthetic valve incompetence secondary to endocarditis, aortic dissection or thrombosis.

Source: 2016 ESC Heart Failure guidelines

The most relevant precipitants of AHF should be detected using the CHAMP rule (see Figure):

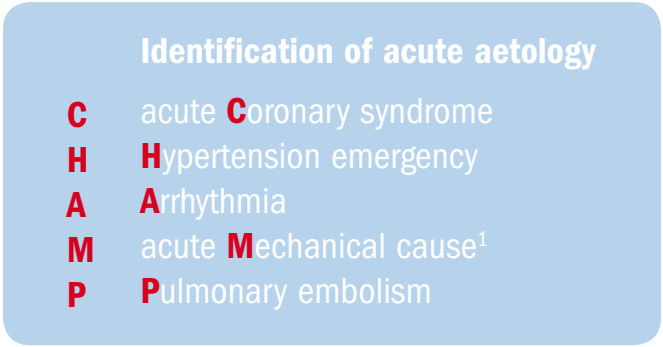


Fig. 19: 2016 ESC Heart Failure Guidelines

Infection and myocardial ischemia are frequent and represent the prognostically most relevant precipitants of acute heart failure

Ninety-days survival according to the presence of identified precipitating factors of acute heart failure (AHF).

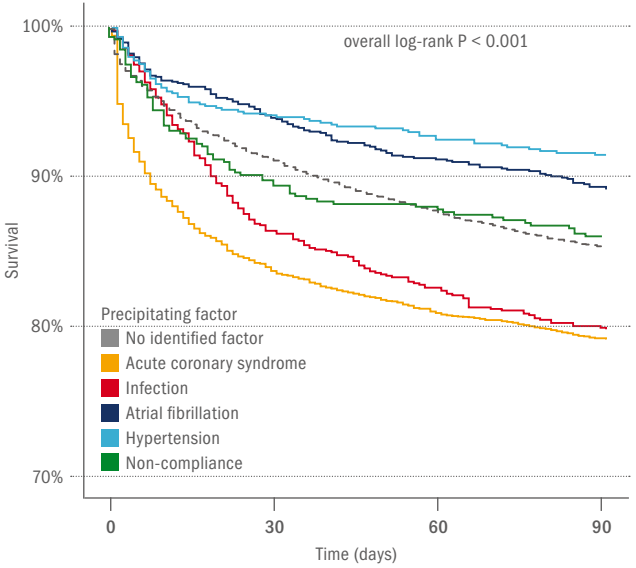


Fig. 20: Arrigo M etal., Eur J Heart Fail. 2017 Feb;19(2):201-208. doi: 10.1002/ejhf.682. Epub 2016 Oct 28

Precipitating factors and 90-days risk of death

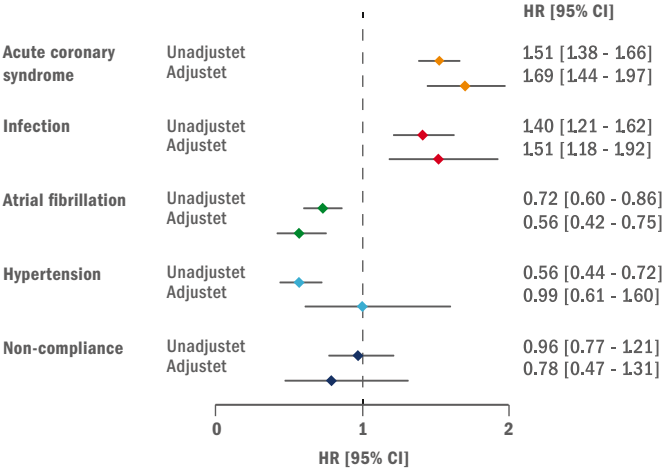
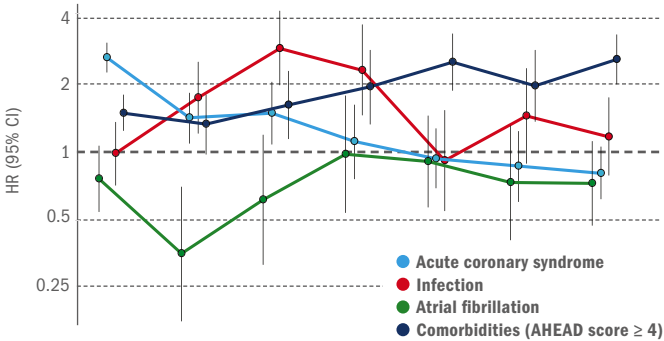


Fig. 21: Hazard ratios relative to cases with no identified precipitating factors
Arrigo M etal., Eur J Heart Fail. 2017 Feb;19(2):201-208. doi: 10.1002/ejhf.682.Epub 2016 Oct 28.

Interpretation: Even after adjustment lower survival in patients with acute coronary syndrome or infection and increased survival in patients with atrial fibrillation or hypertension

Early identification of the precipitant cause of AHF is paramount for outcomes

Time-course of risk of death according to precipitating factors and burden of co-morbidities



	W 1	W 2	W 3	W 4	W 5-6	W 7-8	W 9-13
Patients at risk	14'808	13'959	13'634	13'411	13'245	12'999	12'815
Number of events	849	325	223	166	246	184	339

Fig. 22: Hazard ratios relative to cases with no identified precipitating factors
Arrigo M etal., Eur J Heart Fail. 2017 Feb;19(2):201-208. doi: 10.1002/ejhf.682.Epub 2016 Oct 28.

Interpretation: The prognostic importance of infections are underestimated at presentation!

What is the optimal cutoff for PCT in AHF?

Indication	Cutoff µg/l
Diagnosis of pneumonia in heart failure	0.1
PCT for long-term outcomes over 2 years in acute heart failure	0.1
Diagnosis of infection in patients with acute heart failure Biomarker enrolment criteria: (MR-proANP > 300 pmol/L NT-pro BNP > 1800 ng/L BNP > 350 ng/ml)	0.2
Diagnosis of pneumonia in heart failure	0.21
Exclude systemic bacterial infection and guide antibiotic therapy	0.25

Main findings	Reference
Increased 90-day and 1-year-mortality	Alba et al., Am J Med. 2015
Patients with PCT-values > 0.1 µg/l have a > 2-fold higher risik for mortality (HR 2.32) and almost 2-fold higher risk (HR 1.80) for re-hospitalization than patients with PCT < 0.035 µg/l	Villanueva MP et al., Eur J Int. Med, 2015
IMPACT-EU (actively recruiting)	NCT 02392689
Clinical uncertainty regarding the diagnosis of pneumonia in patients presenting with acute dyspnea is reduced by measurement of PCT If PCT-values > 0.21 µg/l 4-fold higher mortality after 3 months than with PCT < 0.05 µg/l	Maisel A et al. Eur J Heart Fail 2012;14:278-286
with PCT measurement: lower mortality rate or ICU care (4.0 % vs. 20.0 %). Higher survival probability (4.0 % vs. 11.7 %) and shorter duration of antibiotic therapy 3.7 vs 6.5 days	Schuetz P. et al., Int J Cardiol. 2014;175:464-72

CONCLUSION: More evidence is available for PCT at cutoffs between 0.2 (0.21) and 0.25 µg/l; ongoing RCT interventional trial uses pre-specified PCT cutoff > 0.2 µg/l,

PCT cutoff < 0.25 µg/l, i.e. 0.1 µg/l is better suited for low acuity non-pneumonic and moderate-acuity pneumonic infections (Schuetz P, et al. Arch Intern Med 2011)

Overview of 10 clinical cases

Case 1
AHF and pneumonia

Patient

75-year old male

Presentation

Since 5 days onset of shortness of breath at rest, increasing fatigue; no chest pain or angina. Increasing edema of lower limbs for 2 weeks, improvement of symptoms in sitting position, nycturia twice per night. Coughing for 3 weeks, initially with transparent sputum followed by yellow discoloration, no fever, 36.9°C.

History

Arterial hypertension for years, obesity, former smoker (30 pack years), diabetic polyneuropathy with NIDDM, history of pulmonary embolism, paroxysmal non-valvular atrial fibrillation.

Physical examination

Normal cardiac auscultation; pulmonary rales; symmetric ankle edema

Laboratory findings

CRP: 257 mg/L [ULN<2mg/L]

PCT: 0.220 µg/l

Creatinine: 1.21 mg/dl

eGFR: 58.2 ml/min

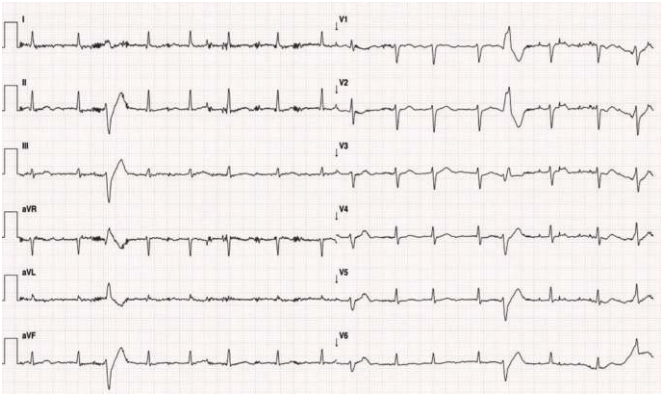
MR-proANP: 402.9 pmol/l

NT-proBNP: 3986 ng/L

hsTnT 12 ng/L at presentation

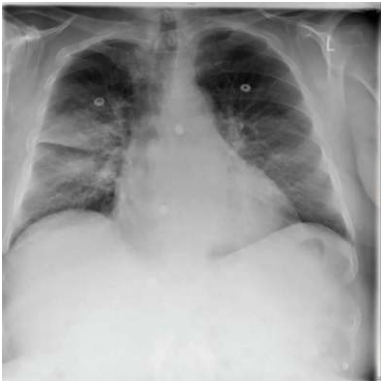
hsTnT 10 ng/L at 3 hours

ECG



Atrial fibrillation, normal ventricular rate, ventricular ectopic beats

Chest radiography (PA)



Diffuse infiltration in the right middle lobe, cephalization of veins, mild congestion.

2-D transthoracic echocardiography with Doppler

Normal dimension of the left ventricle with mild to moderately depressed systolic function, poor visualization of regional wall motion. Normal dimensions of left and right atria and right ventricle; normal right ventricular function; no pericardial effusion, no enlargement of inferior cava vein, normal respiratory reaction; no relevant valvular dysfunction.

Interpretation: Acute heart failure and pneumonia

Elevated values for MR-pro ANP render a diagnosis of acute heart failure very likely. Increased level of PCT suggests presence of a severe bacterial infection with pneumonia as confirmed by chest radiography. Normal cardiac troponin on serial testing excludes myocardial injury as a potential precipitant of acute heart failure.

Elevated natriuretic peptide values (both NT-proBNP and proANP) suggest acute heart failure despite absence of radiographic pulmonary congestion. A relevant pulmonary embolism seems unlikely as the patient was already on therapeutic doses of an oral anticoagulant, and there was no evidence of right ventricular dysfunction or pulmonary hypertension on echocardiography.

Clinical course: The patients was started on antibiotic therapy and received further diagnostic work-up for the underlying reason of acute heart failure. On coronary angiography, an underlying coronary artery disease with obstruction of 2 coronary arteries was identified.

The diagnosis of acute heart failure could have been missed in this patient with a pneumonia and vice versa. Concomitant measurement of both biomarkers add complementary information.

Case 2
AHF with inappropriate administration of antibiotics

Patient

72-year old male

Presenting symptoms

Since 1 week exertional dyspnea, ankle edema and coughing with clear sputum. Patient unable to lie flat, nycturia 3 times per night, no fever.

History

Coronary artery disease with chronically occluded left circumflex and 50% stenosis of LAD, mild to moderate depression of left ventricular function, prior implantation of an ICD due to inducible ventricular tachycardia, mild mitral valve regurgitation, COPD GOLD A.

Physical examination

Normal heart sounds, fine rales on lung auscultation, symmetric edema of lower extremities

Laboratory findings

CRP: 29.5 mg/l [ULN<2mg/L]

PCT: 0.049 µg/l

Leukocytes: 10.32/nl

Creatinine: 0.93 mg/dl

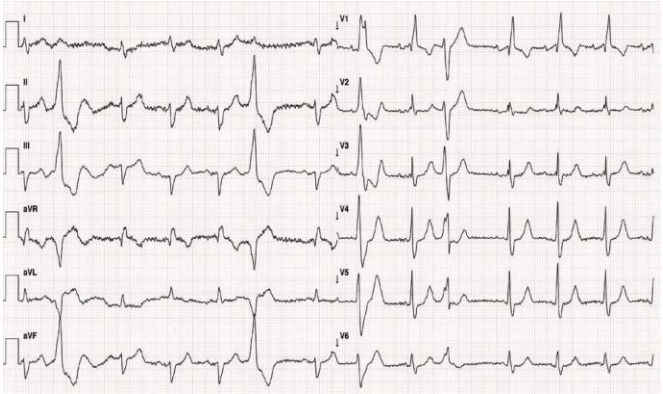
MR-proANP: 587 pmol/l

NT-proBNP: 16190 ng/l

hsTnT: 14 ng/L

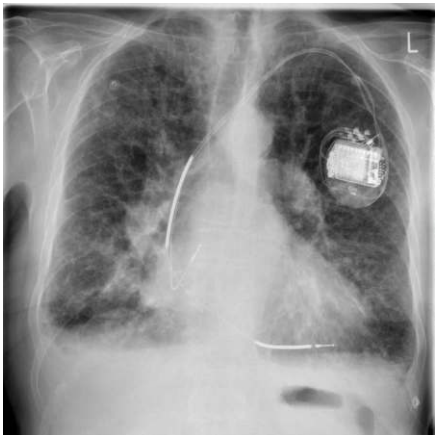
eGFR: 81.7 ml/min

ECG



Sinus rhythm, SIQIII-type,RBBB, monotopic ectopic ventricular beats

Chest radiography (PA)



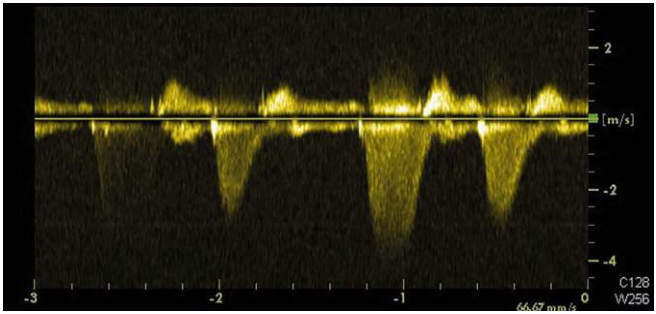
Signs of chronic venous congestion, bilateral pleural

effusions; patchy opacities of right lower lobe,

no pneumothorax, ICD left chest with electrodes

in projection to the right ventricle and right atrium

2-D transthoracic echocardiography with Doppler



Moderate to severe mitral valve regurgitation

Interpretation: Acute heart failure in the presence of progressive moderate to severe mitral valve regurgitation

A diagnosis of pneumonia was suspected in the presence of rales, elevated levels of CRP and patchy opacifications in chest radiography. After three pairs of blood cultures were obtained, antibiotic therapy was started. However, there was no improvement of dyspnea after antibiotic treatment. Echocardiography identified severe mitral valve regurgitation as the cause for acute heart failure.

Interpretation of low PCT and highly elevated proANP could have resulted in earlier exclusion of severe infection as a trigger for AHF and would have prompted an earlier echocardiography to search for the underlying reason of elevated proANP.

Case 3
Atypical pneumonia mimicking AHF

Patient

43-year old female

Presenting symptoms

Since 2 weeks increasing weakness and dyspnea. Progressive white-yellowish sputum, subfebrile temperature (37.9°C), no chest pain or angina, no edema, no fainting or dizziness, no nycturia, no change of body weight.

History

Coronary artery disease with 50% ostial stenosis of the first diagonal branch, prior NSTEMI, mildly depressed left ventricular function, bronchial asthma.

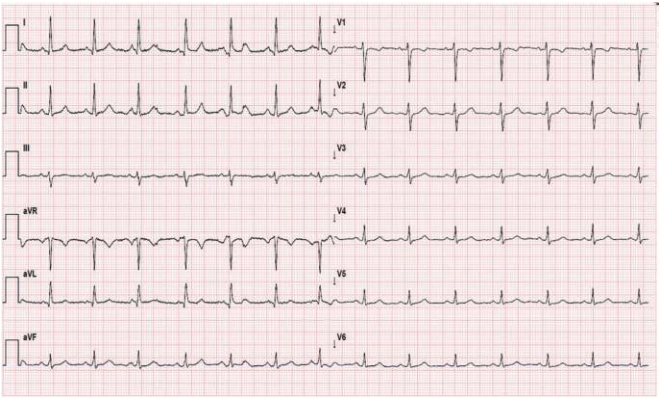
Physical examination

Normal heart auscultation, wheezing on lung auscultation

Laboratory findings

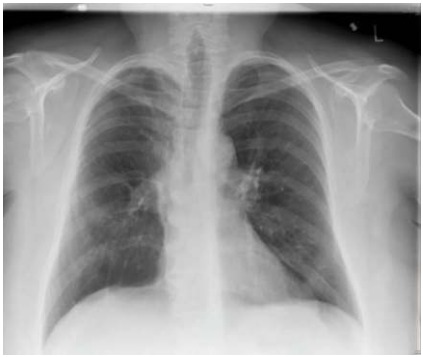
CRP: 194.6 mg/L [ULN<2mg/L]	MR-proANP: 40.8 pmol/l
PCT: 0.52 µg/l	NT-proBNP: 101 ng/L
Leukocytes: 10.56/nl	hsTnT: 6 ng/L
Creatinine: 0.65 mg/dl	eGFR: 99.8 ml/min

ECG



Normal sinus rhythm, left axis, no ST-T wave abnormalities

Chest radiography



Small opacities of both lungs, compatible with atypical pneumonia no congestion, no pleural effusions

Interpretation: Atypical pneumonia

Presence of sub-acute and unspecific symptoms together with normal proANP values renders AHF unlikely. Radiography together with elevated PCT and CRP along with unspecific and non-acute symptoms suggest a diagnosis of atypical pneumonia. However, in the absence of fever or discolored sputum, PCT aids in the discrimination of a relevant bacterial infection from exacerbation of asthma or COPD.

The diagnosis of an atypical pneumonia was supported by detection of Mycoplasma pneumonia in 2 of 3 blood cultures and by rapid clinical improvement and normalization of infection markers in blood after antibiotic treatment.

PCT may guide the decision for early antibiotic therapy in cases with intermediate pre-test probability, equivocal or non-conclusive findings of other markers and x-ray.

Case 4
AHF in a patient with preserved ejection fraction (HFpEF)

Patient

78-year old female

Presenting symptoms

Patient woke up with confusion and circulatory collapse, dizziness and shortness of breath. For several days new onset of progressive edema of lower limbs.

History

Coronary artery disease (3 vessel disease)

Physical examination

Systolic murmur on heart auscultation, no third heart sound, coarse rales on pulmonary auscultation, mild peripheral edema

Laboratory findings

PCT 0.08 µg/L

CRP 7.9 mg/L [ULN<2mg/L]

Leukocytes 10/nl

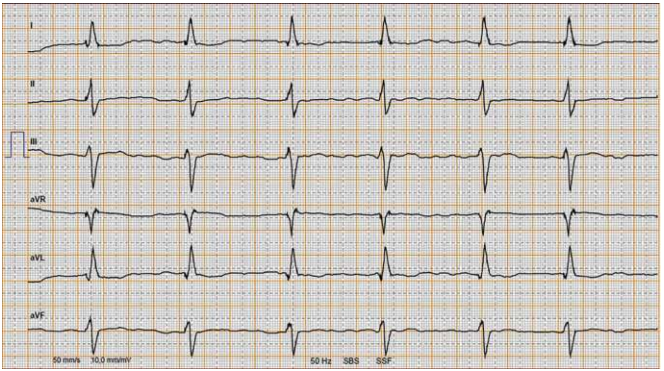
NT-proBNP 6006 ng/L

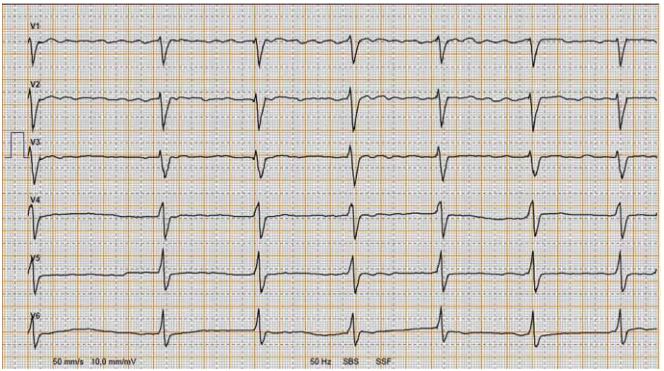
hsTnT 23 ng/L admission

hsTnT 22 ng/l at 3 hours

hsTnT 20 ng/l at 24hours

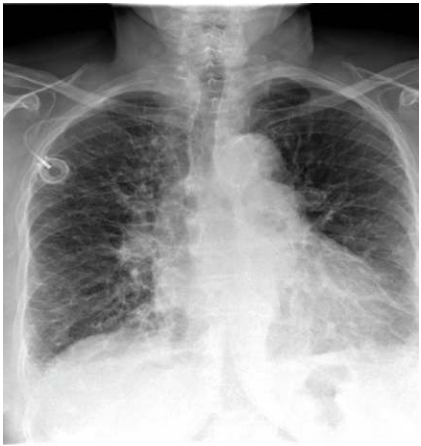
ECG





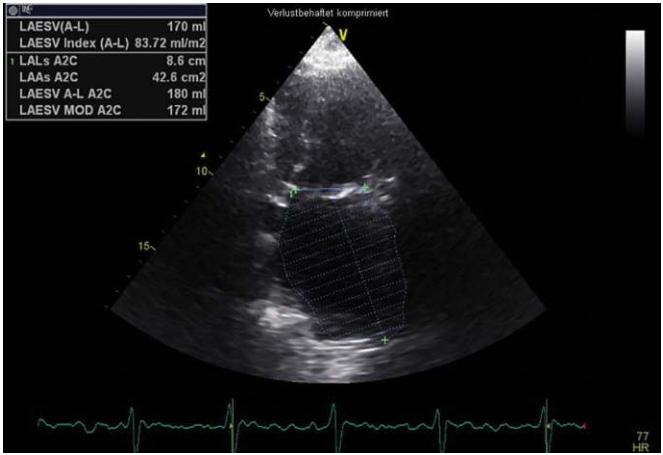
Atrial fibrillation, 65 bpm, left axis, flat ST-T waves

Chest radiography



Cephalization of pulmonary veins, Kerley B lines, bilateral pleural effusions, cardiomegaly with a cardiothoracic index of 0.6. Port system right chest wall with a line draining into superior cava vein; elongation of thoracic aorta.

2-D transthoracic echocardiography:



Echocardiography shows normal systolic LV function (LV-EF 55%) without regional wall motion abnormalities; severely enlarged left atrium; mild mitral valve stenosis and regurgitation; moderate to severe tricuspid regurgitation with an estimated systolic PA pressure of 63 mmHg plus CVP and reversed flow in the hepatic veins.

Interpretation:

Combining echocardiographic findings and NT-pro BNP renders acute heart failure with preserved ejection fraction (HFpEF) likely. Relevant precipitants of acute heart failure such as pneumonia or severe infection, atrial fibrillation or other brady- or tachyarrhythmias or mechanical reasons such as severe heart valve dysfunction were ruled out using a biomarker strategy and imaging.

Myocardial ischemia represents a potential trigger in the presence of known triple coronary artery disease. However, a NSTEMI was ruled-out using serial troponin testing with levels constantly slight above the 99%tile. Nevertheless, elective coronary angiography should be considered in a patient with a recent acute cardiac decompensation in the absence of other explanations.

Case 5
AHF triggered by Atrial Fibrillation

Patient

80-year old male

Presenting symptoms

Development of massive dyspnea at rest during the night, progressive shortness of breath during the past 14 days, chronic dyspnea at exercise for several months. 3 days ago, diagnosis of atrial fibrillation and initiation of therapy with metoprolol and edoxaban for prevention of stroke; CHA2DS2-VASc-Score 5 (adjusted stroke risk 15.26%/year)

History

no previous CV disease, mild hypertension

Physical examination

irregular heart beats, coarse rales over the entire lung, RR 100/60 mmHg

Laboratory findings

CRP: 10mg/L [ULN<2mg/L]

PCT 0.05 µg/l

D-Dimer 1.01 mg/L

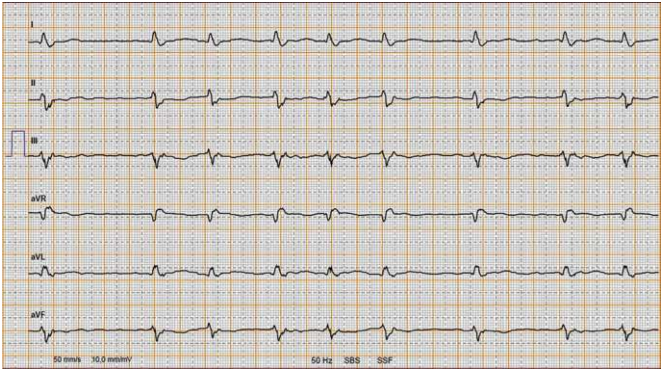
Leukocytes 7,22/nl

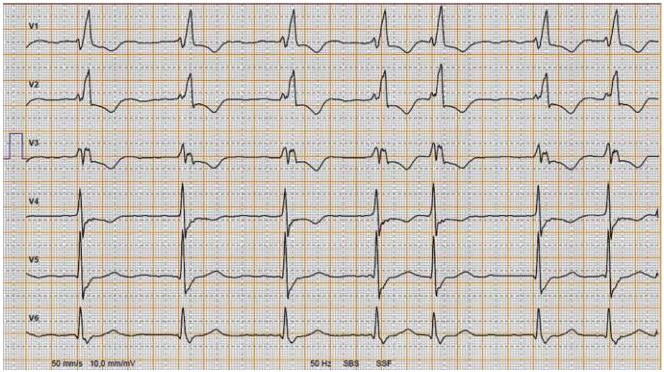
NT-proBNP 5784 ng/L

hsTnT 17 ng/L at admission

hsTnT 21 ng/L at 3 hours

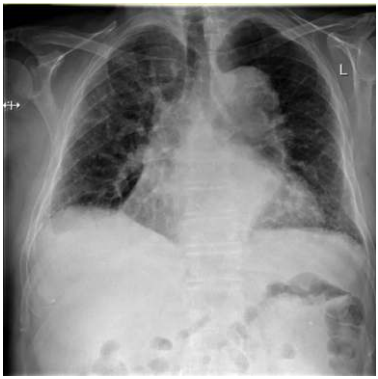
ECG





Atrial fibrillation, 97 bpm, left axis deviation, left anterior hemi block, incomplete RBBB

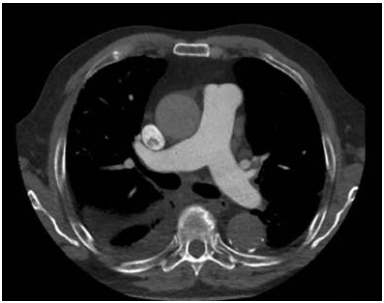
Chest radiography



Cardiomegaly with cardio-thoracic ratio of 0.58, elongation of thoracic aorta,

Interstitial opacities of right lung, prominent hili and signs of venous congestion, small right sided pleural effusion

Ms-CT-Angiography



No evidence for central or peripheral pulmonary embolism, chronic congestion, bilateral pleural effusions

2-D transthoracic echocardiography:

Moderately depressed systolic left ventricular function (LV-EF 40%), mild hypertrophy, severely enlarged left atrium; moderate mitral valve regurgitation, moderate to severe tricuspid valve regurgitation. Estimated systolic pulmonary artery pressure: 58 mmHg plus CVP.

Interpretation:

The clinical picture supported by highly elevated NT-pro BNP values indicate acute heart failure. Pneumonia or other severe bacterial infection was excluded as a precipitant of acute heart failure by normal PCT values. Given a presumably new borderline RBBB and left anterior hemiblock with elevated D-dimers a ms-CT was performed and ruled-out an acute pulmonary embolism.

The episode of paroxysmal atrial fibrillation with inadequate rate control was identified as the most likely trigger for acute cardiac decompensation. As a consequence the patient received metoprolol for immediate rate control followed by electrical cardioversion. Antibiotic therapy was withheld in the presence of a normal PCT and unsuspicious chest radiography.

Case 6
AHF and severe aortic valve stenosis and hypertensive crisis

Patient

81-year old female

Presenting symptoms

Sudden onset of acute dyspnea and subsequent pulmonary edema within few minutes, RR 230/135 mmHg

History

Moderately well controlled arterial hypertension for years, slowly progressive muscular weakness

Physical examination

Systolic murmur, coarse rales over entire lung on auscultation, RR 180/100 mmHg, normal temperature 37.5°C.

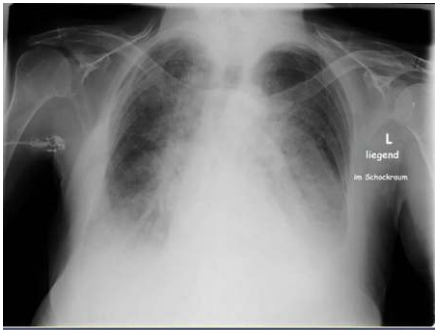
Laboratory findings

CRP: 13mg/L [ULN<2mg/L] NT-proBNP 7.506 ng/L

PCT 0.26 µg/L

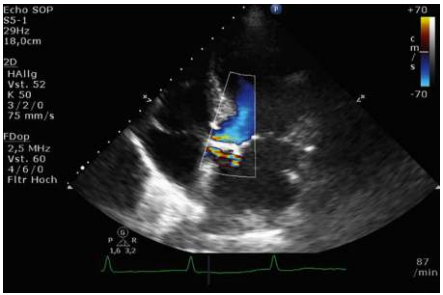
Leukocytes 8.29 /nl

Radiography of chest (supine AP position as upright position impossible)



Limited interpretation due to poor image quality in supine PA position. Diffuse opacities, possible bilateral pleural effusions, possible cardiomegaly, possible venous congestion, no pneumothorax.

2-D transthoracic echocardiography:



Normal dimension of left ventricle with left ventricular hypertrophy, mild depression of systolic LV function (LV-EF 45-50%), enlargement of left atrium, no wall motion abnormalities, severe reduction of aortic valve orifice (0.5 cm^2) and increased transvalvular velocity and pressure gradient (Vmax 5.17 m/s; Pmean 68 mmHg) indicating severe aortic valve stenosis; mild aortic valve regurgitation, mild to moderate mitral valve regurgitation, moderate triscuspid valve regurgitation, estimated systolic PA pressure 43 + 5 mmHg. Inspiratory collapse of non-enlarged inferior cava vein.

Interpretation:

The patient presented with acute pulmonary edema due to a hypertensive crisis and underlying severe aortic valve stenosis. Initially, PCT was elevated stimulating early antibiotic therapy although there was no evidence for pneumonia or severe bacterial infection.

However, fever of 38.5°C started on the next day accompanied by signs of right lower lobe pneumonia. The patient required non-invasive ventilation and loop diuretics before re-compensation followed by trans-femoral aortic valve implantation (TAVI) several days later.

Case 7
Hypertensive lung edema

Patient

69-years old male

Presenting symptoms

Rapid progressive dyspnea, no chest pain, peripheral oxygen saturation 86%, blood pressure RR 161/108mHg, respiratory rate 20/min

History

Non compaction cardiomyopathy, LVEF 25% (emergency echo consistent with prior examinations); no significant coronary artery disease; CRTd; permanent artrial fibrilliation, oral anticoagulation (Phenprocoumon)

Physical examination

Symmetric rales, tachypnea, irregular heart sounds, no murmurs, no peripheral edema.

Laboratory findings

Creatinine 1.25 mg/dL

NT-pro BNP 7473ng/L

Troponin T (POCT) at admission 56 (2h: 79; 12h: 110) ng/L

hs Troponin T 98 ng/L

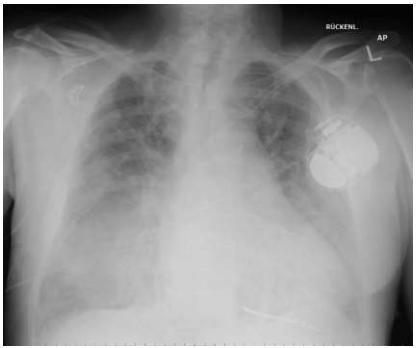
CRP 21.6mg/L [ULN <2mg/L]

Leukocytes 20.5/nL [N: 3.9-10.5]

PCT 0.08 µg/L

INR 3.53

Chest radiography

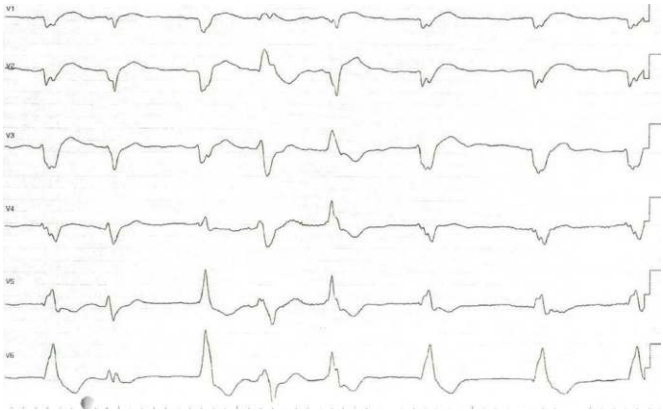


Pulmonary congestion, suspected pleural effusion, CRTd leads in projection to the left and right chamber, pneumonic infiltration right lower and middle field

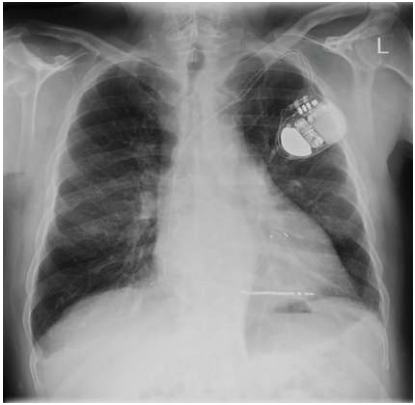
Thoracic sonography:

Typical (up to 4) B-lines per view as in pulmonary edema.

ECG:



Atrial fibrillation, LBB, premature ventricular beats



Follow-up chest radiography after 24 hours

Complete decongestion with clear lung fields following acute heart failure therapy.

Interpretation:

The patient had myocardial injury complicating hypertensive lung edema. Initial treatment was started with loop diuretics, i.e. Furosemid 80 mg i.v. plus morphine 4 mg i.v. and intravenous nitrate. In addition, calculated antibiotic therapy with Piperacillin/Tazobactam and Clarithromycin was started upon the assumption of a pneumonia.

In addition the patient received NIV ventilation via mask as well as oxygen supplementation showing a rapid improvement over the next 12 hours; on the next morning the patient was stable, no more rales, no dyspnea, lies flat in bed, no fever, no cough. The value of the retrospectively measured Procalcitonin in first blood sample was 0.08 µg/l.

Note:

This case clearly shows the unnecessary, often harmful administration of antibiotics following a difficult to interpret chest radiography. Conversely, a low PCT value renders a severe bacterial infection unlikely supporting that the patients had hypertensive pulmonary edema.

The inappropriate use of antibiotics is associated with worse outcome as it detracts from acute heart failure therapy and promotes dangerous bacterial resistence development.

Case 8
AHF and pneumonia

Patient

72-year old male

Presenting symptoms

acute shortness of breath, fever 37.5° C, coughing with yellowish sputum

History

COPD GOLD B, long persistent atrial fibrillation, prior pacemaker implantation

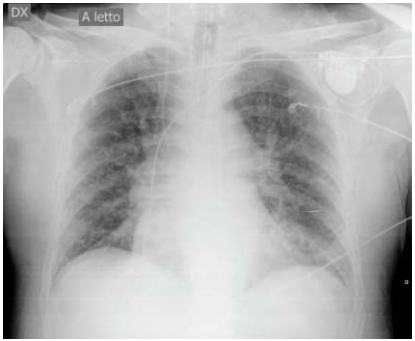
Physical examination

Tachypnea, tachycardia, rales over entire chest, prominent first heart sound, opening snap, diastolic murmur.

Laboratory findings

PCT 48.97 µg/l BNP 207 pg/ml

Chest radiography



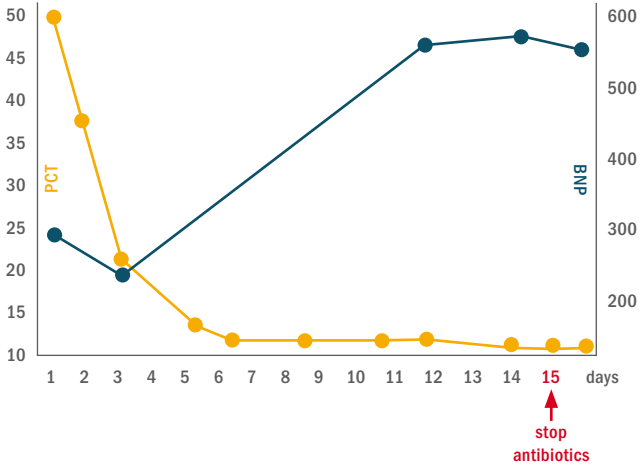
Chest X-ray revealed pulmonary congestion, blood flow redistribution and opacity in the lower left and right lung lobes. Pneumonia was confirmed by a CT scan.

Clinical course:

Search for urinary antigen of pneumococcus and legionella was negative, as the broncho-aspiration for Chlamidia, Legionella and Mycoplasma.

The patient was treated with diuretics for the acute pulmonary edema and with an antibiotic therapy with azithromycin (3 days) and meropenem plus linezolid (14 days).

The PCT blood levels progressively decreased, while the BNP levels increased.



Trans-thoracic echocardiography showed EF = 45%, wall motion score index = 2.00, left atrial enlargement and pulmonary artery systolic pressure = 59 mmHg.

Trans-esophageal echocardiography demonstrated a mitral valve with thickened cusps (5-8mm), mitral valve area = 0.7 cm2, PHT = 338ms, maximum gradient = 12 mmHg and medium gradient = 7.0 mmHg.

Cardiac surgical operation was performed, with mitral valve substitution. The post-operative course was uneventful and the patient was transferred to cardiac rehabilitation after 5 days, with BNP = 105 pg/ml.

Note:
Measuring PCT blood levels made it possible to suspect, diagnose and conveniently treat acute pneumonia in a framework of acute heart failure with elevated BNP. Following PCT blood levels was of great help in determining the length and success of antibiotic therapy, although treatment could have been stopped earlier in the retrospective view (day 9). The increasing values of BNP suggested the need of a surgical correction of the mitral valve disease and maybe also reflect volume changes over the treatment course of infection.

Case 9
Missed pneumonia

Patient

Male patient, 72-year old

Presenting symptoms

Patient was brought to the emergency department by ambulance because he collapsed in the bathroom due “to acute dyspnea”. Immediate treatment with diuretics and morphine was initiated by the ambulance nurses. The patients’ spouse explained that no clear prior signs of dyspnea were present during the last week and that he had a minor cough only. Further, the patient had no chest pain, particularly no peripheral edema, no nycturia, no fever, and no weight gain.

History

Diabetes mellitus type 2, prior MI, mildly depressed LV function, pacemaker in situ due to AV-block, NYHA-II.

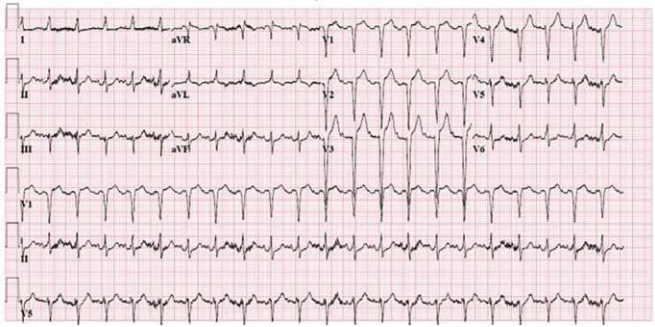
Physical examination

Tachypnea (35/min), peripheral oxygen saturation 97% with 100% O2-insufflation, lung auscultation with basal rales. BP 200/110mmHg, heart rate 135/min. Temp: 36.7 C.

Laboratory findings

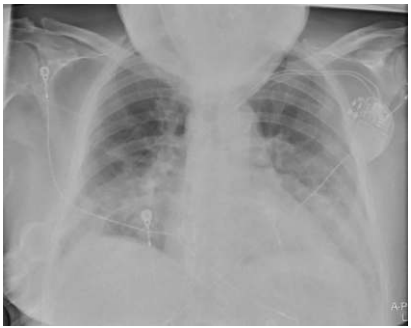
CRP: 64 mg/l [ULN<2mg/L]	Sodium: 135 mmol/l
PCT: 0.46 µg/l	NT-proBNP: 2,742 ng/l
Leukocytes: 15.6/ nl	hs-TnT: 89 ng/l
Creatinine: 112 µmol/l	eGFR: 58 ml/min

ECG



Sinus tachycardia, left axis, signs of previous anterior MI

Chest radiography



Bilateral consolidation with perihilar edema. Suspected for acutely decompensated heart failure

Interpretation: Acute Heart Failure

Treatment with diuretics, nitrates and pulmonary assistance resulted in a stabilization of the patient.

A lower respiratory tract infection based upon the cough could not be discriminated with current diagnostic assessments. PCT provided independent evidence that a (respiratory) infection might also play a contributory role in this presentation. Therefore, based upon the PCT level, antibiotic therapy was initiated and the patient could be discharged 4 days after admission in a good and stable condition.

This patient presented with typical acute heart failure. Heart failure is likely given the history of MI and heart failure, but an infection is a well-known precipitant of decompensation. However, in the current case the infection was not noticed at first view and this could lead to a delay of antibiotic treatment and therefore a prolonged hospital stay and worse outcome. This has been prevented with PCT measurement at admission, clearly indicating concealed infection and prompting antibiotic treatment.

Case 10
Acute heart failure and non-bacterial lung opacification

Patient

81-year old female

Presenting symptoms

Progressive dyspnea for 4 weeks, recently also at rest, stable angina CCS II, no edema, no nycturia, unintended weight loss of 7 kg within 6 months, no fever.

History

Known aortic valve stenosis and mild regurgitation, paroxysmal atrial fibrillation, normal left ventricular function, chronic renal failure Kidney Disease: Improving Global Outcomes(KDIGO):3, history of lung emphysema, medication with amiodarone.

Physical examination

Systolic murmur, normal lung auscultation, fine crackles right basal lung.

Laboratory findings

CRP: 4.2mg/L [ULN<2mg/L]

NT-proBNP: 8,372 ng/l

hsTnT: 17 ng/l

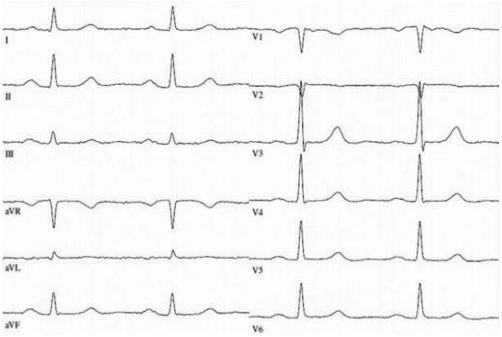
GFR: 45.4 ml/min

PCT: 0.03 µg/l

Leukocytes: 11.3/nl

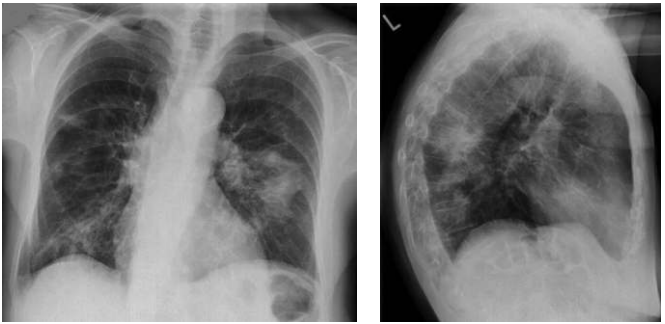
Kreatinin: 1.21 mg/dl

ECG



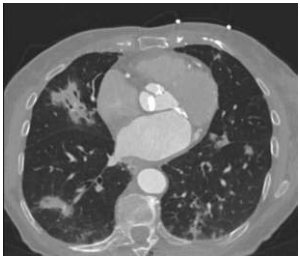
Normal sinus rhythm, normal axis, no ST-T wave changes, no left ventricular hypertrophy.

Chest radiography



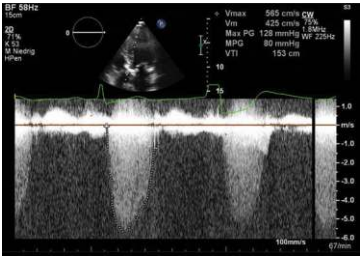
Lung emphysema with diffuse extensive opacifications. Signs of osteopenia and compression of several vertebral bodies of the lumbar spine, no acute venous congestion, no pleural effusion.

CT-lung



Multifocal bilateral lung infiltrates, suspected desquamative interstitial pneumonia or amiodarone-induced pneumonitis

Echocardiography



Normal dimension of LV with normal systolic function and moderate hypertrophy. Insignificant intraventricular obstruction within the left outflow tract (10 mmHg after Valsalva maneuver). Calcified aortic valve with very severe stenosis (aortic valve area 0.5 cm^2, mean gradient 80 mmHg and mild aortic valve regurgitation. Discrete mitral and tricuspid valve regurgitation, right ventricular systolic pressure mildly elevated.

Interpretation

Suspected amiodarone-induced pneumonitis in combination with severe aortic valve stenosis. Symptoms plus elevated NT-pro BNP support cardiac decompensation. In addition, interstitial opacification without venous congestion or pleural effusions argues against cardiac decompensation. A normal PCT and only mild elevation of CRP and leukocytes brings up the suspicion of amiodarone-induced pneumonitis as an additional contributing factor. Exclusion of bacterial iunfection is an important finding as it facilitates the decision to administer corticosteroids for treatment of pneumonitis.

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Notes

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