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Comprehensive Review on Etiologic, Diagnosis, and Therapy of Patients with Acute Heart Failure

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ABSTRACT

Acute heart failure (AHF) represents a critical and complex challenge in cardiology, characterized by its sudden onset and severe impact on patient morbidity and mortality. This condition emerges as a culmination of diverse aetiologies and pathophysiological mechanisms, profoundly disrupting cardiac function and systemic hemodynamics. AHF is frequently associated with dire outcomes, as evidenced by a high in-hospital mortality rate and significant rehospitalization risks within 30 days of discharge. Despite advances in medical and device-based therapies, the prognosis for AHF remains guarded, with 1-year survival rates hovering around 50% in severe cases. Management of AHF is further complicated by the heterogeneity of its clinical presentations, ranging from pulmonary congestion to cardiogenic shock, necessitating rapid and precise therapeutic interventions. This review highlights the persistent challenges in AHF management, including the limitations of current treatment modalities in substantially altering long-term outcomes. Moreover, the global burden of AHF continues to rise, fueled by an aging population and the increasing prevalence of cardiovascular comorbidities. Considering these challenges, there is an urgent need for innovative strategies and a deeper understanding of the disease's pathophysiology to improve survival rates and enhance the quality of life for patients facing this acute cardiac crisis.

Keywords: acute heart failure; pharmacological therapy; heart failure.

INTRODUCTION

Acute Heart Failure has been the number one cause of hospitalizations in the elderly for quite some time. It is life-threatening and must be treated immediately. Acute Heart Failure (AHF) is described as the fast and rapid change of heart failure. AHF has been the number one cause of hospitalizations in the elderly for quite some time. Where in Indonesia it has become quite a problem because the hospitalization and death rates are still relatively high and continue to increase over the years. It shows that worldwide widely AHF has a 10% of mortality rate meanwhile in Indonesia AHF has a mortality rate of 1,5% (Riskedas, 2018).

Improved symptom control and quality of life, fewer hospitalizations, and a lower overall mortality rate are the main objectives of treatment for chronic heart failure. This treatment can be divided into pharmacological and nonpharmacological. Pharmacological treatment by giving drugs to reduce the existing symptoms such as diuretics, inotropic, vasodilators, and vasopressors. Meanwhile, nonpharmacological can be given by surgical management, nutritional support, and psychological support. Pharmacological treatment for acute heart failure varies. There are a lot of different guidelines that guide the given therapy for patients with acute heart failure. The mortality and morbidity of AHF patients are significantly impacted by medical therapy that is guided by guidelines. On the other hand, according to past research, the implementation of these guidelines in the field is very poor. Where the majority of patients do not receive medications at recommended dosages that have been shown to reduce morbidity and death. [3].

In conclusion, this review embarks on a comprehensive exploration of acute heart failure aiming to dissect its complexities across epidemiology, etiology, therapy, and prognosis. The study's impetus lies in the pressing need to decipher the intricacies of this formidable disease,

with the ultimate goal of informing targeted interventions that can transform the current narrative and offer a glimmer of hope to those affected by acute heart failure.

REVIEW CONTENT

Anatomy and Physiology of the Heart

The heart is a vital muscular organ that is situated in the thoracic cavity, between the lungs, enclosed within the protective pericardium-a double-layered membrane that enables its free movement during beats. By structure, the heart is made up of four chambers: the right atrium, which receives blood from the body through the superior and inferior vena cava; the right ventricle, which pumps the blood to the lungs through the pulmonary artery; the left atrium, which collects blood coming from the lungs through the pulmonary veins; and the left ventricle, the most muscular chamber, which sends blood laden with oxygen to all parts of the body through the aorta. A muscular wall, the septum, separates the left and right sides of the heart, preventing the mixing of oxygenated and deoxygenated blood. Movement of blood in the correct direction is ensured by four important valves: the tricuspid valve between the right atrium and ventricle, the pulmonary valve at the exit of the right ventricle, the mitral valve between the left atrium and ventricle, and the aortic valve at the exit of the left ventricle [1].

These valves ensure a one-way flow and prevent backflow during the contraction of the heart. The rhythmic pumping of the heart is driven by the electrical conduction system of the heart, with the sinoatrial (SA) node acting as the natural pacemaker. Electrical impulses fired here conduct through the atria and reach the atrioventricular (AV) node, thus coordinating atrial and ventricular contractions. Functionally, the heart drives two main circulatory pathways: pulmonary circulation, where deoxygenated blood is sent to the lungs for oxygenation, and systemic circulation, where oxygen-rich blood is distributed to nourish the body's tissues. This extensive circulatory system relies on a network of blood vessels that, if laid end-to-end, would span approximately 60,000 miles [1].

This organ has a complex anatomy composed of chambers, valves, and electrical systems that together make the heart ensure proper oxygenation and nutrition while wasting products are removed; in short, it is necessary to maintain life. The heart is a complex and vital organ that functions as a pump, circulating blood throughout the body to sustain life. Its physiology encompasses the electrical conduction system, the cardiac cycle, and the intricate mechanisms of contraction and relaxation. The electrical conduction system regulates the pumping action of the heart, with the sinoatrial node being the major pacemaker, generating impulses at a rate of 60 to 100 beats per minute. These impulses move through the atria, causing them to contract, and then pass to the atrioventricular node, which causes a delay so that the ventricles can fill before contracting. Then the impulse travels down through the bundle of His and its branches, causing coordinated contraction of the ventricles [12].

The cardiac cycle includes the following two events: the systole in which the ventricles contract, sending blood into the pulmonary artery and aorta; and the diastole when the heart relaxes to refill with blood. It lasts for approximately 0.8 seconds for an average heart rate and spends a bit more time in the diastole to adequately fill. Contraction of the heart, mediated by the cardiomyocytes, is initiated through electrical signals provided by the pacemaker cells. The process involves depolarization, where sodium ions Na^+ enter the cells, followed by the influx of calcium Ca^{2+} to trigger contraction, and repolarization, which restores the resting state through potassium K^+ efflux [12].

The autonomic nervous system has a finely tuned balance to control heart rate: the sympathetic division speeds up the rate during stress or exercise, and the parasympathetic division, mainly through the vagus nerve, slows it during rest. Other factors that affect heart rate include emotions, concentration of ions, and body temperature. All of these work in a pattern with each other to create an effective heart that pumps blood containing oxygen and maintains circulation to carry out the body processes [12].

Heart Failure

Heart failure is a disease where there is an abnormality in cardiac function. It is a complex clinical syndrome in which the heart cannot pump enough blood to meet the requirement of the body [11]. It can be the result of having some disorders like impaired ventricular filling or ejection of the blood to the systemic circulations. Patients who suffer from heart failure usually present with fatigue and dyspnoeal, reduced exercise tolerance, and fluid retention [10].

Acute Heart Failure

Acute heart failure is the term used to describe the occurrence or rapid change in signs and symptoms of heart failure. It is also a fast onset and a life-threatening condition. This condition is life threatening and must be treated immediately, and usually results in unplanned emergency hospitalization [9]. Emergency treatment is needed to manage fluid overload and haemodynamic compromise. AHF also become the top cause of hospitalisation for elderly in the western country even if in terms of health technology, they are superior. Patients with AHF require pressing assessment with consequent start or heightened of treatment, like intravenous treatments [5]. It's also said that the most common cause for AHF is hypervolume and hypertension on patients with HFEPF.

There are two types of AHF, de novo AHF and decompensated AHF (ADHF). De novo AHF most common aetiology is cardiac ischemia because there is a sudden increase in intracardiac filling and/or acute

myocardial dysfunction which will lead to the drop of peripheral perfusion and pulmonary oedema. The second type is ADHF whereas not like AHF, ADHF doesn't have pulmonary oedema instead there is a present of congestion and fluid retention. This is the outcome of long-term, frequently dysregulated neuro-humoral compensation systems that work to preserve the status quo in hemodynamic despite deteriorating LV performance. Decompensation happens when the equilibrium leans toward fluid overload and the compensatory mechanisms are insufficient or fail completely [6].

Etiology and Risk Factors

There are several main causes of AHF but the most frequent aetiology that cause AHF is cardiac ischemia where it will lead to sub-total coronary occlusion and furthermore will lead to the decrease of contractility in myocardium. This decrease will then affect the coronary artery system [6]. According to Pedoman Tatalaksana Gagal Jantung written by PERKI itself there are five main causes. The first one is acute coronary syndrome, emergency hypertension, arrhythmic disorders, acute mechanical causes which include mechanical complications due to acute coronary syndromes (such as ventricular wall rupture, inter-ventricular septal defect, acute mitral regurgitation) and the last one is acute pulmonary embolism. There are several conditions that will worsen the sign and symptoms of AHF whether it is cardiovascular or non-cardiovascular. According to EVEREST trial 46% of patients with AHF were hospitalized because of heart failure (cardiovascular risk factors) while the 39% others by non-cardiovascular risk factors. This sign and symptoms will most likely make AHF patients re- hospitalized [2].

It is also shown that there are several clinical and laboratory indications that will predict when AHF patients will be re-hospitalized. Starting from symptoms. It shown that gaining body weight, continuing peripheral oedema, and dyspnoea aggravation can predict AHF re hospitalization. There are also clinical signs like increasing JVP and orthopnoea. For comorbid conditions there are illness like CRD, DM, COPD, and anaemia. Some biomarkers that become predictors such as natrium peptides, cardiac troponins, serum sodium and serum creatine. Echocardiography show that left ventricular filling pattern can be AHF predictor. Psychosocial and quality of life also become an indication, like living alone and low income cause greater risk [2].

Pathogenesis

AHF is a clinical condition defined by the sudden or gradual development of heart failure-related symptoms and/or signs. Most patient seek immediate medical attention if these symptoms or indications are serious enough. There are several clinical manifestations of AHF, but the two most finds in the society are volume overload and then congestive symptoms [4].

Mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles detect arterial underfilling because of the reduction in cardiac output caused by myocardial dysfunction. This increased sympathetic outflow from the central nervous system, activation of the renin-angiotensin-aldosterone system (RAAS), and the osmotic release of arginine-vasopressin follow [4].

These systems are activated, which results in increased release of substances with vasoconstrictive activity (like endothelin and vasopressin), as well as resistance to the action of endogenous natriuretic peptides. This retention of sodium and water tends to counteract the negative effects of AHF on oxygen delivery to the peripheral tissues. But continued stimulation of these mechanisms leads to a dysfunctional control of sodium excretion through the kidneys, which, in turn, causes salt retention and, subsequently, fluid build-up and tissue oedema [4].

AHF is mostly caused by fluid redistribution rather than fluid build-up in individuals with congestion. Congestion during an AHF episode is caused by both fluid build-up and redistribution, although their importance varies depending on the patient profile. While fluid redistribution represents the predominate pathophysiologic mechanism in de novo vascular type AHF in patients with preserved ejection fraction, fluid accumulation represents the primary mechanism of peripheral congestion in patients with worsening heart failure and reduced ejection fraction [4].

AHF with a congestion profile and adequate perfusion is far more prevalent than AHF with poor cardiac output and resultant organ hypoperfusion. This syndrome often presents as overt cardiogenic shock, with systolic arterial pressure values of less than 90 mmHg and mean arterial pressure less than

65 mmHg. Once established, poor cardiac output-related hypoperfusion can adversely influence every organ's performance, leading to a condition known as multiorgan failure. Increased inotropic and chronotropic sympathetic stimulation, increased afterload because of vasoconstriction, and increased left ventricular pressure, all of which can lead to an imbalance between oxygen supply and demand and myocardial damage, are possible causes of heart damage in AHF [4].

Diagnosis

The diagnosis for AHF begins with the initial medical contact and continues throughout the initial patient pathway, with the goal of identifying the clinical presentation and quickly diagnosing and managing any potentially reversible causes/precipitants/coexisting life-threatening conditions [7]. Screening for This diagram provides a diagnostic workflow for new-onset acute heart failure (AHF), based on McDonagh et al. (2021). Here's a step-by-step explanation:

(1) *Initial Assessment:* Begin with the patient's history, focusing on signs and symptoms indicative of acute heart failure.

(2) *Basic Investigations:* Perform diagnostic evaluations, including:
- Electrocardiogram (ECG)
- Pulse oximetry
- Echocardiography
- Initial laboratory tests
- Chest X-ray
- Lung ultrasound

(3) *Natriuretic Peptide Testing:* Measure levels of biomarkers to confirm or rule out acute heart failure B-type natriuretic peptide (BNP):
- <100 pg/mL: Acute heart failure ruled out.
- ≥100 pg/mL: Acute heart failure confirmed.

N-terminal pro-BNP (NT-proBNP):
- <300 pg/mL: Acute heart failure ruled out.
- ≥300 pg/mL: Acute heart failure confirmed.

Mid-regional pro-atrial natriuretic peptide (MR-proANP):
- <120 pg/mL: Acute heart failure ruled out.
- ≥120 pg/mL: Acute heart failure confirmed.

(4) *Outcomes:*
- If biomarker levels are below the threshold, acute heart failure is ruled out.
- If biomarker levels meet or exceed the threshold, acute heart failure is confirmed.

(5) Further Evaluation: For confirmed cases, perform comprehensive echocardiography to assess the heart's function and structure in detail.

Clinical Manifestation

The most typical signs of AHF include orthopnoea, weariness, and a decreased tolerance for exertion, as well as dyspnoea during exercise or at rest. Clinical indicators such peripheral oedema, jugular vein distension, the existence of a third heart sound, and pulmonary rales are frequently present in addition to symptoms. Cardiogenic shock is characterized by signs and symptoms of peripheral hypoperfusion, including oliguria, cold and clammy skin, and impaired mental state [7].

Haemodynamic instability (HR 40 or >130 beats per minute, systolic blood pressure 90 mmHg, or evidence of hypoperfusion) and respiratory distress (RR >25 breaths per minute, peripheral oxygen saturation 90% despite supplemental oxygen, use of accessory muscles for breathing, or need for mechanical ventilatory support) are two conditions that are frequently accepted as prerequisites for hospitalization in an intensive care unit or a cardiac care unit. Acute Heart Failure has four clinical symptoms. These symptoms can occur individually or alongside one another and mostly depends on the existence of congestion and/or peripheral hypoperfusion. These symptoms need different treatment approaches [7].

Management and Treatment

The goal of treating acute heart failure is divided into 3, the first is immediate therapy. This goal is shown when patients enter the ER / ICU. This therapy aims to treat symptoms, restore oxygenation, improve hemodynamic and organ perfusion, limit heart and kidney damage and prevent thromboembolism, minimize length of intensive care. The aim of the second type of therapy is treatment in the treatment room which aims to stabilize the patient's condition, initiation and optimization of pharmacological therapy, identification of the aetiology and associated comorbidities. The goal of the last type is the goal of therapy before the patient goes home. Where the desired outcome is a plan to optimize heart failure drug doses, prevent early rehospitalization and improve quality of life and survival symptoms.

(1) *Oxygen treatment*

Oxygen treatment and/or ventilatory assistance all individuals with dyspnoea should have their oxygen saturation (SpO_2) checked. When SpO2 falls below 90%, oxygen treatment should be started. If necessary, the fraction of inspired oxygen level should be increased up to 100%. This treatment should be monitor because giving too much oxygen causes hyperoxia to the patients and it will lower the coronary and cerebral blood flow [5].

(2) *Diuretics*

Intravenous loop diuretics are an important part of symptomatic therapy in AHF patients who exhibit indications of substantial fluid overload and congestion. They stimulate renal salt and water excretion, act as a vasodilator, and give quick decongestion and symptomatic relief. In most situations, intravenous furosemide is the first-line diuretic. Furosemide can be given as 2– 3 daily boluses or as a continuous infusion. Daily single bolus administrations are discouraged because of the possibility of post-dosing sodium retention. With continuous infusion, a loading dose may be used to achieve steady state earlier. If there is an insufficient diuretic response, the loop diuretic i.v. dose can be doubled, with a further assessment of diuretic response. The loop diuretic dose should be progressively decreased when a significant negative fluid balance has been obtained [5]. According to ACCF/AHA recommendations, diuretics should be administered immediately upon presentation since this method may result in better results.

(3) *Vasodilators*

Diuretics are the second-most often utilised medication in AHF, while intravenous vasodilators, primarily nitrates, offer significant symptomatic relief. The most used vasodilators are Nitrates or nitroprusside. Since nitrates are both venodilators and arteriodilators, they decrease both preload and afterload while simultaneously increasing stroke volume and alleviates symptoms. In AHF with hypertension, intravenous vasodilators are particularly recommended. Nitroprusside, primarily affect the peripheral veins. In individuals whose acute pulmonary oedema is caused by increased afterload

and fluid redistribution to the lungs in the absence or with minor fluid build-up, i.v. vasodilators may be more efficient than diuretics due to their modes of action. When SBP is greater than 110 mmHg, intravenous vasodilators may be thought to treat AHF symptoms. To achieve clinical improvement and blood pressure management, they may be administered at modest dosages and increased [5].

In general, nitrates are given as an initial bolus and then as a continuous infusion. In patients with acute pulmonary oedema who are extremely hypertensive, nitro glycerine can be administered in boluses of 1-2 mg. It's important to take precautions to prevent hypotension brought on by an excessive preload and afterload reduction. They should thus be used extremely cautiously in individuals who have significant aortic stenosis, LVH, or both. However, when vasodilators were administered with careful monitoring of haemodynamic parameters, beneficial benefits were shown in individuals with LV systolic dysfunction and aortic stenosis [5].

In patients with normal to high blood pressure, ESICM advice suggests starting vasodilators as soon as possible. Mortality has been linked to greater rates when vasoactive medication delivery is delayed. Additionally, it has been demonstrated that starting intravenous vasodilators quickly after presentation lowers the likelihood of adverse events and the rate of mechanical breathing. When substantial mitral or aortic valve stenosis is suspected or present, vasodilators should be administered with caution and are contraindicated in shock [9].

(4) *Vasopressor*
Patients with severe hypotension are given drugs with peripheral artery vasoconstrictor effect, such as norepinephrine or dopamine, at larger dosages (5 mg/kg/min). The purpose of administering these medications is to increase blood pressure and redistribute blood to the essential organs. However, when vasopressors are used, LV afterload rises. Norepinephrine could have fewer adverse effects and decreased mortality. Epinephrine (adrenaline) should only be used for resuscitation procedures and in patients with persistent hypotension despite acceptable heart filling pressures and the administration of other vasoactive medications [8].

(5) *Inotropic*
Pharmacological treatments known as inotropes are prescribed for individuals who have acute heart failure (AHF) with concurrent hypoperfusion from a reduced cardiac output. Positive inotropes enhance cAMP and intracellular calcium to promote heart contractility and cardiac output. They are often used briefly during the early therapy of AHF, up until the point at which haemodynamic stabilization and restoration of peripheral perfusion take place. The three primary kinds of inotropic drugs now used in clinical settings are beta-agonists, phosphodiesterase III inhibitors, and calcium sensitizers. However, because to the well-documented possibility of adverse events and their link to higher long-term mortality, doctors should be knowledgeable about the indications and dose methods appropriate for various patient types [5].

(6) *Opiates*
Opioids reduce anxiety and dyspnoea. To help patients adjust, they may be administered as sedatives during non-invasive positive pressure breathing. Nasal irritation, hypotension, bradycardia, and respiratory depression are among the dose-dependent adverse effects. According to retrospective investigations, the use of morphine is linked to higher rates of mechanical breathing, longer hospital stays, more hospitalizations to critical care units, and higher death rates. Although they may be explored in some patients, notably in cases of severe/intractable pain, anxiety, or in the context of palliation, the routine use of opiates in AHF is not advised [5].

(7) *Digoxin*
In individuals with AF and a fast-ventricular rate (>110 bpm) despite using beta-blockers, digoxin should be taken into consideration. If not previously used, it can be administered in boluses of 0.25–0.5 mg intravenously. The maintenance dosage, however, may be challenging to conceptually predict in patients with comorbidities (such as CKD) or other variables affecting digoxin metabolism (including other medicines) and/or the elderly, and measurements of blood digoxin concentrations should be made. A randomized placebo-controlled experiment is now evaluating digoxin as a viable substitute for digoxin [5].

Prognosis
The most common reason for older patients to be hospitalized is acute heart failure, which also accounts for most of the the significant healthcare costs associated with heart failure. The prognosis for acute heart failure is dismal despite treatment advancements, with death rates in hospitals ranging from 4% to 7%, 60–90-day mortality rates from 7% to 11%, and 60–90-day rehospitalization rates from 25% to 30%. The rapid onset or worsening of heart failure signs and symptoms can be caused by several conditions, including cardiovascular and non-cardiovascular diseases, as well as patient-related and iatrogenic factors. This can result in an acute heart failure episode, which typically necessitates hospitalization for the patient. While the secondary prevention of a new episode of decompensation necessitates the optimization of heart failure therapy, patient education, and the creation of an efficient transition and follow-up plan, the primary prevention of acute heart failure primarily focuses on the prevention, early diagnosis, and treatment of cardiovascular risk factors and heart disease, including coronary artery disease [2].

CONCLUSION
This comprehensive review underlines the complex nature of AHF, including its pathophysiology, clinical manifestations, and prognosis. By delving into the complexities of this critical condition, we underscore the urgent need for innovative diagnostic tools and

therapeutic strategies. Despite advances in the treatment of AHF, the persistently high morbidity and mortality rates underline the need for improving early recognition, optimizing management protocols, and addressing the causes of AHF. In this light, as the global burden of AHF continues to increase, this review calls for continuous research effort, collaboration across disciplines, and development of innovative strategies to improve survival rates and the quality of life for patients facing this acute cardiac crisis.

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