Management of Acute Decompensated Heart Failure in Patients With Cancer

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Case Study: H.M. is a 70-year-old woman with a known history of metastatic breast cancer. In 1995, she underwent a right modified radical mastectomy followed by four years of hormonal therapy with tamoxifen. In April 2001, she was diagnosed with bone metastases and placed on letrozole, zoledronic acid, and chemotherapy consisting of gemcitabine and docetaxel. She experienced severe mucositis, and the chemotherapy was discontinued five months later. In October 2001, she was started on 5-fluorouracil, leucovorin, and mitoxantrone, which she continued until she was diagnosed with possible chemotherapy-induced cardiomyopathy in July 2003.

Cardiotoxicity has been reported in patients treated with mitoxantrone and may occur in patients who have no other cardiac risk factors. Risk increases with cumulative doses (Ghalie et al., 2002). H.M. had no known history of coronary artery disease, myocardial infarction, hypertension, hyperlipidemia, diabetes mellitus, or stroke. She had a prior left heart catheterization, which showed normal coronaries.

In September 2003, she had disease progression and was referred to a cancer center for further management. After restaging tests, she was started on capecitabine.

H.M. initially was seen by the cardiology service after a routine electrocardiogram was done for complaints of “fluttering” in her chest. She was diagnosed with atrial fibrillation with rapid ventricular response and cardiomyopathy with an ejection fraction of 25%-30%. She was admitted to the hospital, and the atrial fibrillation was converted to normal sinus rhythm with amiodarone IV. She was discharged home in stable condition several days later with amiodarone 200 mg by mouth twice daily, furosemide 20 mg by mouth twice daily, spironolactone 25 mg by mouth daily, lisinopril 2.5 mg by mouth daily, carvedilol 3.125 mg by mouth twice daily, and warfarin sodium 6 mg by mouth daily.

She was followed regularly by the cardiology and oncology services in the outpatient clinics and remained in stable condition until November 2005, when she was admitted to the hospital in her hometown for shortness of breath, fever, and hypotension. She was diagnosed with pneumonia and heart failure exacerbation.

Following her return home, H.M. continued to complain of weakness, fatigue, and shortness of breath. Despite diuretic therapy, she had two- to three-pillow orthopnea, paroxysmal nocturnal dyspnea, and lower-extremity edema. In December 2005, she underwent placement of a biventricular pacemaker and implantable cardioverter defibrillator (ICD) for episodes of ventricular tachycardia. The following day, she developed acute pulmonary edema requiring intubation and a weeklong stay in the intensive care unit. She developed renal insufficiency with blood urea nitrogen of 85 mg/dl and creatinine of 2.1 mg/dl. Her local cardiologist advised no further treatment and recommended hospice care. The patient and her family refused hospice transfer and instead returned to the cancer center for further management.

Shortly thereafter, H.M. presented to the emergency room appearing ill and weak and had shortness of breath at rest.
Her vital signs revealed a blood pressure of 86/54 mmHg, apical pulse rate of 87 beats per minute, respiratory rate of 24 breaths per minute, and temperature of 97.6°F. Her neurologic examination was grossly normal. Her lung examination revealed decreased breath sounds bilaterally. Her cardiovascular examination revealed regular S1 and S2, loud S3, and a point of maximal impulse that was diffuse and displaced laterally. Jugular venous distention was present at 12 cm H2O. Her abdomen was soft, nontender, and nondistended, with normoactive bowel sounds. No pulsatile masses or vascular bruits were noted. Hepatojugular reflux was present. Her extremities were warm and dry with 1+ pretibial edema bilaterally.

H.M.’s current medications included carvedilol 3.125 mg by mouth twice daily, amiodarone 200 mg by mouth daily, furosemide 20 mg by mouth daily, Singulair® (montelukast sodium, Merck & Co., Inc., Whitehouse Station, NJ) 10 mg by mouth daily, and capcitabine 1,000 mg by mouth twice daily.

Laboratory findings included normal hemoglobin and hematocrit. Her serum sodium was 127 mEq/l, potassium was 5.3 mEq/l, blood urea nitrogen was 78 mg/dl, creatinine was 1.5 mg/dl, and B-type natriuretic peptide (BNP) was 1,221 pg/ml.

A chest radiograph showed enlargement of the cardiac silhouette, moderate pulmonary edema, moderate bilateral pleural effusions, and focal areas of sclerosis in the ribs suspicious for metastatic bone disease. A 12-lead electrocardiogram showed sinus rhythm with a rate of 87 beats per minute. No STT wave changes or Q waves were noted. An echocardiogram showed severely reduced left ventricular systolic function with severe global hypokinesia and a measured ejection fraction of 16%. No pericardial effusion was found. The biventricular pacemaker and ICD were checked and noted to be functioning adequately and were optimized electrically to maximize resynchronization therapy.

Acute Decompensated Heart Failure

Heart failure is a complex clinical syndrome characterized by dyspnea, fatigue, and edema secondary to structural and functional changes in the heart (Francis & Tang, 2003). Mills and Hobbs (2001) defined decompensated heart failure as a decrease of at least one New York Heart Association functional classification (see Table 1). Decompensated heart failure is characterized by hemodynamic abnormalities and neurohormonal activation that contribute to heart failure symptoms, end-organ dysfunction, arrhythmias, and progressive cardiac failure (Fonarow & Weber, 2004). Acute decompensated heart failure (ADHF) is characterized by increases in symptoms such as dyspnea, fatigue, and fluid retention. Patients presenting to an emergency department with ADHF often are hemodynamically unstable and have severe symptoms of dyspnea and fluid overload.

The in-hospital mortality rate for ADHF is 5%–8%, median duration of hospitalization is five days, and the six-month readmission rate is about 50% (American Heart Association, 2003; Hunt et al., 2001). Early diagnosis and effective management of ADHF reduce hospitalizations and intensive care unit admissions, decrease overall length of stay and hospital costs, and reduce readmissions (Peacock, Emerman, & Wynn, 2004).

Diagnosis

Establishing a diagnosis of heart failure in a patient with cancer presents a diagnostic challenge because the presenting symptoms of dyspnea, fatigue, and fluid overload are nonspecific and can be caused by cancer, cancer therapy, or a combination of both. The differential diagnosis is complicated further by many other conditions that can mimic heart failure (see Figure 1). Establishing the correct diagnosis is critical so that appropriate interventions can be administered expeditiously.

A comprehensive history and physical examination are essential for identification of signs and symptoms that lead to a diagnosis of heart failure. Potential precipitating factors (see Figure 2) that may lead to ADHF should be evaluated. Although cardiovascular disease is the leading cause of heart failure in the general population, in patients with cancer, further investigation should include exposure to antineoplastic agents associated with cardiotoxicity (Ewer & Benjamin, 2001). Total drug dosages and

### Table 1. New York Heart Association Functional Classification

<table>
<thead>
<tr>
<th>FUNCTIONAL CLASSIFICATION</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>Class I (mild)</td>
<td>No limitation in physical activity. No symptoms from ordinary activities.</td>
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<tr>
<td>Class II (mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
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<tr>
<td>Class III (moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity causes fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class IV (severe)</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency occur even at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
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- Acute pericardial effusion
- Acute myocardial infarction
- Acute adverse reaction from chemotherapy administration
- Chronic obstructive pulmonary disease exacerbation
- Lung cancer
- Pneumonia
- Pulmonary embolism
- Tension pneumothorax
- Thyroid disease
- Renal failure

Figure 1. Differential Diagnosis for Acute Decompensated Heart Failure
mode of administration also should be assessed. Bolus IV delivery is associated with a higher risk of cardiotoxicity as compared to IV infusion. Chemotherapy-induced cardiomyopathy is becoming an increasing issue in heart failure management as a result of the growing number of long-term cancer survivors who were treated previously with anthracycline-containing chemotherapy.

Patients also should be assessed for the presence of additional risk factors that can increase the occurrence of cardiotoxicity. These include the presence of preexisting cardiac disease, hypertension, diabetes, prior chest irradiation, and extremes of age.

Physical Examination

Physical assessment of patients with ADHF should focus on determining whether the clinical symptoms indicate that filling pressures are elevated (wet) or not elevated (dry) and perfusion is adequate (warm) or inadequate (cold). Measurement of intracardiac pressures with a pulmonary artery catheter will provide valuable information regarding these parameters. ADHF has four possible hemodynamic profiles based on clinical signs and symptoms (see Figure 3).

Most patients presenting to an emergency department with ADHF are volume overloaded. The symptoms associated with volume overload include dyspnea, orthopnea, and paroxysmal nocturnal dyspnea (Stevenson, 1999), and the physical signs are jugular venous distention, hepatosplenic reflex, ascites, edema, and crackles in the lungs. However, crackles are not always present in patients with chronic heart failure because the chronic movement of fluid in the interstitium associated with increased lymphatic drainage allows the alveoli to remain relatively dry (Stevenson & Perloff, 1989). Cool extremities are a manifestation of inadequate perfusion secondary to peripheral vasoconstriction resulting from increased sympathetic stimulation (McBride & White, 2003).

Diagnostic Tests

Although patient history and physical examination findings may provide important clues regarding the underlying cardiac abnormality, invasive and noninvasive testing are necessary to provide a definitive diagnosis of heart failure (see Figure 4). A complete blood count is necessary to assess for anemia and infection, both of which may contribute to the presenting symptoms and patient distress. About half of all patients with heart failure are anemic with hemoglobin of less than 12 g/dl (Silverberg, Wexler, & Iaina, 2002), and anemia is very common in patients with hematologic cancers. The basic metabolic profile will reveal electrolyte abnormalities that can contribute to dysrhythmias and result in heart failure exacerbation. Liver function tests may be elevated in the presence of liver congestion secondary to fluid overload. Early identification of abnormalities will assist with the diagnosis and implementation of appropriate interventions.

Measurement of BNP is a valuable tool for diagnosing ADHF in the emergency department (McCullough et al., 2002). BNP is an endogenously generated natriuretic peptide that is activated in response to atrial or ventricular expansion caused by pressure overload and increased wall tension (Maeda, Tsutamoto, Wada, Hisanaga, & Kinoshita, 1998; Nakagawa et al., 1995). Circulating levels of endogenous BNP are elevated significantly in patients with ADHF (Burger, 2005). Maisel et al. (2002) reported that a BNP cutoff value of 100 pg/ml had a diagnostic accuracy rate of 85.4% in ADHF.

A two-dimensional echocardiogram with Doppler flow study is a very useful diagnostic test to evaluate for abnormalities in myocardial contractility, heart valve structure, and pericardial status that may contribute to ADHF. The ejection fraction may decrease to less than 30% in patients with ADHF (McBride & White, 2003). Inotropic support may be needed to increase cardiac output. The use of inotropic agents is usually limited to patients with low cardiac output who do not respond to optimal diuretic therapy and mechanical interventions. The use of inotropic agents in patients with high cardiac output and Signs and Symptoms

| CI—cardiac index; PCW—pulmonary capillary wedge pressure; SVR—systemic vascular resistance |

**Figure 2. Precipitating Factors for Acute Decompensated Heart Failure**

*Note.* Based on information from Tsuyuki et al., 2001.

**Figure 3. Hemodynamic Profiles and Suggested Therapies for Acute Decompensated Heart Failure**

fraction, either preserved or reduced, can stratify whether ADHF is systolic or diastolic in physiology. Systolic dysfunction occurs when the heart muscle does not contract with enough force to pump blood and is characterized by a decreased ejection fraction (less than 50%). In patients with cancer, the decrease usually is caused by dilated cardiomyopathy resulting from the cardiotoxic side effects of chemotherapeutic agents. However, in diastolic heart failure or preserved systolic function, the ejection fraction is normal (greater than 50%), but ventricular filling is impaired and relaxation is abnormal. This is a sequela of conditions such as long-standing uncontrolled hypertension, aortic stenosis, mitral regurgitation, and hypertrophic cardiomyopathy, which predispose patients to the development of left ventricular hypertrophy. Heart failure associated with diastolic dysfunction is most prevalent among older women with a history of hypertension (Davie, Francis, Caruana, Sutherland, & McMurray, 1997). In most patients, abnormalities of systolic and diastolic function coexist regardless of ejection fraction.

A 12-lead electrocardiogram may show evidence of an acute or prior myocardial infarction, pericarditis, conduction abnormalities, or left ventricular hypertrophy as a result of prolonged uncontrolled hypertension. Atrial fibrillation can be a precipitating factor for ADHF, and anticoagulation should be considered to prevent an embolic event. A chest x-ray may reveal pulmonary edema in cases of fluid overload and show an enlarged cardiac silhouette in cases of dilated cardiomyopathy.

In the case study, H.M.’s BNP was 1,221 pg/ml, indicating ADHF. The diagnosis was confirmed by chest x-ray findings of an enlarged cardiac silhouette and pulmonary edema and an echocardiogram showing severe left ventricular hypokinesis and an ejection fraction of 16%.

### Treatment Strategies

Currently, no clinical practice guidelines exist for the management of ADHF in patients with concurrent cancer diagnoses; hence, the management is based on empirical evidence. The most commonly used pharmacologic agents for ADHF are outlined in Table 2. The goal of therapy is to improve the clinical signs and symptoms by managing fluid overload and improving oxygenation. The pharmacologic management of ADHF is determined by a patient’s hemodynamic profile as shown in Figure 3. The usual treatment of ADHF in an emergency department begins with IV diuretics, except in the presence of renal failure. The majority of patients with ADHF will respond to diuretic therapy

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**Table 2. Acute Pharmacologic Therapy for Heart Failure**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>METHOD OF ADMINISTRATION</th>
<th>INFUSION RATE</th>
<th>INDICATION</th>
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<tbody>
<tr>
<td><strong>Catecholamines</strong></td>
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<tr>
<td>Dobutamine</td>
<td>No</td>
<td>2–20 mcg/kg per minute</td>
<td>Peripheral hypoperfusion refractory to volume replacement, diuretics, and volume replacement</td>
</tr>
<tr>
<td>Dopamine</td>
<td>No</td>
<td>5–10 mcg/kg per minute</td>
<td>Hypotension; improves renal blood flow and diuresis</td>
</tr>
<tr>
<td><strong>Vasodilator</strong></td>
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<tr>
<td>Nitroglycerine</td>
<td>No</td>
<td>5–10 mcg per minute via IV; titrate to total dose of 100–200 mcg per minute until desired hemodynamic effect is obtained.</td>
<td>Adjunctive therapy for congestive heart failure associated or not associated with acute myocardial infarction</td>
</tr>
<tr>
<td><strong>Phosphodiesterase inhibitor</strong></td>
<td>2 mcg/kg IV bolus</td>
<td>0.01 mcg/kg per minute up to a maximum dose of 0.03 mcg/kg per minute</td>
<td>To promote natriuresis and diuresis</td>
</tr>
<tr>
<td>Milrinone</td>
<td></td>
<td>0.375–0.75 mcg/kg per minute</td>
<td>Peripheral hypoperfusion with or without congestion refractory to diuretics and vasodilators, with preserved systemic blood pressure; preferred to dobutamine in patients on beta-blocker therapy</td>
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<tr>
<td><strong>Calcium sensitizer</strong></td>
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<tr>
<td>Levosimendan</td>
<td>6–24 mcg/kg over 10 minutes</td>
<td>0.05–0.2 mcg/kg per minute</td>
<td>Symptomatic, low cardiac output heart failure secondary to systolic dysfunction without severe hypotension</td>
</tr>
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</table>

*Note. Based on information from DiDomenico et al., 2004.*
alone (Dec, 2005); however, if that therapy is not effective, IV nesiritide may be added. Data from the Acute Decompensated Heart Failure National Registry indicated that patients treated with IV nesiritide had lower inpatient hospital mortality as compared to patients who received milrinone or dobutamine (Abraham et al., 2005).

Nesiritide is a recombinant form of BNP identical to the endogenous hormone produced by the ventricles in response to increased wall stress, hypertrophy, and volume overload. It has venous, arterial, and coronary vasodilatory properties and may promote diureses because of the natriuretic property without causing a change in heart rate. These actions may lead to improvement in ADHF symptoms (Burger, Dennish, Horton, Koren, & Torre, 2000). The recommended dose of nesiritide is an IV bolus of 2 mcg/kg, followed by a continuous IV infusion of 0.01 mcg/kg per minute. In the setting of hypotension (systolic blood pressure less than 100 mmHg), however, the initial IV bolus dosage is not recommended and the continuous infusion of 0.01 mcg/kg per minute is given alone.

In hemodynamically unstable patients with systolic blood pressures lower than 90 mmHg, evidence of end-organ hypoperfusion, or cardiogenic shock, inotropic support may be initiated until patients are stabilized.

Healthcare providers must consider that conventional therapies for ADHF, including diuretics, vasodilators, and inotropic agents, may have adverse effects on patients’ neurohormonal systems. Excessive diuretics may cause volume depletion resulting in secondary activation of the renin angiotensin aldosterone system and sympathetic nervous system, which contributes to the pathogenesis of ADHF (Abraham et al., 1998). Vasodilators can cause reflex tachycardia, which could result in further worsening of the neurohormonal profile of ADHF. IV inotropic agents may improve cardiac output initially, but they also enhance the renin angiotensin aldosterone system and sympathetic activation, which can result in worsening heart failure.

After reversal of acute decomposition and achieving clinical euvolemia, patients should be started on a combination of three types of drug therapy as recommended by the American College of Cardiology and American Heart Association guidelines (Hunt et al., 2001): diuretics, angiotensin-converting enzyme inhibitors, and beta blockers, unless contraindicated, such as in the case of allergic reactions to the drugs, elevated creatinine (angiotensin-converting enzyme inhibitors), and the presence of second-degree or complete heart block (beta blockers), unless a patient has a pacemaker (see Table 3). The benefits of the drugs have been established by evidence from numerous large-scale clinical trials (Hunt et al., 2005). Referral to a formal disease management program for comprehensive care is recommended to prevent recurrence of ADHF and repeated hospitalizations.

### Case Study Follow-Up

H.M. was diagnosed with congestive heart failure exacerbation with low output symptoms suggestive of pump dysfunction. She was admitted to the hospital and placed on a dopamine infusion at 3 mcg/kg per minute and diuretic therapy to improve forward flow and hemodynamic pressure. Carvedilol was stopped. She responded well to the dopamine infusion, and her symptoms improved. She was gradually weaned off dopamine and changed to milrinone at 0.2 mcg/kg per minute. Her blood pressure remained stable, with systolic blood pressures measuring in the 90s. Carvedilol 3.125 mg by mouth twice daily was restarted. Her kidney function improved, with serum creatinine returning to 1.0 mg/dl. With the assistance of physical therapy, she was able to increase her six-minute walk to 10 feet on the third day of hospital admission. Dopamine and milrinone were weaned off gradually, and amiodarone IV was changed to amiodarone 200 mg

### Table 3. Recommended Pharmacologic Therapies for Heart Failure

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>INITIAL DOSE</th>
<th>MAXIMUM DOSE</th>
<th>MECHANISM OF ACTION</th>
<th>ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitors</strong></td>
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<tr>
<td>Lisinopril</td>
<td>2.5–5 mg once daily</td>
<td>20–40 mg once daily</td>
<td>Decreased preload and afterload; arterial and venous vasodilation</td>
<td>Hypotension, worsening renal function, hyperkalemia, cough, angioedema, and neutropenia</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice daily</td>
<td>10–20 mg twice daily</td>
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<tr>
<td>Ramipril</td>
<td>1.25–2.5 mg once daily</td>
<td>10 mg daily</td>
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<tr>
<td><strong>Angiotensin receptor blockers</strong></td>
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<td></td>
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<tr>
<td>Valsartan</td>
<td>20–40 mg twice daily</td>
<td>160 mg twice daily</td>
<td>Direct antagonism of angiotensin II</td>
<td>Hypotension, angioedema, cough, and fatigue</td>
</tr>
<tr>
<td>Losartan</td>
<td>25–50 mg once daily</td>
<td>50–100 mg once daily</td>
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<tr>
<td>Candesartan</td>
<td>4–8 mg once daily</td>
<td>32 mg once daily</td>
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<tr>
<td><strong>Aldosterone antagonists</strong></td>
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<tr>
<td>Spironolactone</td>
<td>12.5–25 mg once daily</td>
<td>25 mg daily or twice daily</td>
<td>Increased sodium chloride and water excretion while conserving potassium and hydrogen ions</td>
<td>Hyperkalemia and glycemicostasia</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg once daily</td>
<td>50 mg once daily</td>
<td></td>
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<tr>
<td><strong>Beta blockers</strong></td>
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<tr>
<td>Bisoprolol</td>
<td>1.25 mg once daily</td>
<td>10 mg once daily</td>
<td>Decreased neurohormonal activation and heart rate; slow or reverse ventricular remodeling</td>
<td>Hypotension, bradycardia or heart block, fatigue, and bronchospasm</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25 mg twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5–25 mg once daily</td>
<td>200 mg once daily</td>
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</table>

*Note. Based on information from Hunt et al., 2005.*
by mouth daily. After 10 days in the hospital, she was discharged home in stable condition.

**Conclusion**

ADHF is a serious and potentially fatal condition, especially in the presence of another serious comorbid condition such as cancer. However, with accurate diagnosis and appropriate medical intervention, clinical outcomes can be improved in many patients. The goal of therapy in the management of ADHF is to improve the clinical signs and symptoms by achieving clinical euvolemia and improving oxygenation. The short-term use of inotropic agents may be helpful to improve cardiac function. However, having a treatment strategy post-exacerbation management is equally important to prevent frequent readmissions for ADHF.

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**References**


