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# Rural treatment of acute cardiogenic pulmonary edema: applying the evidence to achieve success with failure

*John Bosomworth,  
MD, CCFP, FCFP  
Clinical Instructor, Department of Family Practice,  
University of British  
Columbia, Vancouver, BC*

*Correspondence to:  
Dr. John Bosomworth,  
Box 887, Princeton BC  
V0X 1W0; john.bosomworth  
@interiorhealth.ca*

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Rural management of acute cardiogenic pulmonary edema should be based on avoidance of adverse outcomes such as in-hospital mortality, the need for intensive care unit care, and the need for intubation and mechanical ventilation. Current evidence suggests that early noninvasive continuous positive airway pressure and early aggressive preload reduction with intravenous nitroglycerin are first-line interventions. Afterload reduction with sublingual captopril, with or without nitroglycerin, improves outcomes and is a second-line intervention. Furosemide is associated with adverse outcomes when used alone and should be given only after vasodilator therapy as a third-line intervention. Inotropes should be used only with demonstrably poor perfusion as they do not improve outcomes and may indeed be associated with increased mortality. Concurrent vasodilator therapy should be considered as soon as possible. Morphine should not be used as it is associated with adverse outcomes. If sedation is desirable, benzodiazepines should be considered.

La prise en charge en milieu rural de l'œdème pulmonaire cardiogène aigu devrait viser avant tout à éviter les résultats indésirables comme la mortalité à l'hôpital, le besoin de traitements aux soins intensifs et le besoin d'intubation et de ventilation mécanique. Les données probantes actuelles indiquent que l'intervention rapide par pression positive continue non effractive dans les voies aériennes et la réduction agressive rapide de la précharge par l'administration de nitroglycérine intraveineuse constituent des interventions de première intention. La réduction postcharge par administration sublinguale de captopril, avec ou sans nitroglycérine, améliore les résultats et constitue une intervention de deuxième intention. Le furosémide est associé à des résultats indésirables lorsqu'il est utilisé seul et il faudrait l'administrer seulement après une thérapie au moyen d'un vasodilatateur comme intervention de troisième intention. Il faut utiliser les agents inotropes seulement lorsqu'il est démontré que la perfusion est médiocre, car ils n'améliorent pas les résultats et ils sont en fait associés à une augmentation du taux de mortalité. Il faudrait envisager le plus tôt possible une thérapie simultanée au moyen d'un vasodilatateur. Il ne faut pas administrer de morphine, car elle est associée à des résultats indésirables. Si une sédation est souhaitable, il faudrait envisager d'utiliser des benzodiazépines.

## BACKGROUND

The improved management of patients with acute myocardial infarction and the management of chronic congestive heart failure using evidence-based guidelines has met with great success, to the extent that patients are living longer with impaired cardiac function.<sup>1,2</sup>

This accumulation of older patients will eventually present to the emergency department with acute decompensation, often with pulmonary edema. Heart failure has become the major admitting diagnosis for patients over 65 years old, and there is a 50% chance of hospital readmission of these patients within 6 months.<sup>3</sup> The development of

cardiogenic pulmonary edema (CPE) portends a particularly high mortality, approaching 15%–20% in hospital.<sup>4</sup>

Contrary to the situation with chronic heart failure, existing guidelines for the management of CPE can give only minimal evidence-based advice.<sup>1,5–7</sup> Much guideline content is based on anecdotal practice and expert opinion.<sup>8</sup> As subsequent discussion and documentation will show, there is outstanding evidence for the early use of noninvasive respiratory support for the patient who might otherwise go on to intubation. Vasodilator therapy is receiving increasing investigational support. At the same time, clear evidence for harm has to be considered with the use of morphine, inotropes and even diuretics.

Rural emergency departments and hospitals do not often have the funding or personnel to staff an intensive care unit (ICU) or to manage more complex monitoring such as central venous catheters or prolonged intubation. Fortunately, the most beneficial evidence-based interventions involve medications and equipment readily available in a rural setting. Also, most patients presenting with acute pulmonary edema have well-preserved perfusion and are symptomatic mainly because of pulmonary congestion (“warm and wet;” Fig. 1).<sup>9</sup> Although this type of presentation engenders anxiety in both patients and physicians, there is a great deal of satisfaction in watching the dramatic clinical improvement when fluid distribution, preload and afterload are properly managed.

## PATHOPHYSIOLOGY

As cardiac function becomes inadequate, the left ventricle can no longer handle pulmonary venous

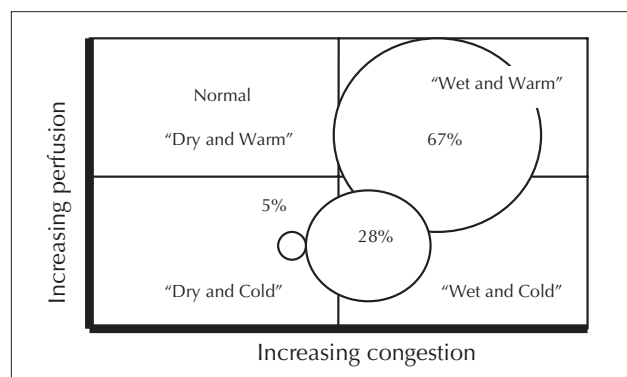


Fig. 1. Clinical spectrum of hemodynamic profiles in 486 patients with reduced left ventricular ejection fraction and presenting with heart failure. Increased ventricular filling pressures produce pulmonary edema (wet lung). Decreased output and vasoconstriction produce poor perfusion (cold extremities). Adapted from Nohria et al.<sup>9</sup>

return, which increases cardiac preload. Hydrostatic pressure builds in the pulmonary capillaries resulting in transudation of fluid into the alveolar space with the beginning of acute CPE. Thus begins a self-reinforcing cycle whereby physiologic attempts at compensation beget further decompensation (Fig. 2).

Alveolar fluid buildup leads to hypoxia, which increases catecholamines, producing increased systemic vascular resistance and blood pressure and raising cardiac afterload. Myocardial oxygen demand is increased, producing myocardial ischemia, reduced cardiac output and increased left ventricular (LV) end diastolic pressure. This again reinforces alveolar fluid buildup aggravating hypoxia. Dyspnea and increased respiratory effort produce anxiety, release further catecholamines, and further raise systemic vascular resistance and blood pressure.

Increased LV end diastolic pressure produces a further self-reinforcing cycle, with the activation of the renin-angiotensin-aldosterone system leading to increased sympathetic tone and rise in afterload. The result is a heart with already reduced contractility pumping against a markedly elevated systemic vascular resistance (afterload) and the inability for the heart to handle continued right-sided filling; this further increases pressures in the pulmonary circuit (preload). Cardiac output falls and alveolar fluid increases unless there is intervention at some level. The options are to

1. reduce preload;
2. reduce afterload; or
3. improve contractility.

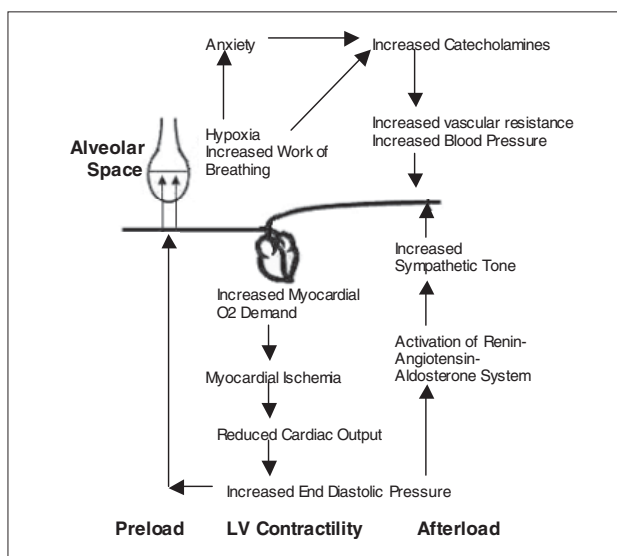


Fig. 2. Pathophysiology of acute cardiogenic pulmonary edema. The cycle begins when the left ventricle (LV) can no longer handle pulmonary venous return. Hydrostatic pressure in the pulmonary capillaries increases until it exceeds alveolar interstitial pressure.

By the time the patient presents, impairment of all 3 processes is usually well advanced.<sup>4</sup>

The clinical spectrum of patients seen with heart failure relates to the degree of congestion and the quality of perfusion (Box 1). Dyspnea on exertion is the most sensitive symptom, whereas paroxysmal nocturnal dyspnea is most specific. Elevated jugular venous pressure (JVP) is the best physical indicator, but it has poor clinical accuracy.<sup>10</sup> Blood pressure is the most accessible measure of perfusion.<sup>9</sup> Two-thirds of presenting patients will be congested but well-perfused, while 28% will be congested and poorly perfused, and 5% will demonstrate no congestion and be poorly perfused (Fig. 1). Successful outcomes are almost always achieved through reduction in LV filling pressures through reduction in preload or afterload. In poorly perfused patients, inotropes have to be considered to improve contractility, but agents to improve preload and afterload need to be added as soon as possible.<sup>3,8,9,11</sup> The 5% of patients in the last category rarely present acutely, as they are not congested.<sup>4</sup>

### *Precipitating causes*

The possible precipitants of CPE will sometimes mandate alternative therapies that are beyond the scope of this discussion. Sometimes, as with hypertension, the treatment may not differ. At other times, as with myocardial infarction, treatment follows another path. The “MADHATTER” mnemonic (Box 2) is a useful memory aid.<sup>7</sup>

#### **Box 1. Signs and symptoms of acute cardiogenic pulmonary edema**

Congestion (volume overload)

- Dyspnea on exertion
- Orthopnoea
- Paroxysmal nocturnal dyspnoea
- Satiety, nausea, vomiting
- Edema
- Increased jugular venous pressure
- Hepatojugular reflux
- Ascites
- Hepatosplenomegaly
- S3 gallop
- Rales

Hypoperfusion

- Fatigue
- Altered mentation
- Narrow pulse pressure
- Hypotension
- Cool extremities
- Worsening renal function

### *Differential diagnosis*

As will be discussed, misdiagnosis is the possible reason for evidence for harm with the use of some of our time-tested therapies. In a study of prehospital treatment of CPE, Hoffman and Reynolds<sup>12</sup> found a 23% incidence of alternative diagnoses, possibly accounting for adverse outcomes in patients given morphine if respiratory disease was the actual cause of symptoms. We will never be exact in all our diagnoses in a rural emergency department, so we must think of the differential diagnosis (Box 3) and avoid therapies that can make an alternative condition worse.

### **THERAPY**

#### *Respiratory interventions*

There is now outstanding evidence for the benefit of noninvasive airway interventions in the treatment of CPE. There is sound data from multiple meta-analyses<sup>13–15</sup> indicating improvement in preload, afterload and outcomes. This intervention is now considered to be a nonpharmacologic treatment measure, rather than a supportive measure,<sup>15</sup> and a first-line intervention in treatment of CPE.<sup>11</sup> Evidence for the benefit of noninvasive airway interventions in CPE includes the following:

#### **Box 2. Precipitating causes of acute cardiogenic pulmonary edema. MADHATTER mnemonic.**

Myocardial infarction  
Anemia  
Drugs, diet (salt)  
Hypertension  
Arrhythmia  
Thyroid disease  
Toxic (infection)  
Embolism (pulmonary), endocarditis  
Renal failure

#### **Box 3. Differential diagnosis of acute cardiogenic pulmonary edema**

- Bronchospasm or asthma
- Chronic obstructive pulmonary disease exacerbation
- Pneumonia
- Pulmonary embolism
- Adult respiratory distress syndrome
- Myocardial ischemia or infarction
- Pulmonary fibrosis
- Other cause of pulmonary edema (altitude, etc.)

- Most of the evidence originally existed for nasal continuous positive airway pressure (CPAP). There is now ample evidence that bilevel positive airway pressure (BIPAP) is as effective.<sup>16,17</sup>
- The most common CPAP setting is 10 cm H<sub>2</sub>O. BIPAP settings are 10 cm H<sub>2</sub>O expiratory positive airway pressure (EPAP) and 15 cm H<sub>2</sub>O inspiratory positive airway pressure (IPAP).<sup>16</sup>
- This intervention should be instituted early in the course of treatment,<sup>4,11</sup> preferably on arrival in the emergency department.
- This intervention is one of the least likely to produce adverse effects when the diagnosis is uncertain as it can also be of benefit in respiratory disease.
- Devices for administration of positive airway pressure are becoming less expensive and more available to rural emergency departments. The 10-cm CPAP setting is easy to set up.
- Most studies show significant reduction in ICU admission, need for intubation and mortality in patients given this intervention. In one prehospital study, intubation was reduced by an odds ratio of 4.04 and mortality was reduced by an odds ratio of 7.48.<sup>18</sup>
- If it is not possible to maintain oxygen saturation above 90 with this intervention, intubation and mechanical ventilation is required. Other intubation indications include a Glasgow Coma Scale score of 8 or less, partial oxygen pressure of less than 60 and a partial carbon dioxide pressure greater than 5 over baseline despite noninvasive treatment. Failed noninvasive ventilation and cardiogenic shock are also indications.<sup>4</sup> If intubation is necessary, CPAP of 10 cm should be maintained.

## REDUCING PRELOAD

### *Morphine*

Although morphine seems to have reliably improved dyspnea in patients with CPE over many years, there are major concerns regarding outcomes in these patients. The assumption that it functions by venodilation, and therefore preload reduction, is also questioned. Major concerns with morphine use include the following:

- Venodilation in the extremities has been demonstrated, but the volume of blood sequestered by this mechanism is trivial.<sup>19</sup>
- Patients with acute myocardial infarction and pulmonary edema were studied by measurement

of pulmonary artery end diastolic pressure<sup>20</sup> and no benefit was found following morphine administration. It was concluded that the action of morphine in relieving dyspnea (all patients improved in this regard) was not explained by venous pooling, but that action on the central nervous system produced the benefit.

- Retrospective studies have now shown increases in ICU admission and intubation rates in patients treated with morphine in the emergency department.<sup>21,22</sup> The largest study from the Acute Decompensated Heart Failure National Registry (ADHERE) also links morphine use with significantly increased mortality.<sup>22</sup>
- Two small prehospital treatment studies have been done. Wuerz and Meador<sup>23</sup> observed that of patients treated with nitroglycerin, furosemide and/or morphine, the ones with final diagnoses of asthma, chronic obstructive pulmonary disease, pneumonia or bronchitis had a higher than expected mortality. Hoffman and Reynolds<sup>25</sup> prehospital study patients received the same drugs in different combinations. Of these patients, 23% were subsequently found to have a diagnosis other than pulmonary edema. Subsequent adverse events or worsening of the clinical condition was seen significantly more often in patients treated with morphine. There is clearly major concern with the use of morphine when the diagnosis is uncertain, which is often the case in a rural setting.
- Morphine has side effects, including myocardial depression, which can reduce perfusion, and nausea and vomiting, which produce catecholamine release and increased afterload. Even morphine's acknowledged beneficial effect of sedation is a side effect. Sedation might be more safely achieved with a benzodiazepine that causes no nausea or hypotension.<sup>11</sup>

In summary, while morphine can produce a dramatic reduction in symptoms, it is a demonstrable risk in patients with respiratory diagnoses who are often thought to have CPE. In addition, the outcomes of ICU admission, intubation and death are significantly increased in patients treated with morphine. Sedation can be achieved more safely with benzodiazepines if desired. Morphine probably has no place in the modern treatment of CPE.<sup>11</sup>

### *Nitroglycerin*

Of the vasodilators capable of reducing pulmonary capillary wedge pressure (PCWP) and preload,

nitroglycerin is the drug available in Canada. Nesiritide, available in the United States, is heavily promoted as being superior to nitroglycerin based on the VMAC (Vasodilation in the Management of Acute CHF) study,<sup>24</sup> which was a randomized trial involving 489 patients with CPE. This trial, supported by the manufacturer, compared nesiritide with an inadequate dose of nitroglycerin (42 µg/min at 3 hours), and, although there was a trend toward superiority for nesiritide, the difference was not significant. Unfortunately, most drug trials involving vasodilators are now reported by clinicians with links to the manufacturer of nesiritide and it is difficult to find new data on nitroglycerin. Because nesiritide is unavailable, is associated with a significant risk of renal dysfunction<sup>10</sup> and shows a trend toward increased mortality,<sup>25</sup> its use cannot be recommended, and nitroglycerin becomes the vasodilator of choice at one-fortieth of the cost. It is a first-line intervention.<sup>11</sup> Advantages of using nitroglycerin include the following:

- Early aggressive vasodilator therapy has been shown to be important.<sup>26</sup>
- Sublingual nitroglycerin is easy to give early, with a 0.4-mg dose every 5 minutes being bioequivalent to 60 µg/minute intravenously. Thereafter, early aggressive advancement of intravenous (IV) dosing to 60–100 µg/minute is important to achieve optimal effect.<sup>11</sup> At higher doses, some afterload reduction is achieved.<sup>27</sup>
- Nitroglycerin is shown to have superior outcomes in comparison with furosemide in patient survival to hospital discharge<sup>28</sup> and reduction in PCWP.<sup>29</sup> One prospective study shows reduced mortality using high-dose nitroglycerin, compared with high-dose furosemide.<sup>30</sup> When it is considered that furosemide is used in 88% of CPE treatment and that 75% of patients receive no vasodilators,<sup>31</sup> we need to review our priorities with respect to these 2 types of therapy.
- Furosemide given alone takes 45–120 minutes to diuresis owing to initial marked vasoconstriction. Vasodilators given early to reduce preload help reverse this initial increase in PCWP and promote early diuresis.<sup>27</sup>
- Because most patients with CPE present with well-preserved perfusion (“warm and wet”), nitroglycerin is usually well tolerated. It should be used with caution or along with inotropic support if systolic blood pressure is below 100 mm Hg.<sup>1</sup> It should be avoided in mitral regurgitation, aortic stenosis, pulmonary hypertension, right ventricular infarction and in patients using

agents for erectile dysfunction. Tolerance can develop after 12 hours of use.<sup>11</sup>

### *Loop diuretics*

Furosemide is a time-tested intervention in CPE. It is often used alone as therapy<sup>31</sup> under the assumption that it is a vasodilator and that along with diuresis it will reduce preload. Best evidence does not entirely support this, and there is evidence for harm that must be taken into account if we are to make best use of this medication. It is probably a third-line intervention.<sup>27</sup> Potential problems with the use of loop diuretics include the following:

- The Studies of Left Ventricular Dysfunction (SOLVD) database indicates that non-potassium sparing diuretic use is associated with an increase in fatal arrhythmias in patients with systolic LV dysfunction.<sup>32</sup>
- Forty to fifty percent of CPE patients have euvolemia or hypovolemia.<sup>11,33,34</sup> These are the patients who develop hypotension the day following initial treatment with diuretics. The problem is one of fluid maldistribution rather than of fluid overload.<sup>11</sup>
- Administration of furosemide produces diuresis after 45–120 minutes. The immediate effect is vasoconstriction with increased afterload, increased PCWP and much-reduced renal perfusion.<sup>27,35</sup> PCWP only falls over time and after diuresis. This delay in effect may be significant in gravely ill patients.
- A prospective study by Kraus and colleagues<sup>27</sup> demonstrated that these adverse effects of furosemide were mediated by the neurohumoural axis, and that immediate diuresis could be achieved by venous or arterial vasodilators given before diuretics. Several authors now recommend use of high-dose nitroglycerin, sublingual captopril or both before diuretic administration.<sup>4,27,35,36</sup>

### **REDUCING AFTERLOAD**

#### *Angiotensin-converting-enzyme inhibitors*

There are several heterogeneous prospective studies to show benefit for both sublingual captopril and IV enalapril in reducing afterload and improving outcomes in CPE. Captopril is inexpensive and easily administered in a small emergency department, while the availability of IV enalapril is problematic. Although there is accumulating evidence, there is no

definitive meta-analysis, and given the generic nature of the medications, funding for such studies is more difficult to obtain. With appropriate caveats, however, sublingual captopril can be presented as a second-line intervention.<sup>11</sup> Available evidence, outlined below, suggests it is safe and effective — certainly much more so in terms of outcomes than morphine and diuretics, which were the previous mainstays of therapy:

- Angiotensin-converting-enzyme (ACE) inhibition can often be given as a single dose in the emergency department and need not be repeated until a decision for chronic dosing is made.<sup>4,37</sup>
- Sublingual captopril has been compared with sublingual nifedipine in acute hypertension and found to be effective, with less flushing, headache and tachycardia. Onset of action was within 5 minutes.<sup>38</sup>
- A sublingual captopril tablet is dipped in water for more rapid absorption. For systolic blood pressures less than 110 mm Hg, the dose is 12.5 mg. For pressures greater than 110 mm Hg, the dose is 25 mg. Captopril can be used in combination with nitroglycerin if systolic blood pressure remains high or side effects of nitroglycerin limit adequate dosing. Combination with nitroglycerin exceeds the benefits of either used alone.<sup>11,27,39</sup> Captopril produces benefit later in onset than nitroglycerin, but the improvement is more pronounced and prolonged.<sup>40</sup>
- Early use of captopril will often produce diuresis without furosemide.<sup>41</sup> There is a reduction of preload and afterload after 10 minutes,<sup>40–44</sup> and it is recommended that diuretics be delayed for 30 minutes after vasodilators are given to allow for an increase in renal blood flow.<sup>11,27,35</sup>
- ACE inhibitors have been administered in acute decompensated heart failure in several trials with good hemodynamic stability and few adverse effects.<sup>41,42,45–47</sup>
- Improved outcomes include fewer ICU days<sup>21,47</sup> and reduced rates of intubation with mechanical ventilation.<sup>21,41,48</sup>

## IMPROVING CONTRACTILITY

### *Digoxin*

Digoxin likely has no place in the emergency treatment of CPE. Some sources still suggest it as an alternative for reducing ventricular response if rapid atrial fibrillation is present; however, amiodarone is now more often used for this indication.<sup>1</sup>

## OTHER INOTROPES

The catecholamine inotropes and milrinone, a phosphodiesterase inhibitor, are capable of improving blood pressure and cardiac output in the poorly perfused patient. Although numbers are improved, outcomes are of concern, with evidence of longer length of stay and increased in-hospital mortality for patients taking inotropes, compared with vasodilators.

These agents are best reserved for patients with impaired LV function and hypotension, and should not be used if perfusion is adequate. The following caveats should be kept in mind with the use of inotropes:

- Dobutamine is potentially the most beneficial of the catecholamine inotropes because it is capable of slightly reducing preload and afterload. Activity is blocked, however, in patients on chronic  $\beta$ -blockade, and higher doses may have to be used. In the event of increasing hypotension, the  $\alpha$ -adrenergic activity of dopamine or norepinephrine may be required. These agents not only improve blood pressure but also increase myocardial oxygen demand, dysrhythmias and ischemia. Vasodilators should be added as soon as possible to further reduce preload and afterload, and to improve congestion.<sup>4</sup>
- Milrinone is an “inodilator” and is unaffected by chronic  $\beta$ -blockade. It is superior to dobutamine in measured cardiac output, PCWP and systemic vascular resistance. Despite this, it has not been shown to improve hospital length of stay or mortality.<sup>4</sup>
- Dobutamine is generally available in small emergency departments. Milrinone, at 7 times the cost, is likely to be difficult to stock in departments that are not associated with an ICU.

## RECOMMENDATIONS FOR RURAL FACILITIES

1. Recognize alternate diagnoses and precipitating factors early.
2. Early institution of CPAP at 10 cm H<sub>2</sub>O is a first-line intervention.
3. Early sublingual nitroglycerine followed by IV administration in high doses (60–100  $\mu$ g/min) is a first-line intervention.
4. Sublingual captopril is a second-line intervention and should be considered at 12.5 mg if blood pressure is less than 110 mm Hg, or 25 mg if blood pressure is greater than 110 mm Hg in the following situations:
  - Nitroglycerine is contraindicated.

- Nitroglycerine does not produce improvement and the patient remains hypertensive.
  - Congestion is resistant to the other usual therapies and perfusion is adequate.
  - The patient presents with intense sympathetic overactivity (the most common presentation), with hypertension, vasoconstriction and poor urinary output (given along with nitroglycerine).
  - If a dialysis patient presents out of hours with volume overload, hypertension and pulmonary edema (given along with nitroglycerine).<sup>11</sup>
5. Furosemide should be given 30 minutes after institution of vasodilator therapy if there is no initial diuresis in nonurgent situations. Subsequently, it will sometimes not be needed at all, or it can be used in lower doses. This is a third-line intervention.
  6. Dobutamine can be given in cases of poor LV function and hypotension. Vasodilators should be initiated or continued if there is a good response. This intervention will not improve mortality rates.
  7. Morphine should not be used as it produces poorer outcomes. If sedation is needed, consider a benzodiazepine.
  8. Critically scrutinize new studies promoting use of new and expensive drugs as methodologies may skew results in favour of newer products. The lack of large studies on outcomes from older therapies usually reflects a lack of funding by industry.

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