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# The recognition and early management of critical illness

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ABSTRACT

INTRODUCTION Critical illness is an emergency because the inflammatory response has redundant multiple pathways; once triggered, it is difficult to control or suppress. Infection is a potent precursor of critical illness and increasing organ dysfunction has a synergistic, rather than purely additive, adverse effect on mortality. The longer the inflammatory process continues unabated, the more advanced and unrecoverable the pathophysiological processes become resulting in a high mortality.

METHODS The review is a statement of the author's opinion supported by selected references. The content of the review was presented as the Tutor Edwards Lecture at The Royal College of Surgeons of England in December 2004.

RESULTS Critical illness is preceded by prodromal signs warning of impending physiological catastrophe. These simple physiological signs, the most sensitive of which is the respiratory rate can be quantified using Early Warning Scores. If patients trigger the Early Warning Score, emergency management is required to reverse the abnormal physiological decline or to prompt admission to a critical care area. The emergency management principles include removal or reversal of the cause so shutting down the inflammatory response, appropriate antibiotic therapy and general organ support.

CONCLUSIONS Formalising measurement of physiological (in)stability on the general ward using Early Warning Scores improves recognition of unstable and potentially critically ill patients. Prompt intervention will either reverse further physiological decline or facilitate timely referral to the critical care service for further, more invasive, organ support.

KEYWORDS

Critical illness – Early Warning Score – Emergency management

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Early recognition of acute severe illness is important because of the redundancy in the multiple cascading pathways of the inflammatory process. If the inflammatory process is allowed to continue unabated in an unregulated manner, then it quickly escapes local control and becomes generalised. Outcome is then poor. Early recognition and management are, therefore, essential if sequential failure of organs (the 'physiological domino effect') is to be avoided. Increasing the number of organ failures has a synergistic, non-linear adverse effect on mortality. For this reason, the recognition and early management of critical illness is an essential principle for the effective management of all patients, not just those undergoing surgery.

## Pathophysiology

The biological response to injury (either accidental trauma or surgery), infection, severe burns, shock or inflammation is complex and usually involves the activation of the innate immune system. If the response escapes local control, the clinical manifestations include the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction (MOD). In the critical care setting, the initiating insult is very frequently a septic challenge. In the UK, 27% of all patients admitted to an intensive care unit (ICU) display the clinical manifestations of severe sepsis within the first 24 h of their ICU admission;[1] these patients have a subsequent 47% hospital mortality.

### Innate immune response

The innate immune response consists of both soluble (such as the complement system, acute phase proteins and cytokines) and cellular elements (including monocytes, macrophages, neutrophils, dendritic cells and natural killer cells). The immune response can be triggered by necrotic and apoptotic cells as well as foreign proteins. Although it can recognise a

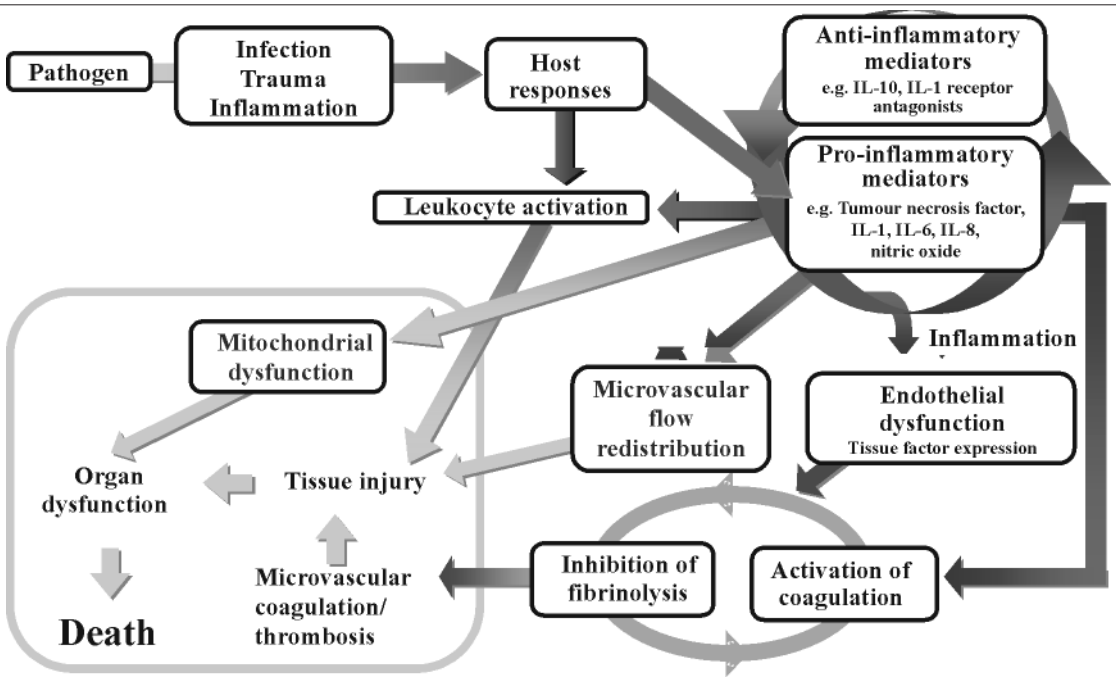


Figure 1 The pathophysiological pathways involved in sepsis. IL, interleukin (with permission from the Sepsis Care Initiative).

huge number of foreign proteins, the immune response is limited to a single (albeit complex) mediator and cellular cascade. The immune response has been fully reviewed elsewhere[2,3] and will only be outlined briefly below.

Bacterial components such as lipopolysaccharide, lipoteichoic acid, peptidoglycan and flagellin interact with pattern recognition receptors such as Toll-like receptors expressed on the surface of immune cells. Binding to Toll-like receptors activates intracellular signals (such as nuclear factor-kappa beta) to promote gene transcription that expresses immune response genes. Genetic susceptibility (to sepsis, for example) may be due to inherited or acquired mutations of these immune genes. Gene transcription results in the release of inflammatory cytokines (such as tumour necrosis factor-alpha [TNF-α], interleukin-1 [IL-1], IL-6 and IL-8). This inflammatory burst orchestrates a hyperactive immune response which results in macrophage activation, increased production of acute phase proteins and activation of the complement and coagulation systems. Gram-positive bacteria may also cause a severe response by producing exotoxins which act as superantigens. These molecules bind to antigen-presenting T cells; this direct binding promotes activation of large numbers of T cells and leads to massive release of pro-inflammatory cytokines. The hyperactive immune response initiates multiple pathways designed to kill bacteria (such as reactive oxygen species and the complement system) but, unfortunately, these mechanisms also contribute to the collateral host damage.

Following a period of hyperactivity, the immune system becomes stressed or paralysed. In contrast to micro-organisms and necrotic cells, the ingestion of apoptotic cells by macrophages signals CD4 T cells to secrete anti-inflammatory cytokines. There is also evidence of immune cell death and dysfunction in immature immune cells, such that antigen recognition is limited. Such depressed immunity is important in the critically ill as it sets the stage for nosocomial infection, the commonest of which is ventilator-associated pneumonia.

## Pathological consequences

The pathological consequences of this immune burst are that oxygen usage declines, metabolic acidosis develops and multiple organ dysfunction ensues (Fig. 1). There are at least three levels at which failure of oxygen usage can occur (mitochrondrial dysfunction, microcirculatory imbalances and cardiorespiratory impairment).

### MITOCHRONDRIAL DYSFUNCTION

At the cellular level, oxygen usage fails as the oxidative phosphorylation processes within the mitochondria malfunction. The inability to increase oxygen consumption after injury and lactate levels above 2.5 mmol/l are associated with the development of multiple organ failure.[4] In sepsis (via endotoxin and TNF-α), trauma, haemorrhagic shock and reperfusion injuries, the supply of electrons from tissue substrates may not match the oxygen supply so that the

redox state of the cell is 'uncoupled' (from the oxygen supply which it usually closely follows in health).[5] Apart from reducing energy supply, the decoupling results in damaging anomalous electron transport and free radical and oxidant production.[5] Decoupling may explain the discordance between the post-mortem histological findings and the degree of clinical organ dysfunction in patients who died of sepsis.[6] The cells may hibernate or become stunned so that their metabolic processes are reduced to only basic obligatory cellular functions. Such dysfunction may occur despite early goal-directed therapy and the delivery of oxygen in adequate quantities. It may explain why some clinical trials of hyperdynamic target achievement failed.[7]

### MICROCIRCULATORY IMBALANCES

At the circulatory level, there is disruption of the normal vasoregulatory mechanisms which promote vasoconstriction in response to hypotension. Vasodilatory shock is most frequently associated with sepsis but can occur in a variety of other situations such as in patients resuscitated after a prolonged period of severe haemorrhagic shock or after prolonged cardiopulmonary bypass. Three mechanisms have been identified as contributing to this abnormal vasodilation:[8]

1. Decreased cellular adenosine triphosphate (ATP) levels and increased hydrogen and lactate levels activate ATP-sensitive potassium channels in the plasma membrane of vascular smooth muscle. This allows the efflux of potassium out of the cell and so hyperpolarises the cell membrane closing voltage-gated calcium channels. Falls in intracellular calcium levels reduce phosphorylation of myosin and so promote vascular smooth muscle relaxation.
2. In septic shock and decompensated haemorrhagic shock, nitric oxide production is increased as a result of increased expression of the inducible form of nitric oxide. Several cytokines including IL-1β, IL-6, TNF-α, and interferon-gamma (IFN-γ) can increase nitric oxide production. Nitric oxide causes vasodilation by dephosphorylating myosin using myosin light-chain phosphatase and so opens the potassium channels to hyperpolarise the cell membrane.
3. Usually vasopressin is responsible for water conservation; however, in response to hypotension (and hence increased baroreflex stimulation) caused by haemorrhage or shock, its release from the neurohypothysis increases from normal water conservation levels (0.9–6.5 pmol/l) to much higher concentrations (9–187 pmol/l). At these levels, vasopressin has a vasoconstricting effect, probably by inactivating the ATP-sensitive potassium channels and decreasing the synthesis of inducible nitric oxide synthase. However, as shock persists, the vasopressin stores in the brain become exhausted and levels fall so allowing unopposed vasodilation.

The inflammatory burst also upsets the usual coagulation status[9] by:

1. Inhibiting or down-regulating anticoagulants such as thrombomodulin and increasing levels of $\alpha_1$-antitrypsin which is an acute phase protein capable of inhibiting the anticoagulant protein C pathway.
2. Stimulating coagulants such as tissue factor production by monocytes. Complement activation by lipopolysaccharide increases exposure of clot-promoting membrane phospholipids to the blood. Levels of fibrinogen may be increased.
3. Inhibiting fibrinolysis by increasing plasminogen activator inhibitor-1.

Once these processes are initiated, it is quickly amplified leading to microvascular occlusion, thrombosis, ischaemia and subsequent organ dysfunction.

### CARDIORESPIRATORY IMPAIRMENT

At the patient level, oxygen delivery may be impaired because of cardiorespiratory involvement, either reducing cardiac output or limiting effective pulmonary gaseous exchange (*e.g.* acute lung injury or the acute respiratory distress syndrome [ARDS]).

In sepsis, left ventricular filling is reduced because increased capillary leak and elevated pulmonary resistance (due to a combination of microvascular occlusion or abnormal vasoconstriction). Endotoxin can directly reduce the contractility of the heart making it more resistant to β-inotropic stimulants.[7] The reduction in systemic vascular resistance partially optimises cardiac output by improving stroke volume at lower contractility and filling. However, while such vasodilation compensates for the cardiac effects of sepsis, it adversely affects end organ function by reduced perfusion pressure.

A wide variety of surgical (and medical) conditions can lead to lung injury, not all of which may involve the lung directly. The pathophysiology and clinical progress of pulmonary lung injury (caused by aspiration, infection, near drowning, inhalation and lung contusion) may be different from extrapulmonary injury (caused by sepsis, severe non-thoracic trauma and excessive fluid resuscitation).[10] The end results are hypoxia caused by increased fluid or cellular infiltration between the pulmonary capillary and the alveolus or loss of alveolar volume by collapse, fluid or infiltration.

## Clinical manifestations

Following the inflammatory burst, oxygen delivery is impaired because arterial oxygen content may be reduced by pulmonary dysfunction and reduced cardiac output. The normal distribution of the oxygen is disrupted by the vascular and endothelial activation so that certain vascular beds, particularly the splanchnic circulation, are under-perfused.

Even if oxygen is delivered in adequate quantities, the mitochondria may not be able to utilise it properly.

The decline into multiple organ failure can be insidious as the clinical signs of tissue hypoxia are non-specific. There is usually an increased respiratory rate, peripheries which are either warm and vasodilated or cold through vasoconstriction, oliguria (*i.e.* <0.5 ml/kg/h) and mental slowing. The patient's clinical state frequently belies the severity of illness. The rate of deterioration may be life-threatening and exponential because of the log growth rate of bacteria, bacterial breakdown products, cascade and redundancy in the inflammatory response. Urgent observation and corrective therapy are required.

Fifteen years ago, Schein *et al.*[11] reported that 84% of patients displayed abnormal respiratory and mental function within 8 h of in-hospital cardiac arrest. More recently, Goldhill *et al.*[12] at the Royal London Hospital reviewed 79 non-operative ward referrals to ICU over a 13-month period. The reasons for ICU referral were most commonly chest infections ($n$ = 23), central nervous system depression ($n$ = 8), immunosuppression ($n$ = 8), sepsis or pancreatitis ($n$ = 7), myocardial infarction ($n$ = 7), and respiratory failure ($n$ = 6). Hypovolaemic convulsions, chest or neck trauma, muscle weakness, pulmonary embolism and airway problems constituted the other causes. None of these causes could be described as unusual. However, 26 patients suffered a cardiac arrest before referral to ICU. In the 6 h prior to their arrest, 75% were receiving oxygen, 37% had their arterial blood gases analysed and 61% had their $SpO_2$ measured (and in 63% of these patients, peripheral saturation was recorded as being < 90%). These interventions suggest that the patients were recognised as being ill, but the therapeutic response was either ineffective or not applied in time to prevent a cardiac arrest.

Unfortunately, clinical management of the sickest patients after hospital admission, but prior to ICU referral, has been reported as sub-optimal and associated with an increase in mortality.[13] McQuillan *et al.*[14] from Portsmouth studied a cohort of 100 consecutive ICU admissions. These patients' management was reviewed by external assessors who were qualified in intensive care. Twenty patients were perceived to have been well managed, 54 received poor management and in 26 patients, the assessors were unable to agree. The reasons for sub-optimal care prior to admission were failure of organisation, lack of knowledge, failure to appreciate the urgency, lack of supervision, or failure to seek advice. Such failures contribute to the critical incidents which result in serious adverse events that are common on the general wards.[15]

## Recognition

In response to these failures, physiologically based warning scores were developed.[16] These scores were not meant to predict or indicate outcome, but rather formalise the routine and comprehensive measurement of basic physiological observations on the ward. The score translates these abnormal recordings into a summary score, which has a critical threshold above which medical review and intervention is required. The scores are designed to alert staff of imminent collapse. The effectiveness of the medical response can be assessed by decreases in the summary score.

Scoring systems now form part of the formal communication of a call-out cascade so that senior help is enlisted for the acutely unwell patients. The call-out cascades also set time limits during which remedial action has to be taken. The scoring systems can also trigger timely referral to critical care.

There are a number of early warning scoring systems in use in the UK and Table 1 shows the early warning scoring system used at the Norfolk & Norwich University Hospital, together with the accompanying call-out cascade in Figure 2.

**Table 1 The early warning score used at the Norfolk & Norwich University NHS Trust**

| | Score 3 | 2 | 1 | 0 | 1 | 2 | 3 |
|---|---|---|---|---|---|---|---|
| Heart rate | | < 40 | 41–50 | 51–100 | 101–110 | 111–130 | > 130 |
| Blood pressure | <70 | 71–80 | 81–100 | 101–199 | | >200 | |
| Respiratory rate | | < 8 | | 9–14 | 15–20 | 21–29 | > 30 |
| Temperature | | < 35.0 | 35.1–36.5 | 36.6–37.4 | 37.5 | | |
| Level of consciousness | | | | A, alert | V, responds to voice | P, responds to pain | U, unconscious |

The individual parameter scores increase with increasing abnormality. The summary score is the total of the individual scores. At the Norfolk & Norwich University NHS Trust, the threshold value is set at 3.

Most early warning scores are based on abnormalities of heart rate, blood pressure, respiratory rate, temperature and level of consciousness. It is important to emphasise that the call-out cascade can be triggered by any member of the general ward staff but escalation goes through the nurse in charge of the ward to the medical team responsible for the

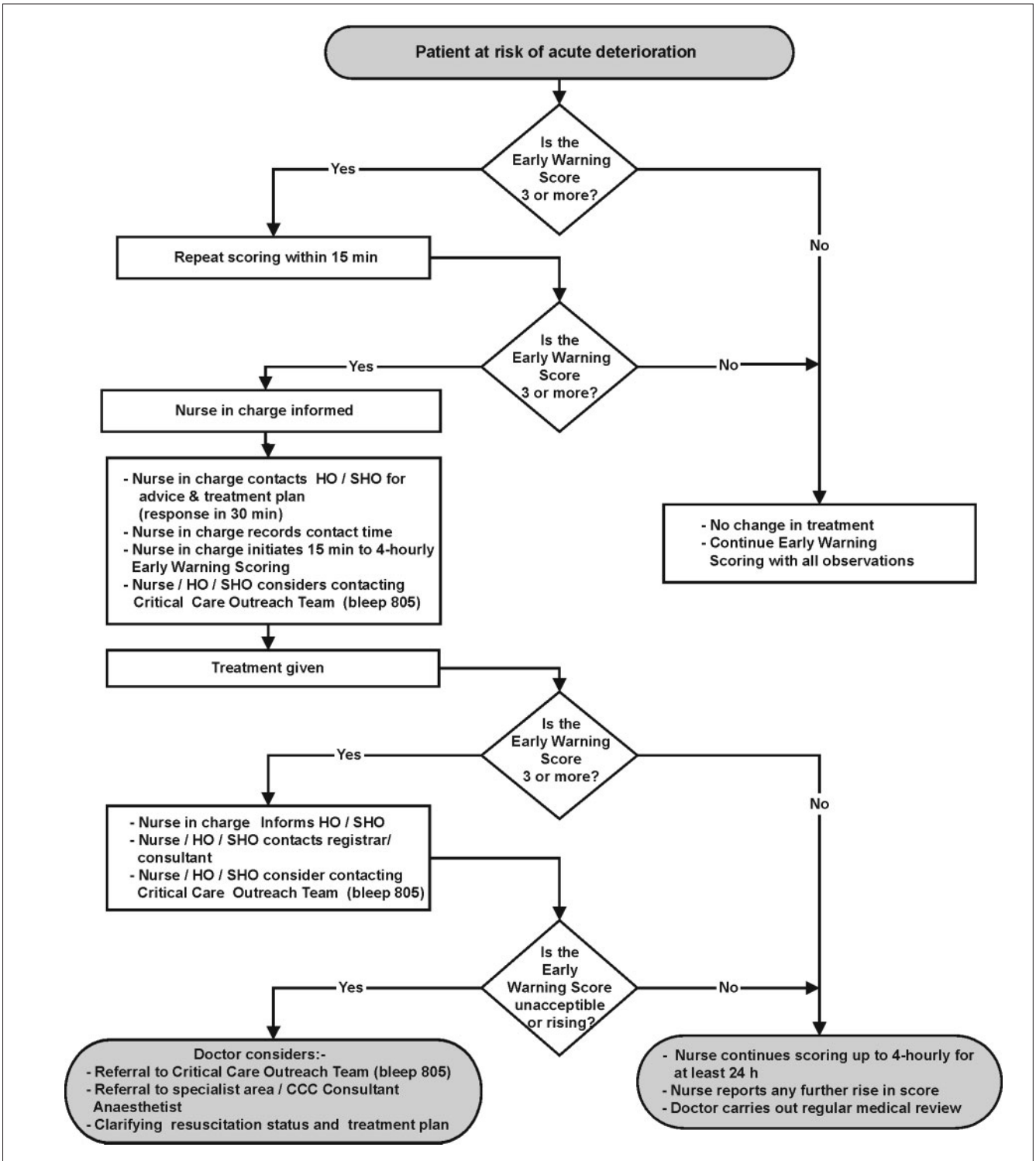


**Figure 2** The call out cascade triggered by the early warning score.

patient. If the patient fails to respond, then the nurse is empowered to contact directly senior members of the medical team and, if required, refer the patient to the critical care unit.

There are various modifications of the early warning scoring system and some have different thresholds to take account of age-related changes in physiological variables.[17] Others use text or percentage changes such as convulsions or falls in arterial saturation. The early warning scores attempt to achieve a balance between accuracy and complexity versus ease of use. At the moment, the sensitivity and specificity of the scoring systems is unknown, but even so their use is increasing in the UK as they represent a good educational resource for general ward staff. Despite the development of early warning scores and call-out cascades, uncorrected abnormal physiology is still not always adequately treated.

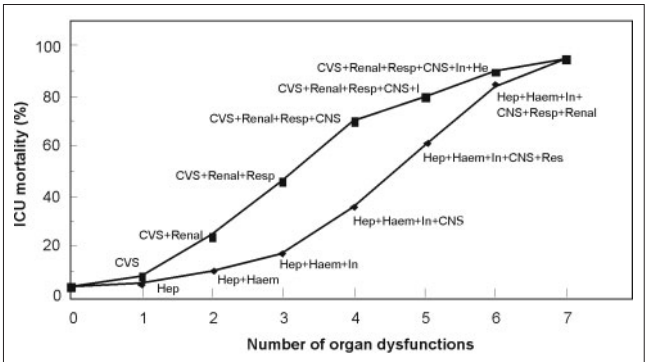


**Figure 3** The ICU mortality varying with increasing organ dysfunction. The shape of both lines is sigmoid and the mortality associated with cardiovascular (CVS), respiratory (Resp) and renal (Renal) failure is much higher than with other failures. CNS, central nervous system; Hep, liver; In, infection; Haem: haematological.

## Early management

The early management of critical illness (*i.e.* within 24 h of an acute deterioration) may be categorised as:

1. Removal/reversal of the cause so shutting down the inflammatory response. This may be achieved by surgery to excise infected, traumatised or necrotic tissue or to drain pus.
2. Appropriate antibiotic therapy. Critically ill patients need the most potent antibiotics available. The choice will depend upon clinical suspicion as definitive but relevant microbiological results may not be available at this early stage.
3. General supportive measures aimed at maintaining organ function while the specific therapy (such as surgery or antibiotics) takes time to work.

### Urgency

The most important aspect of early management is urgency. Once one organ has failed, it puts increased strain on other organs; this is particularly true for the cardiovascular, respiratory and renal systems. If corrective action is not taken, organ failures tend to be sequential (the 'physiological domino effect') and the patient declines into multiple organ failure. Increasing organ dysfunction has a synergistic rather than purely additive adverse effect on mortality (Fig. 3).[18] The longer the inflammatory process continues unabated, the more advanced and unrecoverable the pathophysiological processes become.

Goal-directed therapy attempts to improve or manipulate the cardiac preload, afterload and contractility so that the systemic oxygen delivery is better matched to the oxygen demand. Previous studies in intensive care have shown that forcing the patient's cardiorespiratory systems to supranormal or normal values has not always improved mortality.[7,19] It is possible that the therapies aimed at optimising the cardiorespiratory system instigated on ICU admission are being applied too late. Consequently, the focus has shifted toward haemodynamic optimisation at the earliest presentation of sepsis or the systemic inflammatory syndrome.

A prospective study carried out in an emergency department randomly assigned 263 patients to either 6 h of early goal-directed therapy or to standard therapy prior to ICU admission.[20] Standard therapy included monitoring the central venous and arterial pressures together with urinary output. The haemodynamic end points were a central venous pressure between 8–12 mmHg, a mean arterial pressure over 65 mmHg and a urine output of at least 0.5 ml/kg/h. Patients who received early goal-directed therapy received the standard care, but also had their central venous oxygen saturation measured. In this group, optimisation (*i.e.* fluids to increase central venous pressure, vasopressors to increase mean arterial pressure, transfusion to a haematocrit over 30%, dobutamine to increase mixed venous oxygen saturation) aimed to keep the central venous oxygen saturation above 70%. As a result, the patients who received goal-directed therapy were given more intravenous fluids (including blood transfusions) and more inotropic support (mostly dobutamine). Following the early goal-directed period (7–72 h), optimised patients had higher mixed venous oxygen saturation (70.4% versus 65.3%), lower lactate levels (3.0 versus 3.9 mmol/l), lower base deficits (2.0 versus 5.1 mmol/l) and higher pH (7.40 versus 7.36). The patients' physiologies were also better following the 6 h of early goal-directed therapies with lower Acute Physiology and Chronic Health Evaluation (APACHE) II scores (13.0 versus 15.9). Their subsequent hospital mortality was reduced to 30.5% versus 46.5%. This study emphasises the time-dependent domino effect of multiple organ failure.[21] If the patient's abnormal physiology can be reversed early, then outcome is improved.

The general supportive measures used by Rivers *et al*.[20] follow the recognised principles of management of the airway, breathing and circulation.

### Airway and breathing

In critical illness, circulatory abnormalities are the most important but it is clearly vital to secure the airway and if necessary provide mechanical ventilation. As mechanical ventilation abolishes or minimises the work of breathing, reduces respiratory muscle oxygen consumption and improves ventilation–perfusion mismatch, early respiratory support will benefit most patients. Mechanical ventilation should be instigated earlier than would normally be considered on the basis of blood gas analysis alone (*i.e.* before the blood gas abnormalities suggest severe hypoxic or ventilatory failure).

### Circulation

As discussed above, the predominant pathophysiological dysfunction is failure of oxygen usage which depends upon adequate perfusion pressure. Inadequate perfusion pressure may result from dysfunction of the arterial pressure (afterload), myocardial contractility or fluid sequestration (capillary leak and covert hypovolaemia).

*Correction of the circulatory abnormality involves:*

1. *History, examination and special investigations*. Critical illness imposes new strains on the cardiovascular system and interpreting the patient's cardiovascular parameters will be difficult if the normal pre-morbid function of the heart is unknown.
2. *Invasive measurement of the cardiovascular performance is required*. In critical illness, the usual clinical measures of peripheral perfusion may be lost or misleading. It is almost impossible to identify confidently, by clinical examination alone, whether the hypotension is caused by inadequate preload, contractility or afterload; the incorrect therapeutic choice may exacerbate the cardiovascular dysfunction.[22] Cardiovascular performance can be measured by pulmonary artery catheters, Doppler probes or other advanced forms of monitoring (pulse contour analysis and bio-impedance techniques). The impact of these invasive monitoring measures on mortality may depend more upon the clinician's treatment algorithm rather than the individual choice of measurement device.

*The cardiovascular abnormalities associated with acute inflammation include:*

1. *Hypovolaemia*. If the pulmonary artery occlusion pressure is less than 18 mmHg, cardiac index < 4.5 l/min/$m^2$, or stroke volume below the normal range (~60 ml/beat), then increases in circulating volume are required. The choice of fluid depends upon the underlying cause of the hypovolaemia. No single type of fluid has been shown to be superior to another in clinical trials. However, because critical illness is frequently associated with capillary leak, excessive volumes of crystalloid should be avoided. Colloid solutions (such as hydroxyethyl starch or/and albumin) that remain in the circulation may be more appropriate for resuscitation. Gelatines have a low molecular weight (~35 kDa) and so have a shorter duration of effect. Red cells will increase oxygen delivery and should be given in the resuscitative phase; however, a restrictive transfusion may be more appropriate once the patient has been stabilised on ICU.[25] Volume expansion should continue until the pulmonary artery pressure reaches 18 mmHg or systemic vascular resistance index decreases to the normal range (1050–2000 dynes.s/$cm^5$/$m^2$).
2. *Hypervolaemia may occur if the patient's urine output has been inadequate.* Under these circumstances, diuretics (possibly as an infusion, *e.g* furosemide 10–20 mg/h) may help to off-load the left ventricle. Patients in established anuric renal failure require renal replacement therapy, usually haemofiltration as this has fewer adverse effects on an already strained cardiovascular system. Inodilators, such as milrinone (50 mcg/kg bolus followed by 0.375 mcg/kg/min), are useful, especially if the pulmonary artery occlusion pressure exceeds 20 mmHg and the systemic vascular resistance index is greater than 2000 dynes.s/$cm^5$/$m^2$.
3. *Myocardial contractility is almost universally depressed or requires augmentation*. Drugs with weak β-effects such as dobutamine (5–10 mcg/kg/min) or dopexamine (up to 4 mcg/kg/min) may work but more usually potent catecholamines such as adrenaline (starting at 0.06 mcg/kg/min, increasing as needed) are required.
4. *If afterload is reduced*, a vasoconstrictor such as noradrenaline (starting at 0.06 mcg/kg/min, increasing as needed) is required to push the systemic vascular resistance into the normal range so that an adequate arterial perfusion pressure is achieved. Dopamine is now rarely used in adult general ICUs. Occasionally (usually in association with marked left ventricular failure), the systemic vascular resistance will be high and should be reduced with vasodilators or inodilators once hypovolaemia has been excluded.

The efficacy of such emergency measures may be assessed by improved peripheral perfusion (colour and temperature), urine output (> 0.5 ml/kg/min), falling lactate levels (< 2 mmol/l) and an improvement in oxygen consumption.

*If these strategies are unsuccessful and patients continue to deteriorate, other measures may include:*

1. Renal support to correct the metabolic acidosis and so improve myocardial contractility and possibly filter some of the acute inflammatory mediators.
2. Vasopressin infusions (0.04–0.1 U/min) may improve haemodynamic performance by replacing the covert vasopressin deficiency.[24]

3. Modest dose of steroids (hydrocortisone 200 mg and 50 mcg fludrocortisone (each daily for one week)).[25]
4. If the patients have two or more organ dysfunctions and are septic, activated protein C has been shown to improve mortality via its anticoagulation, profibrinolytic and anti-inflammatory effects.[26]
5. Keeping the blood glucose levels within a tight range (4.4–6.1 mmol/l) using insulin infusions has been shown to improve outcome.[27]

## Conclusions

The inflammatory response cascade has redundant multiple pathways and, once triggered, it is difficult to control or suppress. The inflammatory burst leads to a failure of oxygen usage at the mitochrondrial level and a failure of delivery due to loss of the usual vasomotor control and activation of the endothelium and cardiorespiratory dysfunction. The clinical manifestations tend to be non-specific but the global effects of multiple organ dysfunction can be captured in physiologically based early warning scores. Such scores should prompt effective medical intervention aimed at averting further decline. Increasing organ dysfunction has a synergistic rather than purely additive adverse effect on mortality and the longer the inflammatory process continues unabated, the more advanced and unrecoverable the pathophysiological processes become. The early management of critically ill patients follows the basic principles of airway, breathing and circulation. Such management is not difficult. Early (and hence probably the most effective) interventions can be carried out on the general ward while waiting for critical care review or admission.

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