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SPECIAL ARTICLE

NICEM consensus on neurological monitoring in acute neurological disease

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This manuscript summarises the Consensus on Neuromonitoring in Neuro-Intensive Care promoted and organised by the Neuro-Intensive Care and Emergency Medicine Section of the European Society of Intensive Care Medicine. The meeting was held during the 21st ESICM Annual Meeting in Berlin, 7 October 2007.

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Abstract This manuscript summarises the consensus on neuromonitoring in neuro-intensive care promoted and organised by the Neuro-Intensive Care and Emergency Medicine (NICEM) Section of the European Society of Intensive Care Medicine (ESICM). It is expected that continuous monitoring using multi-modal techniques will help to overcome the limitations of each individual method and will provide a better diagnosis. More specific treatment can then be applied; however, it remains to be determined which combination of parameters is optimal. The questions discussed and addressed in this manuscript are: (1) Who should have ICP monitoring and for how long? (2) What ICP technologies are available and what are their relative advantages/disadvantages? (3) Should CPP monitoring and autoregulation testing be used? (4) When should brain tissue oxygen tension ($PbrO_2$) be monitored? (5) Should structurally normal or abnormal tissue be monitored with $PbrO_2$? (6) Should microdialysis be considered in complex cases? It is hoped that this document will prove useful to clinicians working in NICU and also to those developing specialist NICU services within their hospital practice.

Keywords Intracranial pressure monitoring · Cerebral perfusion pressure · Brain tissue oxygenation · Microdialysis

Introduction

The mission of the Neuro-Intensive Care and Emergency Medicine section of the European Society of Intensive Care Medicine (NICEM; http://www.esicm.org) is to improve outcomes for patients with life-threatening neurological illnesses. In particular, NICEM undertakes to promote and develop standards for training and physician competencies in the subspecialty of neurological intensive care.

NICEM has successfully run two post-graduate courses on neuro-intensive care, directed by P.J.D.A. and G.C., in 2005 and 2006. At the Barcelona congress in 2006 we used high-fidelity simulation as a teaching aid and following that session received many questions about neurological monitoring equipment. It became clear that there was an urgent need for some guidance on advanced neurological monitoring.

We organised, as a satellite to the 2007 Annual ESICM Congress, an academic workshop with the aim of producing a consensus on neurological monitors for the society.

The instructions to the discussants and speakers at the meeting, were to present only level 1 evidence and tertiary research, where this existed, and conclude with three to four bullet points for review by the expert panellists. The questions the experts were asked to address were:

1. Who should have ICP monitoring and for how long?
2. What ICP technologies are available and what are their relative advantages/disadvantages?
3. Should CPP monitoring and autoregulation testing be used?
4. When should brain tissue oxygen tension ($PbrO_2$) be monitored?
5. Should structurally normal or abnormal tissue be monitored with $PbrO_2$?
6. Should microdialysis be considered in complex cases?

There are no studies, to our knowledge, that have shown benefit from any patient monitor. Thus, it appears that many studies support the need for specialist care but several factors, including the use of advanced neurological monitors, subspecialty-trained personnel and the development of evidence-based medicine patient care protocols, may explain the improvements in patient outcomes, making it difficult to distinguish between the effect of specialist personnel themselves, care pathways they initiate and the relative importance of the specialised monitors. There has, however, been a decrease in mortality and an improvement in outcome associated with the development of all these factors.

We will consider the specialised monitors in this monograph.

Who should have ICP monitoring and for how long?

The fundamental principles of raised intracranial pressure (ICP) are condensed in the doctrine credited to Monro (1783) and Kellie (1824). Briefly, this doctrine states that, once the fontanelles and sutures are closed, the brain is enclosed in a non-expandable case of bone, the brain parenchyma is nearly incompressible, the volume of the blood in the cranial cavity is therefore nearly constant and a continuous outflow of venous blood from the cranial cavity is required to make room for incoming arterial blood [1].

Raised ICP is an important "secondary insult" in brain-injured patients and a predictor of poor outcome after TBI [2]. ICP is also used to calculate cerebral perfusion pressure (CPP), which represents the pressure gradient across the cerebral vascular bed and is used as a therapeutic target for brain-injured patients in many intensive care units and is recommended by the Brain Trauma Foundation's (BTF) evidence-based guideline [3].

However, it is important to realise that there has never been a randomised controlled trial showing an outcome benefit for patients with ICP monitoring and ICP-guided treatment compared with patients without ICP monitoring. To date only prospective cohort trials and observational databases in patient groups at greatest risk of raised ICP have shown trends toward better outcomes when ICP is treated at a lower threshold [4]. These data are summarised in the BTF guidelines stating that ICP should be monitored in all salvageable patients with a severe traumatic brain injury (TBI) and an abnormal computed tomography (CT) scan [5].

Patients at risk of neurological deterioration or those who have severe acute brain injury are best cared for in specialist centres where there is a concentration of expertise to address acute brain injury and its complications. Separating the impact of the availability of these specialists on patient outcome from the effect of ICP monitoring and ICP-guided treatments can be difficult [6].

The duration of monitoring will depend on normalisation of ICP and is highly dependent on individual patient characteristics. An option is to stop monitoring after 12–48 h with no pharmacological interventions and normalisation of $PaCO_2$.

In summary, ICP is a complex parameter which contains information about cerebral compensatory mechanisms and mechanisms contributing to cerebral blood flow (CBF) regulation. ICP control requires continuous ICP monitoring and integration of the additional information in the ICP waveforms [7] and their relationship to MAP to help us understand the underlying pathophysiology.

Consensus statement:

- We recommend that all patients with severe TBI should be managed in specialised centres.
- There are insufficient data to recommend ICP monitoring and management as standard care in all brain-injury patients. Nevertheless, the evidence is "good enough" to recommend ICP monitoring of patients with severe injuries who are at increased risk of intracranial hypertension.
- Which patients are at "high risk" of ICP elevation is a matter of controversy. We recommend ICP should be monitored in all salvageable patients with a severe TBI (i.e. Glasgow Coma Scale Score ≤ 8) and an abnormal CT scan.
- We recommend that the management of raised ICP should follow BTF guidelines with care to exclude surgical lesions, including haematoma, contusion and hydrocephalus. Local protocols should be developed that conform to international guidelines and include neurosurgical consultation.

What ICP technologies are available and what are their relative advantages/disadvantages?

The optimal ICP monitoring device should be accurate, reliable, cost effective, and cause minimal patient morbidity, as stated by Lundberg [8]. Accuracy and reliability are defined according to the Association for the Advancement of Medical Instrumentation (AAMI) standards (http://www.aami.org/standards/index.html). An ICP device should have the following specifications: pressure range 0–100 mmHg, accuracy $\pm$ 2 mmHg in the 0–20 mmHg range and maximum error of 10% in the 20–100 mmHg range, ANSI/AAMI NS28:1988/(R)2006 – Intracranial pressure monitoring devices (ANSI: American National Standards Institute).

Ventricular fluid pressure is the established reference standard for measuring ICP. Currently, the ventricular catheter (VC) connected to an external strain gauge transducer is the most accurate, low-cost, and reliable method of monitoring ICP [2]. This method has been proven to be reliable, permits periodic recalibration and allows therapeutic CSF drainage. Nevertheless, obstruction of the system and the requirement to consistently maintain the external transducer at a fixed reference point, usually the external auditory meatus, can lead to inaccuracy during clinical use [9]. The incidence of such problems has not been evaluated precisely. Furthermore, VC requires the implementation of quality control mechanisms, including accuracy and reliability. A major disadvantage is that its performance is dependent on human interaction (calibration, choice of reference level, etc.).

The potential risks of difficulty in placement, the need for frequent recalibration and the risk of obstruction and infection have led to the development of alternative intracranial sites and technologies for ICP monitoring [2]. The most common alternative location for ICP monitoring is the cerebral parenchyma. Intraparenchymal transducers may be classified as solid-state, based on pressure-sensitive resistors, or fiberoptic design (FOD). Although both systems are very accurate at the time of placement, they have been reported to drift over time. Published research on this widely used technology ($>$ 100,000 sensors sold worldwide in 2006) and especially independent comparative tests are scarce [10, 11]. No standard evaluation has been defined. For example, the use of correlation coefficient to compare these monitoring devices against the gold standard is inappropriate, and agreement should be evaluated using the method described by Bland and Altman [12]. Precision of parenchymal ICP monitors has been assessed by comparing the measurement value at the time of ICP monitor removal with atmospheric pressure [13]. Better information about the measurement inaccuracy and tolerance, i.e. the maximum expected error expressed as a percentage of a clinically relevant pressure range, is desirable, and data on this topic should be collected prospectively and independently in large series. The cost of these devices is higher than that of the cheaper ventricular system and FOD devices suffer from a higher intrinsic fragility.

Subdural and epidural monitors and externally placed anterior fontanelle monitors are less accurate than the above-mentioned devices. The overall safety of ICP monitoring devices is good, with clinically significant complications (e.g. infection and haematoma) occurring infrequently in centres with enough expertise [2]. Further improvement in ICP monitoring technology should focus on developing systems incorporating derived information, for example software for estimating autoregulation, and/or multi-parametric devices that could also monitor parameters such as $PbrO_2$, temperature, CBF and other metabolic parameters in addition to ICP. Several techniques for non-invasive (indirect) assessment of ICP have been proposed over the years; at this stage none of them has reached sufficient maturity for clinical use.

Consensus statement:

- There is a need for standardisation and independent testing of ICP devices that verify the AAMI's standards in real life. These tests should be conducted both in the laboratory and in the clinical environments. Larger studies than have so far been published are required.
- Despite the limitations described above, according to the BTF guidelines the VC should be considered as the "gold standard" for ICP monitoring. Errors may be more common in routine clinical practice than in laboratory tests, and the human factor should also be con-

sidered a potential source of error. Alternatively, intraparenchymal devices are an adequate choice for ICP monitoring.
- New multi-parametric devices and non-invasive systems are expected to reach the market in the near future. They require further validation and identification of clinical situations in which they could be used instead of invasive monitoring.

Should CPP monitoring and autoregulation testing be used?

The indications and thresholds for monitoring of CPP i.e. the difference between mean arterial pressure (MAP) and ICP, remain controversial. According to BTF guidelines, the general recommendation for target CPP values lies within the range of 50–70 mmHg [4]. CPP values below 50 mmHg carry a 2–3 times higher risk of cerebral ischaemia and cerebral hypo-perfusion, while CPP values beyond 70 mmHg may be associated with an increased incidence of systemic complications such as cardio-respiratory failure [14, 15].

Recently, it has become clear that these broad recommendations are non-physiological. In fact, the risk/benefit ratio of CPP-directed therapy aiming at CPP target value of 70 mmHg versus an ICP-directed therapy tolerating lower CPP values depends on the state of the individual's cerebrovascular autoregulation.

In the recent BTF guidelines, autoregulation has been mentioned for the first time and the caveat has been raised that in individual cases the traditional CPP limits may not be appropriate. Some evidence as to whether ICP-guided or CPP-guided therapy is better may depend on the state of autoregulation: if the autoregulation is intact a CPP-directed therapy could be used, with a higher probability of favourable outcome, whereas if autoregulation is absent ICP-guided therapy may yield better results [16].

Because of these findings, a continuous assessment of both static and dynamic cerebral autoregulation has become an interesting adjunct to current neuromonitoring strategies. Cerebrovascular autoregulation may be determined by various approaches. One of the two most used bedside techniques is the online correlation between ICP and MAP (pressure reactivity index, PRx) and between middle cerebral artery (MCA) blood flow velocities and MABP (Mx) [17, 18]. Both strategies provide immediate and dynamic information on autoregulation at the bedside.

Using these techniques cerebral autoregulation can be monitored continuously and the decision between ICP-directed and CPP-directed therapies could be based on the autoregulatory state. It is noteworthy that the autoregulatory state is not a static but rather a dynamic variable, suggesting that the individualised treatment strategy should be re-evaluated regularly over the time course of the acute phase following brain injury.

In the future, ICP and CPP may not be the sole target parameters for managing brain-injured patients. Additional parameters, such as cerebral perfusion, cerebral oxygenation and cerebral metabolism, are currently being evaluated for their ability to guide treatments in acute brain injury. For example, manipulation of individual CPP targets based on monitoring of cerebral oxygenation ($PbrO_2$) and/or cerebral blood flow (rCBF), has been used successfully to decrease episodes of brain hypoxia [19].

Consensus statement:

- In general, ICP and CPP target values should be ≤ 20 mmHg and ≥ 50 to ≤ 70 mmHg, respectively.
- CPP values > 70 mmHg should only be targeted if cerebrovascular autoregulation is intact.
- If cerebrovascular autoregulation is lost, ICP-directed therapeutic strategies should be considered.

When should $PbrO_2$ be monitored?

The goal of monitoring the injured brain is to enable the detection of harmful physiological events, collectively defined as "secondary insults", before they can cause irreversible damage to the brain. The cause of secondary insults can be generalised, i.e. affecting the entire brain – for example, episodes of hypotension/decreased CPP, global hypoxaemia or increased ICP – or local, i.e. occurring only in the injured area of the brain. The latter category is more difficult to detect than the former. Whether or not secondary insults lead to permanent brain injury depends on the intensity and duration of the harmful physiological event and on the susceptibility of the brain [20].

In theory, the detection of tissue hypoxia is of even greater importance in the area of neurocritical care, because the brain and spinal cord have a poorer tolerance for ischaemia than most other tissues, and because hypoxia/ischaemia are central mechanisms underlying brain damage in various types of acute neurological injury, e.g. TBI, subarachnoid haemorrhage (SAH), stroke and global anoxia. The only currently available device uses a miniaturised Clark electrode to measure PO_2 and the device also measures temperature, so that the oxygen tension can be adjusted. The physiological idea behind cerebral oxygen monitoring is that the $PbrO_2$ value accurately represents the balance between oxygen delivery and oxygen consumption in brain cells, and that changes in $PbrO_2$ will therefore reflect pathophysiological alterations. These changes could then be used to guide treatments to prevent or mitigate hypoxic injury. In addition, $PbrO_2$ probes can also be used to directly measure brain temperature in injured and non-injured areas of the brain. There is mounting evidence suggesting that high brain temperatures can

Table 1 Summary of the evidence from clinical and in vitro studies assessing the usefulness of $PbrO_2$ in critically ill patients with brain injury

Meta-analyses	None
Prospective randomised clinical trials with hard endpoints	None
Prospective clinical trials with outcome assessment	None
Observational clinical studies linking low $PbrO_2$ to adverse outcome	Five small to medium-sized studies; total of 216 patients [24–28]
Clinical studies using $PbrO_2$ to guide interventions using hard endpoints to compare efficacy	One study with historical controls providing outcome data [31]
Clinical studies using $PbrO_2$ to guide interventions using secondary parameters to compare efficacy	One study [29]
Animal studies	Limited number of studies in cats and pigs [48–50]

aggravate brain injury, and that brain temperature often exceeds core temperature measured at other sites [21]; thus, direct measurements of brain temperature could be helpful in treating brain-injured patients.

As is the case with many other monitoring tools, there is a lack of data from clinical studies in critically ill patients. The available evidence is summarised in Table 1.

$PbrO_2$ appears to correlate well with regional CBF [22], and PET scan studies have suggested that $PbrO_2$ correlates with changes in regional SjO_2 (jugular venous oxyhaemoglobin saturation) in brain-injured patients in the clinical setting [23]. This supports the physiological notions underlying the usage of $PbrO_2$ to monitor brain injury, but provides no direct evidence that this can be used to guide treatments and improve outcome.

The two major conditions in which $PbrO_2$ monitoring has been applied are TBI and SAH.

Use of $PbrO_2$ monitoring in TBI

Five observational studies have reported that low $PbrO_2$ values in patients with TBI predict adverse outcome [24–27]. The largest study was performed by van den Brink et al. [28], who reported higher mortality and worse neurological outcome in a series of 101 patients with an initial $PbrO_2 < 10$ mmHg for ≥ 30 min and in those with $PbrO_2 < 15$ mmHg lasting ≥ 4 h. In addition, both the level and duration of low $PbrO_2$ correlated with mortality.

Longhi et al. [29] observed multiple episodes of brain hypoxia in the days following severe TBI both in peri-contusional tissue and in normal-appearing tissue. Moderate hypoxia was detected in over half of the patients, and severe hypoxic episodes in 23% in normal appearing tissue and 34% in peri-contusional areas, even when ICP and CPP were normal.

The question whether these measurements can be used to improve outcome has not been well studied. Tolias et al. [30] studied the effect of normobaric hyperoxia treatment (FiO_2 of 1.0 beginning within 6 h of admission) on a number of secondary parameters, including $PbrO_2$. The authors reported improvements in $PbrO_2$ as well as in other secondary parameters (lactate/pyruvate ratio, brain glucose, glutamate, lactate levels etc.) in patients treated with a FiO_2 of 1.0 compared to baseline and compared to historical controls.

Only one study has specifically used $PbrO_2$ to guide treatment. Stiefel [31] enrolled 28 patients with severe TBI in a protocol combining "traditional" ICP and CPP targets (ICP < 20 mmHg, CPP > 60 mmHg) with $PbrO_2$ monitoring (target $PbrO_2 > 25$ mmHg). Outcomes were compared to 25 historical controls that had been monitored with ICP and CPP targets only. Mortality rates were lower (25% vs. 44%, $p < 0.05$) in the group with the combined monitoring. However, it should be noted that mortality in the control group was high by current standards and that no neurological outcome assessment was reported.

Use of $PbrO_2$ monitoring in SAH

SAH is a condition that carries a high risk for delayed focal ischaemia [32]. The causes are:

1. Vascular compression (by intraparenchymal haematoma or a retractor during surgery).
2. Thromboembolic complications during aneurysm coiling procedures.
3. Temporary/permanent vascular occlusion during surgical clipping.
4. Development of vasospasm.

$PbrO_2$ monitoring has been used in the following situations:

1. Intraoperative monitoring for diagnosis of vascular occlusion [33].
2. Monitoring of the compressed peri-haematoma tissue [34].
3. Diagnosis of vasospasm-associated delayed ischaemia and evaluation of the efficacy of treatment for this condition [35, 36].

Suggested thresholds for brain hypoxia are in the range of 10–20 mmHg [37]; however, more preclinical investiga-

tion needs to be performed to determine the threshold and duration of brain hypoxia associated with irreversible histological brain damage and to establish which is the best therapeutic strategy to increase $PbrO_2$.

Consensus statement:

$PbrO_2$ measurement has not been tested in a prospective randomised controlled trial, but there is a physiologically plausible basis to suggest that $PbrO_2$ is a useful monitoring tool in patients following TBI and SAH.

- $PbrO_2$ monitoring can detect changes in regional brain oxygenation that may be missed by global monitoring such as SjO_2/$AjDO_2$, and can provide data continuously over long periods.
- Low $PbrO_2$ is associated with raised ICP, low CBF (global/regional) and with adverse clinical outcomes.
- Large prospective clinical trials are necessary to better evaluate this device and associated interventions.
- Relevant issues associated with $PbrO_2$ monitoring are costs, fragility and invasiveness of the technology. Costs and risk to the patients need to be justified. Coagulation parameters (especially platelet number and function) should be normal before insertion of a monitoring probe.

Should structurally normal or abnormal tissue be monitored with $PbrO_2$?

$PbrO_2$ value is highly dependent on O_2 diffusion from vasculature to a small amount of tissue [38]. Therefore, it is a regional monitoring, whose values are highly dependent on the location of the probe. The target area for $PbrO_2$ monitoring is a subject of debate.

TBI (normal tissue)

Most centres have measured $PbrO_2$ in the right "normal appearing" frontal subcortical white matter [37]. The most relevant data derived from $PbrO_2$ measured in normal tissue are:

- During the acute phase following TBI, $PbrO_2$ might be pathologic, despite a normal ICP/CPP, suggesting that $PbrO_2$ might become a novel target for resuscitation following TBI [39].
- There is an association between low $PbrO_2$ values and poor outcome [25, 40].
- $PbrO_2$-pressure reactivity might be used to assess cerebrovascular pressure reactivity and might help individualise CPP [41].
- In the presence of normal CPP, several episodes of regional brain hypoxia (not disclosed by parameters of global oxygenation) occur up to 5 days post-injury, suggesting that $PbrO_2$ is complementary to SjO_2/$AjDO_2$ (arterio-jugular venous oxygen content difference) when monitored in normal appearing tissue [29].
- Because there is an association between brain hypoxia and outcome, a strategy of detection and correction of brain hypoxia is advisable [19].

TBI (peri-contusional tissue)

In patients with focal lesions such as cerebral contusions/subdural haematomas there is a considerable amount of cerebral tissue at risk of ischaemia [42]. In the hypodense peri-contusional tissue, $PbrO_2$ is lower than measured in the normal appearing tissue, despite a greater CPP, and regional hypoxia lasts longer than in normal appearing tissue. Normalisation of low $PbrO_2$ around cerebral contusions occurs over a period of days [29]. This vulnerable tissue could be an appropriate target for focal invasive monitoring of brain oxygenation. However, more preclinical work is needed to test whether interventions aimed at correcting peri-contusional brain hypoxia are associated with histological and functional improvements in models of focal injury.

SAH

$PbrO_2$ has been used for early detection of cerebral ischaemia by placing probes in vulnerable areas of the brain, for example near the area of the aneurysm and in the area perfused by the artery where the aneurysm has been coiled or clipped.

Consensus statement:

The preferred location for $PbrO_2$ monitoring depends on what information is sought.

- *TBI:* The choice should be individualised for each patient.
  - The target should be the vulnerable and potentially salvageable tissue: peri-contusional tissue (not the core of the lesion) and tissue underneath a subdural haematoma.
  - Eloquent locations should be avoided (i.e. left temporal lobe, motor cortex etc.).
  - Where structurally normal tissue is monitored, $PbrO_2$ should be monitored in the sub-cortical white matter of the more injured hemisphere.

- *SAH*
  - The target should be the cortex within the expected distribution area of the parent artery of the aneurysm, which is at highest risk for developing vasospasm and delayed ischaemia.

Should microdialysis be considered in complex cases?

Although we do not have robust evidence as to when or how to use this technique, a consensus conference published in 2004 recommended that microdialysis (MD; see ESM) could be used in patients with TBI who require ICP monitoring [43]. Regarding catheter placement, this conference recommended placing a single catheter in the right frontal region in patients with diffuse injuries, and two catheters (one in normal tissue and one in the pericontusional tissue) in patients with focal injuries (brain contusions, non-evacuated haematomas etc.) [44]. Concerning the biochemical markers to monitor, it was stated that the lactate/pyruvate ratio was currently the best marker of the brain redox state and an early biomarker of secondary ischaemic injury glucose; glycerol and glutamate are additional markers of developing brain tissue hypoxia [45]. Regarding ischaemic damage, it is important to remember that ischaemic hypoxia is just one of the many types of hypoxia that can be detected in the injured brain [46].

The use of new high cut-off membranes may make the future of MD look bright, with the potential to study all the neuro-inflammatory cascades elicited by TBI [47]. High-resolution MD also opens potential avenues in translational research, allowing in the near future the solution to the puzzle of the physiopathology of TBI and the development of potential therapeutic targets.

Another avenue that can be explored with MD is the profiling of new potentially neuroprotective drugs. Although the presence of the drug in the extracellular fluid does not guarantee a neuroprotective effect, if the drug does not cross the blood–brain barrier it would plausibly indicate an inability of this drug to target the brain. A better understanding of the true concentrations of any drug found in the brain tissue should be the first step in selecting good candidates for neuroprotection. The system cost varies depending on the number of channels measured, and consumables cost approximately 570 euros per patient.

Consensus statement:

- Despite the increased use of MD in the management of severe TBI, there is no class I evidence for its routine use at the bedside.
- Microdialysis is the only tool that allows continuous measurement of tissue chemistry in the brain extracellular space. This information, when adequately integrated into the clinical management of severe TBI, is potentially more useful than the analysis of any biomarker in the peripheral blood.
- There is an increasing body of evidence stressing the relevance of non-ischaemic forms of brain tissue hypoxia. MD is an essential tool for a better understanding of these forms.
- High-resolution MD using membranes with a high cut-off will enable the recovery of cytokines, interleukins and other inflammatory mediators, which may increase the usefulness of MD.
- MD is also an excellent tool in evaluating the ability of potentially neuroprotective drugs to cross the blood–brain barrier

Conclusion

It is hoped that continuous monitoring using multi-modal techniques will help to overcome the limitations of each individual method and will provide a better diagnosis. More specific treatment can then be applied; however, it remains to be determined which parameters are optimal. The use of these techniques requires highly trained personnel to avoid the potential of generating artefacts and possible misinterpretation. We strongly recommend that all patients with acute life-threatening illness be managed in specialist units.

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