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A New Monitor of Patient Sedation in the ICU?

ABSTRACT & COMMENTARY

This paper reports a clinical evaluation of the bispectral index (BIS), in comparison with the revised sedation-agitation scale (SAS), to assess the level of sedation in a series of mechanically ventilated adult patients in a multidisciplinary ICU. The BIS is an electronically generated value based on the electroencephalogram (EEG) that attempts to quantitate a patient's level of sedation. Processing the EEG signal with Fourier transformation produces a power-frequency spectrum from which a number of derived indices can be obtained and that has been used in the operating room to assess sedation level during anesthesia. The BIS is an attempt to generate a single value indicating sedation depth despite the biphasic effects many medications used for sedation have on the EEG signal. It consists of a whole number between 0 and 100, with awake patients scoring in the 90s, conscious sedation dropping the value into the 70s and 80s, and general anesthesia further depressing the BIS into the 40-60 range.

Simmons and associates had previously devised the SAS, a seven-point subjective but standardized scale for assessing the level of sedation in an ICU patient. In the present study they simultaneously determined SAS and BIS data on 63 patients during mechanical ventilation. BIS values were assigned to baseline, stimulated, and average conditions for each patient by an investigator unaware of the SAS scores.

In the patients evaluated, sedation varied from very deep (SAS score 1, BIS score 43) to mild agitation (SAS score 5, BIS score 100). More heavily sedated patients by clinical criteria also had lower BIS scores, whereas the opposite trend was observed in more lightly sedated patients. Average BIS score correlated statistically with average SAS score ($r2 = 0.21$; $P < 0.001$). Simmons et al conclude that both the SAS and the BIS work well to describe the depth of sedation for ventilated ICU patients. (Simmons LE, et al. *Crit Care Med* 1999;27:1499-1504.)

COMMENT BY DAVID J. PIERSON, MD, FACP, FCCP

Although the degrees of analgesia, amnesia, and immobilization have been standardized in the operating room, such is not the case in the ICU, despite the need for prolonged sedation and sometimes also

Volume 7 • Number 8 • November 1999 • Pages 57-64

INSIDE

Growth hormone deadly in the critically ill **page 58**

Laryngeal mask airway in patients who cannot be intubated **page 59**

Special Feature: Advances in the hemodynamic therapy of septic shock **page 60**

muscle relaxation in critically ill, ventilated patients. The BIS is an attempt to bring a greater degree of objectivity and standardization in patient sedation to the bedside in the ICU.

In an editorial accompanying this article, Shapiro (Shapiro BA. *Crit Care Med* 1999;27:1663-1664) lists five features of the BIS that clinicians should understand:

1) Bispectral analysis of the EEG provides information about interactions between cortical and subcortical areas that change with increasing amounts of hypnotic drugs.

2) The BIS is an empirical, statistically derived measurement that was generated by analysis of a large database of EEGs from subjects receiving hypnotic agents and applying multivariate statistical methods to derive apparently optimum combinations of these features.

3) The BIS measures the state of the brain, not the concentration of any drug.

4) Interpretation of the BIS is predicated on the assumption that sedation is intended to produce a state of sleep that includes a lack of awareness and a lack of recall (amnesia), in contrast to analgesia, which is intended to produce a state of reduced pain perception.

5) In general, a BIS score of 100 reflects the awake state, 80 reflects some sedation, 60 reflects a moderate hypnotic level, and 40 reflects a deep hypnotic level.

I first encountered the BIS monitor when I came back on service in the medical ICU a couple of months ago, after being away from the unit for only a few weeks. During the presentation of the first patient on rounds, the managing intern included a BIS score of 70 as part of the morning's neurological findings. Although the intern hesitated when I interrupted to ask what that was, the patient's nurse quickly interjected that it was a new index of how sedated the patient was, which we were now monitoring on all ventilated patients in the unit. That last part turned out to be an exaggeration, but this vignette illustrates how quickly a previously unknown new technology can be put into routine clinical use in the ICU.

It is easy to see the potential advantages of something like the BIS in managing critically ill patients during mechanical ventilation. However, if the BIS monitor follows its predecessors, the pulse oximeter and the in-line capnometer, from the operating room to the ICU and becomes part of the "standard of care," will it produce clinically helpful, reliable data in this setting, under what are likely to be quite different conditions of use? Will the numbers have the same meaning as they do in the operating room? Will the use of this device permit less use of some other expensive monitor or therapy, thus justifying the added cost? Will it make patients more comfortable and easier to manage, decrease complications, reduce the duration of mechanical ventilation, or shorten average length of stay? Chances are, this latest in a long line of rationally intended, vigorously promoted electronic devices will see a lot of clinical use on ICU patients before data from properly designed clinical trials begin to answer these questions. ❖

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Growth Hormone Deadly in the Critically Ill

ABSTRACT & COMMENTARY

Synopsis: *Administration of GH has been suggested to modify the catabolic response to critical illness. Two European studies with a total of 535 patients demonstrate a doubling of mortality with high doses of GH as compared to placebo.*

Source: Takala J, et al. *N Engl J Med* 1999;341: 785-792.

The loss of protein that accompanies critical illness contributes to morbidity and mortality. Growth hormone (GH) resistance has been suggested as one pos-

sible mechanism contributing to the negative nitrogen balance observed. Therapeutic administration of GH, at 5-20 times the normal replacement dose, in some patient groups (burns, trauma, other critically ill patients on hyperalimentation) is associated with improvement in nitrogen retention. However, the latter result is not the same as an improvement in overall outcome. The effect of therapeutic GH administration on survival was investigated in the two studies reported in this paper.

These two randomized, prospective, double-blind, placebo-controlled evaluations were carried out in parallel in Finland (247 patients) and in several other European countries (285 patients). Patients were enrolled on the fifth to seventh ICU day if they were expected to require at least 10 days of ICU care. Patients received 0.10 mg/kg of GH per day, or placebo, until ICU discharge or for 21 days. Forty-seven of the 119 patients receiving GH in the Finnish group expired (39%), as compared to 25 of the 123 controls (20%), while 61 of the 139 treated patients in the European study died (44%) compared to 26 of 141 controls (18%). Txhese differences are highly significant.

Patients in the treatment and control groups were similar in diagnosis, reason for ICU admission, and severity of illness (APACHE II Score). Most of them were male (74% and 65%), elderly (61 years), and admitted following cardiac (26%) or abdominal surgery (25%), after trauma (10%), or for acute respiratory failure (39%). The average APACHE II score was 18. The increased mortality occurred earlier in the European group, which also initiated GH therapy at the full therapeutic level, while in the Finnish group the dose was increased to treatment levels over a three-day period. The increased mortality was associated with an increased incidence of sepsis, septic shock, and multiple organ failure. It persisted through hospital discharge and at three months. Ventilator length of use, ICU length of stay, and hospital length of stay were longer in the survivors who received GH. No early or late benefit could be identified in patients who received GH.

COMMENT BY CHARLES G. DURBIN, Jr., MD, FCCM

Preliminary reports of improvement in survival and nitrogen retention from administration of GH to small groups of critically ill patients were not supported by these two large, placebo-controlled, randomized trials. The use of GH was associated with a much worse outcome and demonstrated no value to any subgroup of these patients. GH administration was associated with more hyperglycemia and this may have been a contributing factor to the higher incidence of systemic infectious complications. There may be a role for GH in the critically ill, but given at a high dose after the first week of illness it doubles mortality with no benefit. Until additional information is available, this convincing report should be believed. ❖

Laryngeal Mask Airway in Patients Who Cannot Be Intubated

ABSTRACT & COMMENTARY

Synopsis: *Investigators report a high success rate with the laryngeal mask airway in patients who fail standard endotracheal intubation.*

Source: Martin SE, et al. Use of the laryngeal mask in air transport when intubation fails. *J Trauma Inj Infect Crit Care* 1999;47:352-357.

In a study by martin and colleagues at the Memorial Health University Medical Center in Savannah, Georgia, patients who could not be intubated by the flight team during aeromedical transport were instrumented with the laryngeal mask airway (LMA). Over a 22-month period, conventional endotracheal intubation failed in 25 patients, with 17 of the 25 meeting study inclusion criteria. Causes of airway instability included motor vehicle crash (14), fall (1), pedestrian struck (1), and stroke (1).

The LMA was correctly inserted with one attempt in 16 of 17 patients. In the remaining patient, insertion of the LMA was not successful after two attempts. In the 16 patients who were successfully instrumented with the LMA, correct placement was obtained in less than 10 seconds. Oxygenation and ventilation were measured with a continuous O_2 saturation monitor and end-tidal CO_2 ($ETCO_2$) monitor while in the helicopter and by arterial blood gas on arrival in the ED. All patients achieved O_2 saturation of 97-100% and $ETCO_2$ of 24-35 mmHg. On arrival, all patients were satisfactorily oxygenated (pO_2 range, 65-628) and all but one patient were successfully ventilated (pCO_2 range, 29-52). In summary, the investigators report a high success rate with the LMA in patients who fail standard endotracheal intubation. They recommend it as an important tool for airway management in the prehospital setting.

COMMENT BY JEFFREY W. RUNGE, MD, FACEP

Currently, there is no worthy substitute for properly performed endotracheal intubation in patients who require control and management of an unstable airway. Outside of the setting of cardiac arrest, this procedure should be car-

ried out using rapid sequence techniques that facilitate intubation and provide neuroprotection. Unfortunately, the majority of EMS professionals in this country work in locales where it is difficult to maintain skills in this vital and relatively complicated technique. It is extremely important that EMS medical directors provide their prehospital crews with a variety of "tricks in their bags" to take care of those who require airway management.

The LMA has been successfully used by anesthesiologists in the operating room for years. It is popular with many pediatric anesthesiologists for short cases that would have otherwise required brief mask anesthesia. Any questions about adequacy of ventilation and oxygenation have long been answered, but the possibility of aspiration of gastric contents with the LMA is still under discussion. There are proponents and detractors who express very strong opinions about chances of gastric aspiration with the LMA vs. bag valve masks, but data are lacking. Much of the information on the device comes from the anesthesia literature, which is quite different than the prehospital setting where patients often have full stomachs.

With the understanding that any procedure or instrument has complications, good judgment must prevail when seeking to protect a patient's airway, ensuring tissue perfusion with oxygenated blood and ventilation to alleviate the sequelae of hypercapnia. Recognizing that the bag valve mask is no simple procedure, especially if not used frequently, the LMA certainly should be considered as an alternative step to endotracheal intubation for patients who cannot be intubated following neuromuscular blockade. It should also be considered for those EMS services where intubation cannot be taught or where skills cannot be maintained. The goal of EMS is to deliver the patient to the hospital in the best shape possible. Clearly, the LMA has distinct advantages over the bag valve mask in selected patients, and should be available when endotracheal intubation is not possible in patients who require airway management. (*Dr. Runge is Assistant Chairman and Clinical Research Director, Department of Emergency Medicine, Carolinas Medical Center, Charlotte, NC.*) ❖

Special Feature

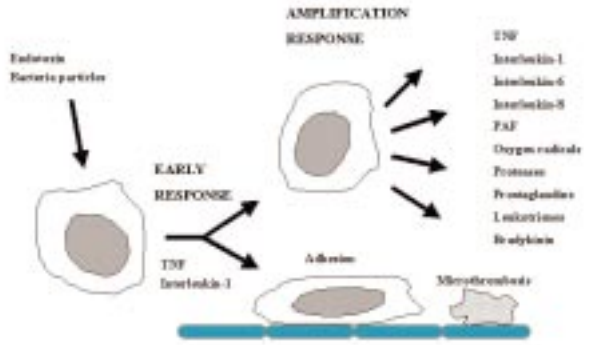
Advances in the Hemodynamic Therapy of Septic Shock

By Francisco Baigorri, MD, PhD

There have been significant advances in our knowledge of the pathogenesis of sepsis and septic shock in the last few years. The concept has emerged that the host's inflammatory response contributes substantially to the development of septic shock and organ failure.[1] Both exogenous mediators, such as endotoxin, and endogenous cytokines have been implicated in this inflammatory response. The most widely investigated cytokines are tumor necrosis factor (TNF), interleukin-1, and interleukin-8, which are generally pro-inflammatory, and interleukin-6 and interleukin-10, which tend to be anti-inflammatory (*see Figure*). TNF and interleukin-1 promote endothelial cell-leukocyte adhesion, release of proteases and arachidonate metabolites, and activation of clotting. Nitric oxide has also been implicated in the pathophysiology of the cardiovascular response to sepsis. This complex immunologic cascade causes hemodynamic changes that may be detrimental to the host. There is depression of cardiac function, a mixture of vasoconstriction and vasodilation, capillary blockage by cellular and protein material, and capillary leak.[2] These changes lead to a maldistribution of blood flow with altered organ perfusion and organ failure.[3] Moreover, there has been remarkable progress in our understanding of the cellular injury from subsequent reperfusion and the role of oxygen-free radicals in these circumstances.[4]

Figure

Overview of Cytokine Responses



An initial toxic stimulus triggers the production of pro-inflammatory cytokines (early response). These cytokines result in generation of numerous secondary inflammatory mediators (amplification response). TNF, tumor necrosis factor; PAF, platelet-activating factor.

In this decade, we have also learned about the limitations of changes in oxygen delivery (DO_2) and oxygen consumption (VO_2) values extrapolated from pulmonary artery (Swan-Ganz) catheter measurements of global hemodynamics to detect occult tissue hypoxia.[5] Finally, it has been a "rediscovery" of the significance of blood pressure as an important determinant of regional perfusion and to avoid organ dysfunction.[6,7] This brief essay discusses recent investigations into the therapy of septic shock in the light of these events.

Modification of Defense Mechanisms

Immunomodulators—Experimental observations prompt-

Table

Mortality Rates in Clinical Trials of Nonglucocorticoid Mediator-Specific Anti-Inflammatory Agents (modified from Reference 8)

Agent	No. of Studies	No. of Patients	Mortality (%)	
			Control group	Treatment group
Interleukin-1 receptor antagonist	3	1898	35	31
Bradykinin antagonist	2	755	36	39
Platelet-activating factor antagonist	2	870	50	45
Anti-TNF monoclonal antibodies	8	4130	42	39
Soluble TNF receptors	2	639	37	40
Prostaglandin antagonist: ibuprofen	3	514	40	38
All studies	20	8806	41	38

ed large-scale, randomized clinical trials with a variety of immunomodulators such as glucocorticoids, ibuprofen, anti-endotoxin monoclonal antibodies, antagonists of platelet-activating factor, bradykinin-1 or interleukin-1 receptor, and monoclonal anti-TNF antibodies or soluble dimeric TNF receptor fusion proteins. Individually, each of these studies failed to show clinical benefit. There are several possible reasons for these disappointing results. Septic shock patients are too diverse, with differences in comorbidity, severity of illness, types of infecting pathogens, and sources of infection. Conventional management is variable and uncontrolled. It has even been argued that clinical investigation is premature, given the extreme complexity of the inflammation cascade and the present-day limitations in our understanding of the underlying fundamental biology.

A meta-analysis of pooled data from 20 trials testing nonglucocorticoid, mediator-specific agents provides another perspective to assess the value of these agents (*see Table*).[8] The nonglucocorticoid mediator-specific agents produced a small but significant beneficial effect on mortality: the treatment group had a mortality rate of 38%, while the control group had a mortality rate of about 41% ($P = 0.04$).[8] To demonstrate such a modest benefit, a clinical trial would have to enroll 6000-7000 septic patients. For drugs that cost, say, $4000-$5000 per dose, the question raised is whether the price of therapy per patient saved may turn out to be prohibitive in today's cost-conscious health care environment.

The use of glucocorticoids in septic shock deserves special consideration. Clinical trials of high-dose glucocorticoids indicate a trend toward a harmful effect.[8] However, in recent years, several authors have hypothesized a syndrome of relative adrenocortical insufficiency in septic shock in the presence of normal or even elevated serum cortisol concentrations. Moreover, a few uncontrolled studies indicate that stress doses of hydrocortisone improve hemodynamics in patients with hyperdynamic septic shock unresponsive to conventional therapy. The data of recent double-blind studies suggest that moderate doses of glucocorticoids given as a prolonged treatment contribute to control the systemic inflammatory response.[9,10] Further investigation should elucidate this inexpensive approach to immunomodulation.

Nitric oxide synthase (NOS) inhibitors have also been tested in patients with septic shock. The administration of NG-methyl-L-arginine (L-NMA, 546C88), the most widely used nonselective NOS inhibitor, is associated with an increase in peripheral vascular tone and a fall in cardiac index. Preliminary results of the phase III prospective, randomized, double-blind, placebo-controlled trial of 546C88 have been recently reported.[11] Unfortunately, the study had to be discontinued due to increased mortality in the group treated with 546C88.[11]

Hemofiltration—Another approach to the management of septic shock may be to remove inflammatory mediators by extracorporeal methods. Various forms of hemofiltration have been investigated. There is evidence that high-volume hemofiltration/hemodiafiltration with a large-pore membrane is able to improve the left ventricular systolic function in septic shock. However, the mechanism by which hemofiltration acts is not as simple as was previously expected. The critical review of existing literature on cytokine removal with renal replacement therapy leads to the conclusion that their characteristics are not compatible with clinical relevant removal. It is possible that hemofiltration removes some other mediators, such as arachidonic acid metabolites, beta-endorphin, bradykinin, or complement factors, but their role in sepsis-induced left ventricular dysfunction seems weak.

Thus, the effects of hemofiltration on left ventricular function may be explained by its ability to remove water from plasma or by changes in plasma osmolarity. In addition, other metabolic events, such as hypothermia, altered glucose concentration, or acidosis correction, may play a more important role in myocardial

function improvement in sepsis than any mediator removal.[12] The question of whether this technique should be used in patients with septic shock before the appearence of renal failure remains unanswered.

Supernormal Oxygen Delivery

Studies using independent methods to determine systemic oxygen delivery (DO_2) and oxygen consumption (VO_2) have not found pathologic dependency of the latter on the former in septic patients. Nevertheless, although pathologic dependence of VO_2 on DO_2 has not been confirmed using a whole-body approach, we cannot be sure that the VO_2 of individual organs behaves in a parallel manner with whole-body VO_2. In addition, it has been observed repeatedly that critically ill patients who survive usually have higher values of cardiac output, DO_2, and VO_2 than those who do not survive. Consequently, supranormal values of cardiac output and DO_2 may be proposed as targets of resuscitation trying to correct occult tissue hypoxia.

Several randomized control trials of supernormal compared with normal DO_2 in critically ill patients have been carried out. A systematic review of the current data was published recently.[13] Heyland and colleagues cited seven studies involving 1016 patients. They found that interventions designed to achieve supraphysiologic goals of cardiac index, DO_2, and VO_2 did not significantly reduce mortality rates in all critically ill patients, but concluded that methodologic limitations prevented making any general conclusion. On the other hand, the maintenance of DO_2 at supranormal levels in all patients could result in overzealous administration of fluids and vasoactive agents, with evident hazardous effects.[14] Thus, current evidence does not support values of cardiac output and DO_2 as targets of resuscitation in patients with sepsis, shock, or trauma, other than those able to correct hypotension and signs usually associated with inadequate tissue perfusion, such as metabolic acidosis, elevated blood lactate levels, abnormal mentation, and low urine output.[15]

The quest continues for better methods for identifying dysoxia that provide not only systemic but also regional data for individual vital organ systems. In this respect, tonometry can uncover regional hypoxia and hypoperfusion involving the gut. However, it is increasingly evident that intracellular metabolic derangements also contribute to defects in adenosine triphosphate synthesis and accelerated anaerobic metabolism in sepsis.[16] However, elevated tissue PCO_2 values are not incontrovertible evidence of inadequate microvascular perfusion in sepsis.[17]

Blood Pressure

Blood pressure is an important determinant of regional perfusion, particularly in the presence of ischemia when conductance is at a nadir. Normal mean arterial pressure is in the range 80-100 mmHg. However, mean arterial pressure necessary to maintain urine output in septic patients may frequently need to be much higher than this. Then, the end points of circulatory resuscitation are the provision of an adequate systemic DO_2 and perfusion pressure. The first step is to restore and maintain circulating blood volume and then restore interstitial fluid volume. Nevertheless, volume resuscitation alone, and perhaps administration of inotropes, is often insufficient to adequately augment blood pressure, and vasopressor drugs are required.[18]

Although vasopressor catecholamines may theoretically reduce tissue perfusion through their vasoconstrictor action, this deleterious effect may be offset by a rise in blood pressure, provided adequate volume expansion and systemic DO_2. In this respect, norepinephrine seems to be more efficient and reliable than dopamine to reverse the hemodynamic abnormalities seen in hyperdynamic septic shock.[19] A number of studies in patients with septic shock support this notion by showing that norepinephrine infusion is associated with an increase in urine flow and creatinine clearance.

Another important concern is whether norepinephrine could reduce splanchnic bed perfusion. But norepinephrine administration in septic shock patients has been associated with an increase in VO_2 and a reduction of blood lactate levels, suggesting correction of splanchnic ischemia with an efficient hepatic lactate uptake. Moreover, it has also been shown that norepinephrine, compared to high-dose dopamine, increased gastric intramucosal pH.[20]

Whether using norepinephrine in sepic shock patients affects mortality, as compared to the use of dopamine or epinephrine, still requires a prospective clinical trial. This notwithstanding, reported overall survival in patients with septic shock treated with norepinephrine when volume and dopamine therapy has failed to increase blood pressure is approximately 40%, a substantial survival for such a critically ill patient group. In our clinical experience, norepinephrine has been increasingly used and started earlier in the course of septic shock. In the 1950s Dr. Moyer indicated in the first publication on the use of norepinephrine in septic shock: “When the use of this drug is contemplated, it should be used as early as possible in order to prevent damage of the brain, kidney, liver and other vital organs. It should not be withheld as a last resort.”[21]

Conclusion

Over the last decade, our understanding of the biochemistry of sepsis has improved dramatically. This knowledge has led to test novel immunomodulating agents in the management of sepsis. Unfortunately, the efficacy of these drugs in lowering the mortality rate among critically ill patients with sepsis remains unproved. New anti-inflammatory agents continue to be tested. In the meantime, the treatment of septic shock continues to focus on eradicating infection and supporting failing organs.[22] Therapeutic end points of cardiovascular support remain the achievement of those values of blood pressure and DO_2 that reverse the evidence of inadequate tissue perfusion. It requires restoration of intravascular volume. However, volume resuscitation alone is often insufficient to adequately augment blood pressure, and vasopressor drugs are required without delay.

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CME Questions

6. High doses of growth hormone:

a. increase mortality in the critically ill.
b. improve outcome of the most seriously ill patients.
c. reduce the incidence of infection in critically ill patients.
d. improve renal function but not mortality in severely ill patients.
e. reduce the time on mechanical ventilation.

7. Patients receiving high-dose growth hormone:

a. should have their serum phosphate carefully monitored.
b. will often develop hyperglycemia.
c. will have better exercise tolerance at three months.
d. will need fewer days of mechanical ventilation.
e. will experience a shorter length of ICU stay.

8. Monitoring the level of sedation of mechanically ventilated ICU patients using the bispectral index (BIS) has been shown to:

a. reduce ICU length of stay.
b. reduce the utilization of neuromuscular blocking agents.
c. decrease the incidence of ventilator-associated pneumonia.
d. All of the above
e. None of the above

9. The bispectral index (BIS):

a. is derived from 12 measures of neurological status and level of consciousness.
b. incorporates pulse oximetry, hemodynamic, and urine output data.
c. is an electronically generated value based on the electroencephalogram.
d. is calculated by dividing cerebral perfusion pressure by the Glasgow coma scale score.
e. None of the above

10. Which of the following seems to be useful to treat patients with septic shock?

a. Hemofiltration used even with normal renal function.
b. High doses of glucocorticoids.
c. Supranormal DO_2 levels in all patients.
d. Vasopressors used to adequately augment blood pressure provided an adequate volume expansion and systemic DO_2.
e. Treatment with nitric oxyde synthase inhibitors.

11. Which of the following is not one of the hemodynamic changes commonly associated with septic shock?

a. Depression of cardiac function.
b. Vasodilatation.
c. Hypervolemia.
d. Vasoconstriction.
e. Capillary leak.

12. Which of the following is correct regarding septic shock?

a. Stress doses of hydrocortisone may have a beneficial effect in septic shock patients.
b. Hemofiltration must be used to treat patients with septic shock without renal failure.
c. High doses of glucocorticoids are beneficial in septic shock patients with poor clot retraction.
d. Vasopressors should be avoided in septic shock patients with systolic blood pressure higher than 70 mmHg.

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Publisher *(Name and Complete Mailing Address)*: Donald R. Johnston, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*: Michelle Moran, same as above

Managing Editor *(Name and Complete Mailing Address)*: Glen Harris, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Medical Economics Data, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name	14. Issue Date for Circulation Data Below
Critical Care Alert	November 1999

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1076	1045
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	874	845
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	0	0
	(4)	Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			877	848
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	0	0
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			11	11
f. Total Free Distribution *(Sum of 15d and 15e)*			11	11
g. Total Distribution *(Sum of 15c and 15f)*			888	859
h. Copies Not Distributed			188	186
i. Total *(Sum of 15g. and h.*			1076	1045
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			99	99

16. Publication of Statement of Ownership
Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/24/99

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

Readers are Invited...

Readers are invited to submit questions or comments on material seen in or relevant to *Critical Care Alert*. Send your questions to: Michelle Moran—Reader Questions, *Critical Care Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. Or, you can reach the editors and customer service personnel for *Critical Care Alert* via the Internet by sending e-mail to michelle.moran@medec.com. We look forward to hearing from you. ❖

In Future Issues:

Noninfectious Pulmonary Complications in Immunocompromised Patients