Four questions for Dr. MacIntyre on his editorial

To the Editor:

We thank Dr. MacIntyre for his editorial (1) on our article (2). We have four questions for him.

One, we identified more than 15 methodologic errors in the meta-analysis performed by the Evidence-Based-Medicine Task Force on weaning (3). Our article holds no importance if we are wrong about the methodologic errors we identified (2). Dr. MacIntyre does not contend a single one of these errors. He writes “I’m not going to address the methodologic criticisms” (1). Yet, this is the very core of our article.

The primary means for correcting scientific error is the dialectic process (4). Avoiding engagement in argument and counter-argument is the antithesis of science (4). We ask Dr. MacIntyre: “If we mistakenly identified some methodologic errors, which ones are they?” (Dr. MacIntyre writes “the methodologic criticisms are addressed in accompanying editorial”). But Dr. Marini did not write that we made methodologic errors.

Two, Dr. MacIntyre continues, “Rather I will clarify how the McMaster findings were used by the task force to create operational guidelines for clinicians at the bedside.” (1) In this sentence, Dr. MacIntyre implies that the Task Force created clinical guidelines without analyzing the primary data (5). Our questions to Dr. MacIntyre: “Did Task-Force members check for errors in the analyses undertaken by the McMaster group? (If the Task Force’s primary role was to imprint a seal-of-approval on a meta-analysis conducted by another group, readers should be so informed).

Three, Dr. MacIntyre notes their meta-analysis revealed “consistently significant likelihood ratios” (1). But consistency is no guard against systematic error. If a spirometer contains a positive bias, the recorded volumes will overestimate true volume in a “consistent” manner (2). Dr. MacIntyre writes “the task force concluded that the individual likelihood ratios were not sufficiently high enough to drive clinical decision making at the bedside.” (1) We ask Dr. MacIntyre: “Is it wise to drive clinical decisions based on likelihood ratios that involve a series of compounded methodologic errors?”

Four, Dr. MacIntyre writes “The guidelines seem to be standing the test of time and are continuing to serve as an important tool to reduce iatrogenic delays in mechanical ventilation withdrawal.” (1) We ask Dr. MacIntyre: “If these are not mere assertions, please present the data that warrant your conclusion: that the guidelines are (a) standing the test of time and (b) reducing iatrogenic weaning delays?”

We listed more than 15 methodologic errors in the Task Force’s meta-analysis (2). If we are wrong about these, we welcome correction from any member of the Task Force (3, 5). If the methodologic errors cannot be refuted, then what is the validity of the evidence on which the Evidence-Based-Medicine Task Force base their conclusions?

The authors have not disclosed any potential conflicts of interest.

Martin J. Tobin, MD, Amal Jubran, MD, Division of Pulmonary and Critical Care Medicine, Edward Hines Jr. Veterans Affairs Hospital and Loyola University of Chicago Stritch School of Medicine, Hines, Illinois

REFERENCES


DOI: 10.1097/CCM.0b013e31817c44fa

The author replies:

Let me take each question submitted by Drs. Tobin and Jubran one at a time:

1. What are the specific responses to the methodologic concerns raised by Drs. Tobin and Jubran in their original critique (1)?

My charge from the editor of Critical Care Medicine for my editorial (2) was to address how the American College of Chest Physicians, the Society of Critical Care Medicine, and the American Association for Respiratory Care (ACCP/SCCM/AARC) Ventilator Discontinuation (“Weaning”) Guidelines (3) were developed. The specific response to the Drs. Tobin and Jubran’s methodologic concerns regarding the meta-analysis of the frequency/tidal volume (f/VT) measurement, were to be addressed by one of the authors of the actual McMaster University Agency for Health Care Policy and Research Evidence Based Report (4). This should have been done at the time of my original editorial but was not; a development I was not made aware of at the time and that hopefully can be corrected now by the editor of Critical Care Medicine.

2. Did the ACCP/SCCM/AARC Guidelines Committee consider the potential flaws in the f/VT meta-analysis?

I want to reiterate what I stated in my original editorial (2); the Guidelines were developed by a multi-society group of experts who reviewed all of the available literature. The f/VT meta-analysis of concern to Drs. Tobin and Jubran was only one small piece of a large evidence base that was considered. The Committee was keenly aware of the limitations of meta-analyses in general, and thus, did not restrict the evidence review to only these secondary analyses—the members went to the original data. From this extensive review, the Guidelines committee unanimously agreed that the f/VT measurement had utility in predicting discontinuation success but clearly should not be used in isolation—a conclusion I suspect Drs. Tobin and Jubran probably agree with. Underscoring this conclusion is a recent report by Tanios et al. (5) who showed that rigid application of only the f/VT to guide discontinuation actually delayed ventilator withdrawal.
3. Did the ACCP/SCCM/AARC Guidelines Committee base its recommendation only on the f/Vt meta-analysis conclusions?

This question is similar to the issue addressed above in question two. The Guidelines Committee considered all the available data, not just meta-analyses to draw the conclusions, they did. The net result was a strong recommendation to use routine spontaneous breathing trials, with an integrated assessment of respiratory system mechanics (including f/Vt), hemodynamics, gas exchange, and patient comfort to guide the discontinuation process. It does not appear to me that Drs. Tobin and Jubran are challenging this conclusion.

4. What is the evidence that the Guidelines recommendations are “standing the test of time?”

This spontaneous breathing trial-based approach to ventilator discontinuation has been integrated into the ventilator management protocols of many of the major clinical trials groups (e.g., the National Institute of Health, Acute Respiratory Distress Syndrome Network, the Canadian Clinical Trials Group). Furthermore, the use of a integrated assessment of a patient’s response to a spontaneous breathing trial to guide ventilator withdrawal was recently endorsed by another multi-society task force consisting of the European Respiratory Society, the American Thoracic Society, the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the Societe de Reanimation de Langue Francais (6). I would call this standing the test of time.

The author has not disclosed any potential conflicts of interest.

Neil MacIntyre, MD, Duke University Medical Center—Respiratory Care, Durham, North Carolina

REFERENCES


*Multiple attempts have been made to obtain a response from the McMaster Group who performed the meta-analysis for this study, but they have refused to give a response to Dr. Tobin’s queries. They did not give any reason for their nonresponse. I regret that the group has chosen not to respond and participate in this scientific dialogue.

—Editor

DOI: 10.1097/CCM.0b013e31818476e6

Constipation, critical illness and mortality: Gut-derived toxidromes—real and now imagined

To the Editor:

Although the health benefits of bowel purgation have been recognized for centuries and “colon cleansing” is a fundamental tenet of many holistic therapies, champions of aggressive treatment of constipation in the critical care unit are rare. We applaud the editors and investigators of Critical Care Medicine for emphasizing this oft neglected but vital component of intensive care (1).

The legions of untoward consequences of intestinal ischemia have aptly earned its designation as the “engine” of the sepsis syndrome. The massive amount of lymphoid tissue embedded within the gut and the activation of this enormous system coincident with altered gut permeability and endotoxaemia contribute to the cytokine storm that characterizes the systemic inflammatory response of multi-trauma and sepsis.

Although endotoxaemia represents the most universally acknowledged example of systemic illness of enteric origin, several rarely recognized conditions are gut-derived toxidromes. Although these syndromes are rarely diagnosed, we believe the pathophysiology involved may relate to many ill patients with constipation and may contribute to their increased morbidity.

Three syndromes are illustrative: (1) auto-brewery syndrome; (2) d-lactic acidosis; (3) purple urinary bag syndrome (PUBS). All three are conditioned by intestinal atony and altered bacterial flora.

In auto-brewery syndrome, sugars from enteral feeding are fermented to alcohols which are absorbed. If hepatic function is compromised, these fermentations products increase and can cause metabolic encephalopathy. Also, we have seen a case of an antabuse-like reaction from metronidazole when given for bacterial overgrowth—the unexpected source of the alcohol being endogenous.

In d-lactic acidosis the enteric bacterial metabolism of carbohydrate yields racemic lactic acid which is absorbed. The notion that d-lactic acid is not normally metabolized by humans is clearly erroneous. The normal liver can metabolize d-lactate rapidly as is attested to by the absence of rising anion gaps in patients receiving high volume Lactated Ringers infusions. The impaired liver in multorgan dysfunction may, however, be incapable of degrading d-lactic acid and an anion gap metabolic acidosis ensues. The acidosis in conjunction with other released bacterial toxins induces an encephalopathy. The standard clinical laboratory measures only L-lactic acid and therefore will not disclose the presence of d-lactic acidosis. So this must be deduced on the basis of clinical and laboratory data.

PUBS is recognized due to the conjunction of intestinal bacterial overgrowth and urinary tract infection with bacteria producing sulfatases. In PUBS, enteric bacteria degrade dietary tryptophan to indole. Indole is absorbed through the portal circulation, sulfated by the liver and excreted in the bile and in the urine as indoxyl sulfate (IS). Urinary IS, in the presence of bacterial sulfatases, is converted to indoxyl. Indoxyl undergoes rearrangement to form indigo (blue) and indirubin (red), which yields purple urine. These products are hydrophobic and color the plastic Foley bag and tubing and the urinary sediment, but standing urine and centrifuged urine are relatively clear (2).

IS has strong binding to albumin, induces allosteric changes in the protein and would predictably displace many drugs causing their free levels to elevate. Altered pharmacokinetics of all predomi-
nately albumin bound drugs would be expected. This may cause an increase in drug toxicities, a known cause of increased hospital mortality. IS especially accumulates in renal failure. A recent report of PUBS in a dialysis patient noted the presenting symptoms of syncope and Torsades de pointes (3), both conditions are frequently due to drug toxicity.

Specific gut-derived toxidromes remind us that there exists a panoply of unrecognized toxins being released systematically and these may well be covert agents endangering the lives of our critically ill and constipated patients.

The authors have not disclosed any potential conflicts of interest.

Raymond E. Garrett, MD, Swedish Medical Center, Trauma Research Department, Englewood, CO; David Bar-Or, MD, FACEP, Swedish Medical Center and St. Anthony Central Hospital Trauma Research Departments, Englewood and Denver, CO

REFERENCES


DOI: 10.1097/CCM.0b013e318184705b

The authors reply:

We are grateful to Dr Garrett and Dr Bar-Or for their kind words about our study ‘Laxation of critically ill patients with lactulose or polyethylene glycol: a two-center randomized, double-blind, placebo-controlled trial’ (1). In this study, we showed that both lactulose and polyethylene glycol promoted early defecation in constipated intensive care patients, and that early defecation was associated with a decreased length of stay in the intensive care unit (ICU).

Dr Garrett and Dr Bar-Or now emphasize a possible explanation for our study findings, namely that early defecation, apart from diminishing gut-derived endotoxemia, reduces three rarely diagnosed specific gut-derived toxidromes associated with gut atony and altered gut flora.

We agree, to a point, with their view of the consequences of constipation in the critically ill. In the introduction of our article, we pointed at the risk of translocation of both bacteria and endotoxins in constipated ICU patients. We believe that reducing the load of intestinal bacteria and endotoxins is beneficial for our patients. In addition, maintaining bowel movements is crucial, when selective decontamination of the digestive tract is applied. To make selective decontamination of the digestive tract treatment successful, early defecation is necessary, as the passage of nonabsorbable antibiotics through the entire gut is needed to reduce the load of potential pathogenic bacteria.

On the other hand, there are other explanations than reducing gut-derived translocation and toxidromes for the shorter length of stay in the group of critically ill patients with early defecation. Constipation may lead to intra-abdominal hypertension and colonic distension and may thus impair colonic perfusion and cause gut ischemia. Defecation reduces abdominal distension and intra-abdominal pressure, and may thus improve the perfusion of intra-abdominal organs. The lower abdominal pressure may also facilitate enteral feeding, which is associated with better outcome of ICU patients (2). The reduction of abdominal distension and pressure also improves the mechanics of ventilation. This may accelerate successful weaning from the ventilator, because the lungs become less compromised. We did, however, not include these variables as end points in our study. Finally, it cannot be excluded that defecation may just be a sign of an improving patient.

In conclusion, although we agree that early defecation may benefit our patients by reducing gut-derived translocation and endotoxemia, we think that additional explanations contribute to the advantages of early defecation.

The authors have not disclosed any potential conflicts of interest.

Johan I. van der Spoel, MD, Heleen M. Oudemans van Straaten, MD, PhD, Peter HJ. van der Voort, MD, PhD, MSc, Durk F. Zandstra, MD, PhD, Department of Intensive Care Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; Peter HJ. van der Voort, MD, PhD, MSc, Michael A. Kuiper, MD, PhD, FCCP, FCCM, Department of Intensive Care Medicine, Medical Centre Leeuwarden, Leeuwarden, The Netherlands

REFERENCES

 DOI: 10.1097/CCM.0b013e31818472d3

Effect of prone positioning in patients with acute respiratory distress syndrome and high Simplified Acute Physiology Score II

To the Editor:

We read with interest the recent meta-analysis by Alsaghir and Martin (1) regarding prone ventilation for acute respiratory distress syndrome. Our systematic review shares many similar findings (2). One difference, however, concerns the subgroup of patients with high illness severity. Alsaghir and Martin reported that prone ventilation significantly reduced mortality in patients with acute respiratory distress syndrome and Simplified Acute Physiology Score (SAPS) II ≥50. Combining subgroup data from two trials (3, 4), the pooled random-effects odds ratio showed lower mortality with proning (Review Manager, version 4.2.9, Oxford, UK): 0.29 (95% confidence interval, 0.12–0.70; p = 0.006; Fig. 3 in Ref. 1, adapted in Fig. 1, Panel A). Patients with SAPS II <50 did not demonstrate statistically significant lower mortality (Fig. 1, Panel B).

We believe that this subgroup analysis should be interpreted cautiously. The finding is driven by the trial of Gattinoni et al. (3); in contrast, the trial of Mancebo et al. (4) suggests similar efficacy in patients regardless of illness severity. When the effect of prone ventilation is directly compared between patients with SAPS II ≥50 and those with SAPS II <50 using an interaction test, there is no evidence of a subgroup effect: the interaction p value is 0.16 for odds ratio and 0.52 if risk ratio (RR) is used as the effect measure [see Figure; raw proportions for one trial (3) generated using data presented in the meta-analysis (1)]. Therefore, differences...
in mortality between subgroups are not beyond those expected by chance. Furthermore, if this subgroup analysis had used RR as the effect measure, it would not have found a statistically significant lower risk of death in sicker patients despite the point estimate suggesting benefit: RR 0.60 (95% confidence interval, 0.25–1.40; \( p = 0.24 \)) (Fig. 1, Panel C). The major reason for this inconsistency is the substantial statistical heterogeneity between the two studies when RR is used, reflected by a point estimate for \( I^2 \) of 71%. \( I^2 \) is the percentage of total variation in results across studies due to heterogeneity rather than chance (5). This heterogeneity results in a higher weighting of the trial of Mancebo et al. (4), which did not show a significant benefit in patients with SAPS II \( \geq 50 \), and generates a broader confidence interval for the pooled RR. In contrast, the point estimate for \( I^2 \) is 0% in the pooled odds ratio analysis for the SAPS II \( \geq 50 \) subgroup; however, the confidence interval for \( I^2 \) is wide. Therefore, substantial heterogeneity is either present or cannot be excluded in all these analyses (6). Finally, the small number of deaths in each subgroup may lead to an overly optimistic estimate of the effect of prone ventilation on mortality (7).

The suggestion that prone positioning is more beneficial in sicker patients with acute respiratory distress syndrome is intriguing and congruent with some clinicians’ expectations. However, any definitive conclusion would require data from an additional randomized control trial enrolling many such patients.

The authors have not disclosed any potential conflicts of interest.

Sachin Sud, MD, Interdepartmental Division of Critical Care, University of Toronto, Toronto, ON, Canada; Maneesh Sud, BSc, Faculty of Medicine, University of Manitoba, Winnipeg, MB, Canada; Jan O. Friedrich, MD, DPhil, Interdepartmental Division of Critical Care, University of Toronto, Toronto, ON, Canada, Critical Care and Medicine Departments and Li Ka Shing Knowledge Institute, St Michael’s Hospital, Toronto, ON, Canada; Neill K. J. Adhikari, MDCM MSc, Interdepartmental Division of Critical Care, University of Toronto, Toronto, ON, Canada, Department of Critical Care Medicine and Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

REFERENCES


DOI: 10.1097/CCM.0b013e3181846fc0

The authors reply:

We appreciate the comments of Sud and colleagues regarding our meta-analysis of prone ventilation in adult respiratory distress syndrome (1). They provide some additional analysis of the subgroups based on Simplified Acute Physiology Score II using relative risk (RR), and caution that subgroup analysis should be interpreted with caution and tested with an additional randomized control trial.

We could not agree more with that assertion, and stated that clearly in our own conclusion. Our statements about this subgroup analysis were qualified with “perhaps” and “may.” We did not explore the low illness severity subgroup either directly or through a test of interaction because our interest and hypothesis was that the high illness severity group experience benefit.

Despite the different statistical conclusion and heterogeneity resulting from the use of relative risk (RR) and the possible influence of low event rates, the data still support a new randomized trial in this population, as concluded in this letter

Figure 1. Weight is the relative contribution of each study to the overall estimated odds ratio or risk ratio assuming a random-effects model. Effect measures and \( I^2 \) are shown with 95% confidence intervals. n, number of deaths; N, number of patients randomized; SAPS, Simplified Acute Physiology Score.
and our article. In our analysis, we provided a sample size estimate based on the odds ratio. The sample size may be higher using the RR, but in our article we also discussed nonrandomized data and reasons for clinical heterogeneity that all need to be considered when designing this trial.

Sud and colleagues also raise general issues regarding meta-analysis, such as the need to consider confidence intervals for tests of heterogeneity and differences in results obtained if odds ratio or RR are used for binary outcomes. We believe these points add to our understanding of how results from meta-analysis should be interpreted. Although systematic reviews and meta-analysis are often considered the top level of evidence, methodologic and content-specific considerations of the analysis and the underlying studies need to be evaluated. If these are found wanting, the meta-analysis should be hypothesis-generating rather than definitive. At the same time clinicians need to weigh the current best-available evidence, values, and preferences. In that context, and given that this is a relatively low-cost, simple intervention with overall physiologic benefit (improved oxygenation), we stand by our statement that prone ventilation should be considered in this population, pending a definitive study.

The authors have not disclosed any potential conflicts of interest.

Abdullah Alsaghir, MD, Claudio Martin, MSc, MD, London Health Sciences Centre—Victoria Hospital, London, Ontario, Canada

REFERENCE


DOI: 10.1097/CCM.0b013e3181847097

Anatomical intrapulmonary shunt

To the Editor:

Dr. Cressoni et al. (1) used whole-lung computed tomography (CT) scans to measure intrapulmonary shunt, expressed as anatomical intrapulmonary shunt, which was defined as a ratio of nonaerated lung tissue-to-total lung tissue, in patients with acute lung injury/acute respiratory distress syndrome. Their definition of anatomical intrapulmonary shunt deserves some comments.

In no way can one measure intrapulmonary shunt based on lung tissue aeration ratio alone without considering regional distribution of pulmonary perfusion. Anatomical intrapulmonary shunt fraction refers to the ratio of the amount of venous blood that passes through the nonaerated part of the lung to the whole lung blood volume (perfusion ratio, different from the same term that Dr. Cressoni et al. defined), not to a ratio of nonaerated lung tissue-to-total lung tissue (nonaerated ratio). The perfusion ratio and nonaerated ratio are not the same and the difference becomes greater particularly when the patient is on positive pressure ventilation and positive end-expiratory pressure (PEEP). If PEEP recruits nonaerated lung tissue, then lung compliance increases, and physiologic dead space-to-tidal volume ratio (VD/VT) decreases, so does intrapulmonary shunt. However, if PEEP cannot recruit nonaerated lung tissue, then PEEP overinflates aerated lung tissue resulting in increase in VD/VT as shown in a classic study of optimal PEEP (2). This increase in VD/VT is the result of a reduced perfusion to the overinflated aerated part of lung tissue. With the same token, perfusion to the nonaerated part of lung increases, leading to an increase in intrapulmonary shunt. However, an increase in VD/VT because of the overinflation of aerated lung tissue should contribute to the decrease in nonaerated ratio, which was defined by Dr. Cressoni et al. (1), and hence a decrease in anatomical intrapulmonary shunt, because CT scan would read this overinflated aerated lung tissue as an increase in aerated lung tissue. Thus, the results are totally opposite. There is another example for this. A previous report has shown that in a patient with unilateral left lung disease, PEEP of 10 cm H2O induces acute life-threatening ventilation-to-perfusion inequality with severe worsening hypoxia that requires independent differential ventilation and PEEP with double lumen endobronchial tube (3). In this patient, PEEP overinflated the uninvolved (aerated) right lung and diverted pulmonary perfusion to the nonaerated left lung, resulting in an increase in intrapulmonary shunt and VD/VT. Diversion of pulmonary perfusion was confirmed with pulmonary artery angiogram in this patient, which showed no pulmonary blood flow in the aerated right lung. If we assume that 20% of left lung (10% of a whole lung) is aerated in this case, anatomical intrapulmonary shunt could be calculated as 80% by perfusion ratio. This is because there is no blood flow in the right lung. However, if shunt is calculated by nonaerated ratio, anatomical intrapulmonary shunt would be 40% (aerated parts include 50% for the right lung and 10% for the left lung). As such, the difference between perfusion ratio and nonaerated ratio can be tremendous.

The lung region with low ventilation-to-perfusion ratio (V/Q) produces shunt-like effect. In a patient with a significant part of lung region of low V/Q, a CT scan cannot differentiate shunt from shunt-like effect, because the CT scan reading should be either aerated or nonaerated. The lung region with low V/Q is barely aerated but not collapsed, and would be read as nonaerated by CT scan. PEEP may be able to inflate the lung region with less low V/Q, but not very low V/Q. The assumption that the difference between Riley’s venous admixture and nonaerated ratio by CT scan is due to the presence of the lung region with very low V/Q is not correct. CT scan cannot eliminate shunt-like effect either.

The author has not disclosed any potential conflicts of interest.

Charles Her, MD, FCCP, Department of Anesthesiology, New York Medical College, Valhalla, NY

REFERENCES


DOI: 10.1097/CCM.0b013e3181847321

Anatomical and functional intrapulmonary shunt in acute respiratory distress syndrome

To the Editor:

We read with interest the recent article of Cressoni et al. wherein the authors investigated the relationship between values of venous admixture (functional shunt), and the fraction of nonaerated lung tissue (anatomical shunt) (1). In our opinion, the authors’ main conclusion
that functional shunt represents only a poor estimate of anatomical shunt should be carefully reconsidered. The investigated patients were ventilated with a fraction of inspiratory oxygen (FiO₂) of 0.51 ± 0.15. Determination of shunt from venous admixture of oxygen is, however, only accurate at FiO₂ of 1.0. The reason is that the capillary oxygen content which has to be inserted into the shunt formula cannot be measured. Instead, it is approximated that all blood passing ventilated alveoli is completely saturated with oxygen. As was pointed out in the fundamental work of Berggren, the determination of shunt, therefore, requires to eliminate the effects of diffusion difficulties, and poorly ventilated lung areas as far as possible by breathing pure oxygen (2). Accordingly, calculation of venous admixture at considerably lower FiO₂ than 1.0 as performed in the study by Cressoni et al. will result in values, which are influenced by lung sections with low ventilation-to-perfusion ratios. Upon computed tomography (CT) these lung areas have densities between 100 Hounsfield unit (HU) and 500 HU (3). It is therefore expected that the functional shunt determined in the study by Cressoni et al. rather reveals a stronger correlation with the sum of nonaerated and low VA/Q areas (corresponding to a CT density <500 HU) than with anatomical shunt alone (CT density <100 HU). If true, this might contribute to restore confidence in venous admixture as a surrogate parameter for lung damage and gas exchange impairment. We would suggest that Cressoni et al. provide the reader with the corresponding additional analysis, which will either provide evidence to confirm their conclusion or to put it into perspective.

The authors have not disclosed any potential conflicts of interest.

Thilo Busch, PhD, Sven Laudi, MD, Udo Kaisers, MD, Anesthesiology and Intensive Care Medicine, University of Leipzig Medical Faculty, Leipzig, Germany

REFERENCES


DOI: 10.1097/CCM.0b013e31818473a6

The authors reply:

It is difficult to answer Dr. Her as he completely misunderstood our article. Maybe we were not clear enough. Actually we never claimed to measure the intrapulmonary shunt with the computed tomography (CT) scan; we just pointed out that the nonaerated tissue is the anatomical compartment, through which the true shunt occurs. However, for a given anatomical shunt compartment, let’s say 50%, the intrapulmonary shunt may range from zero to very high values depending on several mechanisms, as we discussed. We suggest rereading our article considering the anatomical shunt compartment is not a “flow,” but a tissue with widely variable perfusion.

We thank Dr. Thilo for his letter, which offers us the possibility to further explain and clarify our results.

The analysis requested by Dr. Thilo is presented in Figure 1. As suggested by Dr. Thilo and previously shown by Malbouisson et al. (1), the correlation between the venous admixture and the fraction of poorly inflated tissue plus not inflated tissue, although a little bit better than the correlation with the noninflated tissue alone still presents a wide dispersion of the experimental data. Actually, only about one third of the venous admixture could be explained from the sum of poorly inflated and not inflated tissue. We would like to point out, however, that the purpose of our article was not to find a good correlation between gas exchange and CT data by selecting the best CT threshold for fitting. In fact, in the framework of lung protective strategy, we believe that what matters is the assessment of gas-less tissue, which is recruitable, and its management. Our data show that lung recruitability, a key determinant for safety of mechanical ventilation, cannot be accurately estimated by gas exchange.

The authors have not disclosed any potential conflicts of interest.

Luciano Gattinoni, MD, FRCP, Ospedale Maggiore di Milano, Milano, Italy; Massimo Cressoni, MD, Fondazione Policlinico, Mangiagalli, Regina

Figure 1. Black circles and straight line represent data at PEEP 5 (venous admixture = -0.07 ± 0.61, *Not inflated plus poorly inflated tissue, \( r^2 = .34, p < 0.0001 \)), white circles and dotted line represent data at PEEP 15 (venous admixture = 0.05 ± 0.38, *Not inflated plus poorly inflated tissue, \( r^2 = .25, p < 0.0001 \)).
occurred in study of Shapiro et al. (3), severe sepsis suspect of sepsis. Indeed, in the pivotal documented sepsis and not in patients score should be validated in patients with high risks of dying. 

First of all, we believe that the MEDS score should be validated in patients with documented sepsis and not in patients suspect of sepsis. Indeed, in the pivotal study of Shapiro et al. (3), severe sepsis occurred in <25% of the patients admitted and who had a blood culture performed. Furthermore, in the study by Sankoff et al. (1) that enrolled 385 patients, only 165 of them met the criteria for sepsis with a source of infection. In contrast with those series, our group and Chen and coworkers studied the performance of the MEDS score in medical intensive care unit patients with documented sepsis (4, 5). Furthermore, we found that patients with a MEDS score >10 had six-fold risk of dying (odds ratio 5.91, 95% confidence interval 3.00 –11.6), whereas Chen et al. observed that patients with MEDS score ≥12 had a higher mortality rate (48.9% vs. 17.5%, p < 0.001). Thus, we believe that a larger multicenter prospective study focusing on documented sepsis is warranted to confirm MEDS usefulness and to assess with better accuracy the risk of dying for the patients with a MEDS score between 8 and 12, for instance (8% and 19%, respectively, in the two cohorts). Furthermore, determination of cutoff values for intensive therapy and intensive care unit placement could be of interest.

Second, the usefulness of SIRS for ED triage or to predict mortality remains questionable. Even if SIRS is a sine qua non criterion for a sepsis trial, we need other selection criteria owing its high sensitivity. Indeed, SIRS being so common has no clinical implication and cannot per se discriminate septic patients with high risk of dying (1, 3). A patient’s stratification according to the number of SIRS criteria they met in the ED could have been of interest to increase the SIRS performance for the sudy, but we believe that it will not be clinically relevant in the ED. On the other hand, we must remember that not all patients who appear septic demonstrate an infection and that scoring systems do not perform well when compared with physician judgment.

To conclude, we believe that the MEDS scale may have an importance for ED triage in the future—but before, we need larger validation and we must define cutoff values for high risk of dying and to calculate an observed-to-predicted mortality ratio.

The authors have not disclosed any potential conflicts of interest.

François G. Brivet, MD, Frédéric M. Jacobs, MD, AP-HP, Service de Réanimation Médicale, Hôpital Antoine Béclère, and INSERM, Clamart, France, Dominique Prat, MD, AP-HP, Service de Réanimation Médicale, Hôpital Antoine Béclère, Clamart, France

REFERENCES
DOI: 10.1097/CCM.0b013e3181847777

How “Dear SIRS” and MEDS can help for ED triage

To the Editor:

In the recent issue, systemic inflammatory response syndrome (SIRS) and Mortality Emergency Department Sepsis (MEDS) score usefulness are discussed after the publication by Sankoff et al. of their multicenter study of the MEDS score in patients with SIRS (1, 2). Dr. Nguyen et al. (2) suggested that the association of these scales could be of interest for the emergency department (ED) triage of adult patients suspect of infection.

At evidence, accurate predictive models for ED triage may be useful, but at the present time, we think that the MEDS score and SIRS are not sufficiently validated for the ED triage of septic adults with high risks of dying.

First of all, we believe that the MEDS score should be validated in patients with documented sepsis and not in patients suspect of sepsis. Indeed, in the pivotal study of Shapiro et al. (3), severe sepsis occurred in <25% of the patients admitted and who had a blood culture performed. Furthermore, in the study by Sankoff et al. (1) that enrolled 385 patients, only 165 of them met the criteria for sepsis with a source of infection. In contrast with those series, our group and Chen and coworkers studied the performance of the MEDS score in medical intensive care unit patients with documented sepsis (4, 5). Furthermore, we found that patients with a MEDS score >10 had six-fold risk of dying (odds ratio 5.91, 95% confidence interval 3.00 –11.6), whereas Chen et al. observed that patients with MEDS score ≥12 had a higher mortality rate (48.9% vs. 17.5%, p < 0.001). Thus, we believe that a larger multicenter prospective study focusing on documented sepsis is warranted to confirm MEDS usefulness and to assess with better accuracy the risk of dying for the patients with a MEDS score between 8 and 12, for instance (8% and 19%, respectively, in the two cohorts). Furthermore, determination of cutoff values for intensive therapy and intensive care unit placement could be of interest.

Second, the usefulness of SIRS for ED triage or to predict mortality remains questionable. Even if SIRS is a sine qua non criterion for a sepsis trial, we need other selection criteria owing its high sensitivity. Indeed, SIRS being so common has no clinical implication and cannot per se discriminate septic patients with high risk of dying (1, 3). A patient’s stratification according to the number of SIRS criteria they met in the ED could have been of interest to increase the SIRS performance for the sudy, but we believe that it will not be clinically relevant in the ED. On the other hand, we must remember that not all patients who appear septic demonstrate an infection and that scoring systems do not perform well when compared with physician judgment.

To conclude, we believe that the MEDS scale may have an importance for ED triage in the future—but before, we need larger validation and we must define cutoff values for high risk of dying and to calculate an observed-to-predicted mortality ratio.

The authors have not disclosed any potential conflicts of interest.

François G. Brivet, MD, Frédéric M. Jacobs, MD, AP-HP, Service de Réanimation Médicale, Hôpital Antoine Béclère, and INSERM, Clamart, France, Dominique Prat, MD, AP-HP, Service de Réanimation Médicale, Hôpital Antoine Béclère, Clamart, France

REFERENCES
DOI: 10.1097/CCM.0b013e3181847421

The authors reply:

We thank Dr. Brivet et al. for their comments regarding our recently published manuscript. As emergency physicians, we are routinely confronted with undifferentiated diseases and increasingly, these take the form of critical illnesses either as the systemic inflammatory response syndrome or as sepsis if an infectious etiology is identified. Although sepsis is associated with substantial morbidity and mortality, systemic inflammatory response syndrome arising as a result of other noninfectious etiologies, carries a lesser but still significant risk of death (1). We therefore decided to include patients who met systemic inflammatory response syndrome criteria and those with likely infectious sources (i.e., sepsis) in our study (2). This is similar to what Shapiro et al. (3) did in their original study, as only 25% of their sample included patients with sepsis, and is consistent with how the Mortality in Emergency Department Sepsis (MEDS) score was originally intended (i.e., application in the emergency department to patients with suspected, but not confirmed, sepsis).

Dr. Brivet worries that the relatively small number of sepsis patients in our sample may somehow make the MEDS score less useful in predicting mortality because the observed mortality was lower than that in their own work and in that done by Chen et al. (4, 5). However, it should be pointed out that in each of those examples, patients were already admitted to the intensive care unit when their scores were calculated. In contrast, in our study the MEDS score was determined earlier in the patients’ courses and on a larger group of patients with a lower overall expected mortality. Nonetheless, in all cases, significantly higher mortality was observed in patients with increasing or higher MEDS scores. These findings further contribute to the validity and generalizability of the MEDS score, and strengthen our assertion that it should be used more liberally among patients with noninfectious systemic inflammatory response syndrome and sepsis.

Although no scoring system should ever replace clinical judgment in ascribing care to critically ill patients, the nature of undis-
differentiated disease earlier, in its presentation and course makes that judgment difficult to effectively use. Emergency physicians rarely have the luxury of positive blood cultures or readily identifiable sources of infection, and so they must often make decisions about care based on a paucity of specific objective evidence. Frequently, this results in an underestimation of risk to the patient and ensuing delays in the administration of appropriately aggressive therapies. It is our hope that the MEDS score could be used in these early stages of care, to help emergency physicians and intensivists augment their clinical judgment by more accurately identifying patients with higher than expected mortalities.

The authors have not disclosed any potential conflicts of interest.

Jeffrey D. Sankoff, MD, Division of Emergency Medicine, Department of Surgery, University of Colorado at Denver and Health Sciences Center, Denver, Colorado; Jason S. Haukoos, MD, MSc, Department of Emergency Medicine, Denver Health Medical Center, Denver, Colorado, Department of Preventive Medicine and Biometrics, University of Colorado at Denver and Health Sciences Center, Denver, Colorado

REFERENCES


DOI: 10.1097/CCM.0b013e31818477cc

Surviving Sepsis Campaign needed consensus to exclude selective decontamination of the digestive tract

To the Editor:

Weren’t we naive when we replied to the first guidelines that “we are confident that selective decontamination of the digestive tract (SDD) will be incorporated in the dynamic, electronic, web-based guideline process of the Surviving Sepsis Campaign” (1)! We believed that providing overwhelming evidence could change the minds of the guidelines group.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients Enrolled</th>
<th>No. of Patient With Sepsis at Study Entry (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SDD</td>
<td>C</td>
</tr>
<tr>
<td>Abele-Horn</td>
<td>58</td>
<td>30</td>
</tr>
<tr>
<td>Aerdts</td>
<td>17</td>
<td>49</td>
</tr>
<tr>
<td>Bergmans</td>
<td>87</td>
<td>139</td>
</tr>
<tr>
<td>Blair</td>
<td>161</td>
<td>170</td>
</tr>
<tr>
<td>Camus</td>
<td>130</td>
<td>126</td>
</tr>
<tr>
<td>Cerra</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Flaherty</td>
<td>51</td>
<td>56</td>
</tr>
<tr>
<td>Gastinne</td>
<td>220</td>
<td>225</td>
</tr>
<tr>
<td>Hammond</td>
<td>114</td>
<td>125</td>
</tr>
<tr>
<td>Jacobs</td>
<td>36</td>
<td>43</td>
</tr>
<tr>
<td>Kerver</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>Krueger</td>
<td>265</td>
<td>262</td>
</tr>
<tr>
<td>Luiten</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Pugin</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Ruza</td>
<td>116</td>
<td>110</td>
</tr>
<tr>
<td>Sanchez-Garcia</td>
<td>131</td>
<td>140</td>
</tr>
<tr>
<td>Ulrich</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>Wiener</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Winter</td>
<td>91</td>
<td>92</td>
</tr>
</tbody>
</table>

Table 1. Summary of randomized controlled trials of SDD including patients with sepsis at study entry and meta-analysis of the impact of SDD on infections and mortality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. RCTs</th>
<th>No. patients</th>
<th>Events</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall infection</td>
<td>18</td>
<td>1687</td>
<td>1748</td>
<td>0.42 (0.30–0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LRTI</td>
<td>13</td>
<td>1351</td>
<td>1443</td>
<td>0.38 (0.25–0.57)</td>
<td>0.0024</td>
</tr>
<tr>
<td>BSI</td>
<td>8</td>
<td>788</td>
<td>837</td>
<td>0.57 (0.37–0.89)</td>
<td>0.014</td>
</tr>
<tr>
<td>UTI</td>
<td>7</td>
<td>669</td>
<td>712</td>
<td>0.60 (0.42–0.86)</td>
<td>0.0052</td>
</tr>
<tr>
<td>Mortality</td>
<td>19</td>
<td>1704</td>
<td>1797</td>
<td>0.78 (0.67–0.92)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data were retrieved after reviewing 56 published randomized controlled trials of selective decontamination of the digestive tract (3). SDD, selective digestive decontamination; C, control; RCT, randomized controlled trial; OR, odds ratio; CI, confidence interval; LRTI, lower respiratory tract infection; BSI, bloodstream infection; UTI, urinary tract infection.

Results are presented as odds ratios with 95% confidence interval using the random effects model. Heterogeneity was assessed by the Cochran Q statistic and the I² measure of inconsistency. No heterogeneity was found in all comparisons, except for overall infection where I² was 30%, indicating a mild heterogeneity.

Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
group acknowledged the evidence, but failed to make a recommendation “as the guidelines group was evenly split on the issue of SDD with equal numbers weakly in favor and against recommending the use of SDD” (2). The final consensus on the use of SDD in severe sepsis was achieved at the last nominal committee meeting and subsequently approved by the entire committee.

Remarkably, the guidelines group stated that “no studies of SDD specifically focused on patients with severe sepsis or septic shock” (2). Although this criterion was also used for deep vein thrombosis and stress ulcer prophylaxis, these two maneuvers received better appraisal than SDD, as “the prevalence of infection/sepsis was 17% in all studies on deep vein thrombosis prophylaxis with a 52% prevalence of infection/sepsis in the study including intensive care unit patients only,” and “20% to 25% of patients enrolled in stress ulcer prophylaxis studies have sepsis.” Therefore, the authors concluded that “the benefit should be applicable to patients with severe sepsis and septic shock.”

We believe that SDD is an intensive care unit intervention indicated for patients admitted with severe sepsis and septic shock. Indeed, of 56 randomized control trials of SDD (approximately 10,000 patients) (3), 19 randomized control trials included a total of 3501 patients (1704 SDD, 1797 controls) with data available on patients septic at study entry. There were 1266 patients (36.16%) with sepsis on admission (606 SDD and 660 controls) (Table 1). We performed a meta-analysis of those 19 studies with the end point of assessing the impact of SDD on infection and mortality. The analysis showed a significant reduction in overall infections, lower airway infections, bloodstream infections, and mortality (Table 1). These data are in line with the results of two recent systematic reviews demonstrating a significant reduction in lower respiratory tract infections (4), bloodstream infections (5), and mortality (4) by 65%, 37%, and 22%, respectively.

Finally, we were surprised by the results included in Appendix H, in which the group voted the use of systemic antibiotics alone. The use of systemic antibiotics alone has never been supported by SDD advocates as single measure to prevent infection. The authors of the guidelines should be aware that the full protocol of SDD includes the combination of parenteral and enteral (i.e., oropharyngeal and intestinal) antimicrobials. Systemic antibiotics are administered for the first days of intensive care treatment to prevent primary endogenous infections, but are unable to prevent acquisition and secondary carriage with often multiresistant bacteria for which enteral nonabsorbable antimicrobials are essential. If anything, a comparison should be made between parenteral/enteral (i.e., the full SDD protocol) and only enteral antimicrobials.

The authors have not disclosed any potential conflicts of interest.

Luciano Silvestri, MD, Department of Emergency, Unit of Anesthesia and Intensive Care, Presidio Ospedaliero, Gorizia, Italy; Hendrick K. F. van Saene, MD, PhD, FRCPath, Department of Medical Microbiology, University of Liverpool, Liverpool, UK; Miguel A. de la Cal, MD, Intensive Care Unit, University Hospital of Getafe, Getafe, Madrid, Spain; Durk F. Zandstra, MD, PhD, Intensive Care Unit, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; Mario Viviani, MD, Department of Anesthesiology and Intensive Care, University Hospital, Trieste, Italy; Mladen Perić, MD, PhD, Department of Anesthesiology and Intensive Care, “Sestre Milosrdnica” University Hospital, Zagreb, Croatia; Antonino Gullo, MD, Department of Anesthesia and Intensive Care, University Hospital, Catania, Italy

REFERENCES


DOI: 10.1097/CCM.0b013e31818474a2