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Evidence in Intensive Care: An Interview with Professor John Marini



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You presented at ISICEM 2014 on the Round Table conference on “Evidence-based care: New directions”. What were the key themes from this?

The rationale was to draw together experts from diverse areas to share ideas regarding how to do better in gathering the data needed to guide clinical practice of intensive care. As a field, we have made good progress toward improving rescue and survival, but not as well in restoring our patients to robust health. Many patients encounter chronic critical illness or lingering disabilities that follow them for months to years afterwards. We remain uncertain as to how much of this ‘ICU hangover’ is part of the innate process and how much is inadvertently caused by the care we administer. We have looked for guidance regarding patient care to randomised clinical trials (RCTs), observational studies and experimental laboratory work using models of disease. Often, the results of such work have been conflicting or misleading, and at times progress seems to be painfully slow. Population-based answers often do not apply to the specific problem of the individual. Interpretation of RCTs is tricky, and judicious application of population-based findings to decisions for the individual even more so. What we have been slow to understand is that we have imprecise definitions and imperfect models. At the same time, the problems we face involve patients who are heterogeneous in severity, susceptibility and responsiveness, pathologies and treatments that are complex and incompletely understood, and timing issues of the progressing condition that affect the effectiveness and side effects of our treatments.

We discussed new methods for targeting the population tested in our trials, identifying and dissecting the interactions among the key variables and ‘personalising’ the treatments given. New methods for interpreting individual sensitivity and adaptive response were also of major interest. The novel tools we discussed included statistical approaches to data analysis and study design as well as molecular and genomebased diagnostic and monitoring methods. I think we all went away from the Round Table with sharpened awareness and fresh ideas regarding better directions for our work.

You have previously recommended against over-reliance on evidence. What is the role of evidence-based care in intensive care? How can intensivists be sure of new treatments, unless they have been tested in large RCTs?

If by the term evidence you mean the RCT, then I plead guilty as charged. But useful ‘evidence’ comes in many forms. When faced with a complex, quickly evolving and changeable clinical problem at the bedside, a logical approach based on mechanistic understanding, expert opinion and/or personal experience may be the best we have to guide us. Many factors interact to determine outcomes for individuals. In such a rapidly evolving and non-linear system, integrating all key information, making an informed, reasonable decision and then committing to short loop feedback and mid-course corrections is the way to go. In reality, this is an N-of-1 empirical trial, not an application of a deterministic one, as the RCT-guided approach would imply. Often, you cannot simply choose an option from a picklist or guideline, and then set it and forget it. I have long been concerned that we over-emphasise the results from RCTs. Within the data of any RCT you have patients who had neutral or contradictory responses to the group average. For example, prone positioning might be perfect for some but ineffective or dangerous for others. Lumping all results to draw one conclusion may be misleading for the appropriately selected subpopulation. It might seem that the question is simple and the choice clear—prone the ARDS patient or not? But we now understand that the dosing (hours per day and days prescribed) of prone positioning is important to its efficacy, as is the recruitability and severity of the lung disease (What exactly is ‘ARDS’, anyway?). That is not to say that certain specific problems should not be subjected to RCT—ones that are unambiguously defined, candidates appropriately identified, likely mechanisms for benefit or harm are known, and outcomes are directly traceable to the intervention. When RCTs are performed the question should be logical, the subject population sharply defined, the enrolment large, and the co-morbidities and co-interventions well controlled. These trials are expensive, usually take a long time to complete and publish, and, even when accurate, the results are relevant only to the specific patients and specific medical environment that was studied. Medicine often changes impressively over time. RCTs are not the

pinnacle of the evidence base for issues in critical care but rather a blunt tool that provides more questions than answers. They often make us stop, think and try to explain—a good thing. However, when published, their relative influence on practice is often both enormous and immediate. In my view, RCTs represent an overused research option that should be undertaken primarily when a serious question exists at the end of a more basic (and hopefully mechanism-defining) chain of observations and research that alone are not persuasive. When results are puzzling and/or practice changing, replication should be mandated.

What are the most serious challenges in ventilator management?

I hope to give a succinct answer. The goal of invasive ventilation is to provide cardiopulmonary support that is effective, safe, and comfortable. We currently do quite well in achieving life-sustaining CO₂ elimination and acceptable arterial oxygenation. Unfortunately, we do not do as well with safety and comfort. The potential damages that result from inappropriate and protracted sedation, ventilator and oxygen-associated lung injury, intubation-related infection and laryngeal dysfunction, psychic distress, interrupted communication, patient-ventilator asynchrony and excessive right ventricular afterload are always a challenge to prevent. We know that ventilatory support is often required, but when do we cross the line that demarcates harm from benefit? Sometimes taking full control is best; at other times we should aggressively transition to spontaneous breathing. Finding safe and effective ways of reducing the intensity of invasive ventilation (as by adapting the patient to permissive hypoxaemia as well as hypercapnia) or by using extrapulmonary gas exchange (ECMO, ECCO₂R) hold promise. Our bedside processes of care must also be perfected—positioning, protocols, monitoring, early intervention etc. If I had to single out one all-encompassing challenge it would be to reduce the unintended consequences of mechanical ventilation.

Is it possible to ventilate obese patients? What are the challenges?

Learning the nuances of ventilating obese patients should be a priority for intensive caregivers, as the prevalence of obesity, already high, is slowly rising in all age groups and in every geographic sector and economic stratum of the world. The physiologic hazards that these folks confront are clear. The lungs operate at a low resting volume (FRC), so that they have limited oxygenation reserve. Many have baseline hypercapnia and most have a vulnerable upper airway that predisposes to obstructive apnea. Attention to CO₂ monitoring is especially important. The drive to breathe tends to be blunted. They often have pulmonary hypertension and are at risk for right ventricular decompensation when it rises further due to acidosis, hypoxemia, or excessive alveolar pressure. Obesity predisposes to venothrombosis, systemic hypertension, and oesophageal reflux. They encounter problems with airway closure in the usual supine, 30 degree position, and the heaviest should be managed in a more upright beach chair posture. After extubation, these patients are at higher risk for upper airway obstruction and sleep apnea due to abnormal neck anatomy—especially in the first post-extubation days, since they may slowly release fat-stored sedative agents. These many hazards pre-dispose to sudden, unexpected crises both during and after mechanical ventilation.

In an article on the future of critical care you noted emerging economic realities related to critical care that must be confronted in the future: fewer personnel, faster hospital throughput, increased needs for safety, timely intervention, quicker assessment of therapy and decision support (Marini et al. 2013). Which of these realities is the most challenging, and how can intensivists address it?

Among these, one of the most challenging is to better time what we do. In my opinion, many of our problems relate to our failure to first intervene quickly enough and then to time our 'therapeutic flip' toward withdrawal of supports and strengthening the rescued patient. The ability of the patient to adapt to the abnormal physiology that accompanies acute illness is really an underexplored but vitally important area. I strongly suspect that we do too much for too long, not only wasting resources but extending the duration of ICU stay, interfering with the patient's adaptive potential and unintentionally promoting chronic critical illness and encouraging lasting disabilities.

We can address efficiency issues and achieve better timing by deploying care extenders (e.g. nurse practitioners) and other helpers to attend to the mandated chores of modern medicine (e.g. documentation) that tend to disconnect us from the patients we treat. In principle, the electronic medical record and better monitoring systems can aid timely intervention, enable short loop feedback, and improve efficiency of hand-offs, but the obligation to document and to process communications electronically currently works in the other direction.

What is your view on prone positioning in ARDS, given recent findings?

My view today is almost exactly what it has been for the past 20 years. Prone positioning reduces the mechanical heterogeneity that predisposes to ventilator-induced lung injury, helps recruit the dorsal lung zones, improves oxygenation and contributes to effective airway secretion drainage. It is universally available, poses modest and preventable hazards, and once the turn has been made, requires little more personnel time to maintain than supine management. It can be life-saving for our most severely affected patients. Guérin and the PROSEVA team did intensive care a great service in showing its worth for the appropriately selected patients (Guérin 2013). Although some would disagree, I do not think that we can recommend proning for every ARDS patient—at least, not at this time.

By the way, the proning story is a good example of how misinterpretation of inconclusive RCTs can mislead us into discarding a valuable option. We need to know the 'why', not just the 'what' behind these interventions and studies. I was recently asked by a journal editor why so many practitioners are now so willing to prone their ARDS patients whereas they were hesitant before. My answer: proning makes good mechanistic sense for these patients—always did. Moreover many physicians have seen positive results with those who were desperately ill. Now we have meta-analytic suggestions of whom to target and a strong RCT mandate to make it more routine.

You spoke at ISICEM 2014 in favour of plateau pressure's ability to guide ventilation in ARDS? What are the main arguments for this in your opinion?

Please bear in mind that the setting was an intentionally polarised 'pro-con' style debate. Plateau pressure is universally available, easy to

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measure, and potentially valuable. This number tends to relate more directly to injury risk than tidal volume, whose impact varies with the volumetric capacity of the injured lung. Clearly, plateau pressure is only one of the things to consider when trying to prevent ventilator-induced lung injury. For example, it may be misleadingly low when the patient makes strong breathing efforts and misleadingly high when the chest wall is stiff. It is risky to set a precise numerical guideline for what is a safe or hazardous plateau that applies across a diverse population of patients. However, the utility of the plateau pressure is still significant when caring for the individual patient. An increase or decrease of plateau pressure obtained under passive conditions tends to affect the maximum tidal stress and the driving pressure in the same direction, and both are linked to ventilator-induced lung injury risk. In fact, at sites of stress focusing, the potentially damaging tissue tension is a non-linear function of the plateau. An upward change of plateau disproportionately increases the tissue tension, and the opposite (disproportionate lowering of tension) will apply if the plateau can be reduced. When the patient is passive and the chest wall is normally compliant, plateau pressure—keeping PEEP and tidal volume the same—helps gauge the hazard, the trajectory of illness, and the progress toward recovery. I realise that for any airway pressure the associated stress we apply is not uniform in the injured lung and that the recordable parameter of most interest is not the plateau pressure but the average pressure across the lung—plateau minus pleural (oesophageal) pressure.

This interview will appear in the Summer issue of ICU Management, which focuses on prevention of critical illness. What do you see as the main challenges in prevention?

Some categories of life-threatening problems (for example those that develop from trauma, violence, mental illness, and self-abuse) will always be there. Improved public awareness of behavioural hazards, the benefits of exercise and good nutrition, and warning signs of impending disease will have a positive effect, as has already been amply shown. But a considerable volume of critical illness develops out of milder disorders that are mistakenly ignored or improperly treated. Deterioration can be targeted earlier, especially after the patient comes to medical attention. Within the hospital, for example, rapid response teams have really helped interrupt the downward spiral toward the need for ICU attention.

It can be argued that the biggest challenges in the prevention of critical illness are to address those of our own making. As medicine advances, our delivery system is inadvertently growing an ageing population of patients with multiple serious chronic diseases that often eventuate in repeated needs for intensive care. The associated costs are staggering. With notable exceptions, our transitions from intensive care to general inpatient care to outpatient care are clearly imperfect. We do not have delivery systems to 'catch' and strengthen rescued but fragile patients once they leave the ICU. As a result, recurrent ICU admissions are frequent. Expectations and incentives are aligned to quickly address problems with drugs and interventions. These folks are often seen by multiple specialty providers who place them on many different medications—often without the patient's understanding of what they are intended for, how they should be used, or whether they are still needed. In my country, the over prescription of narcotics for chronic pain and of beta blockers for nonessential conditions in the elderly provide a case in point, as both predispose to hypotension, altered mental status and blunted response to stress. Unnecessary ICU admissions often result. Better patient education, less medical meddling, more efficient access to medical help, and good follow-up will help, as will timely telecommunication and better integration of provider services. Perhaps most important of all in preventing critical illness, we need to re-establish and/or strengthen the connections between committed, caring, and well informed providers with the patient. In the hectic, rapidly changing and 'bottom line' oriented environment that surrounds us, achieving this ideal is indeed a major challenge that must be confronted at all stages of medical education and levels of practice.

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