

## Occasional essay

### Please read the fine print

I was called to see a patient who had just been admitted to the intensive care unit (ICU) from one of the general wards, and entered the patient's bay just after he had been intubated and ventilated. The medical registrar was at the end of the bed looking at the patient's ECG, the ICU registrar was securing the endotracheal tube and the nursing staff were busy preparing to set up for an arterial line and a Swan-Ganz catheter.

The ICU registrar looked up, raised his eyebrows and smiled a little as he began to tell me the story. The patient was an 86 year old man with severe ischaemic heart disease, chronic atrial fibrillation and mitral regurgitation who had had numerous episodes of pulmonary oedema over the past 12 years. His medications included pirinodipril, digoxin, frusemide, amlodipine, spironolactone, warfarin and amiodarone. He had been admitted to a medical ward three days ago with a two-day history of increasing dyspnoea and resistant peripheral oedema. However, while he had improved initially with CPAP, graduating to oxygen at 4 L/min via nasal cannulae, during the morning of the third day he became progressively more dyspnoeic and hypotensive. When the ICU team arrived in response to a 'medical emergency' call, he had marked cyanosis and was gasping for breath.

As the ICU registrar appeared to have the clinical situation under control and as a 'Swan' and an 'art line' were about to be inserted, I decided to review the case notes quietly in a corner before I examined the patient.

It appeared that during his three-day inpatient workup, the chest X-ray demonstrated a large heart in failure, the plasma biochemistry revealed features of a resolving ischaemic hepatitis with an INR that had decreased from 8.2 to 3.3 and a creatinine that had decreased from 0.52 mmol/L to 0.46 mmol/L. The echocardiograph confirmed severe global left ventricular dysfunction with mitral regurgitation. I also noticed that one hour before the ICU team was called he was given carvedilol 3.125 mg orally.

"Why was he given carvedilol?" I asked.

"To help his heart failure" replied the medical registrar as he continued to peruse the ECG. He quickly followed with "The latest '*New England*' reported a huge multicentre trial where carvedilol reduced the mortality of patients who had grade IV heart failure".

"Nice study, but didn't it exclude patients with renal failure?" I inquired provocatively.

The registrar immediately looked up, probably to assess whether he was talking to a true believer or not.

"Patients with renal failure were included" he blurted and nervously began to fidget with his stethoscope.

At this stage we both knew that the important features of this study were a little hazy in both our minds, but I can remember thinking as I read the article that carvedilol was probably not an agent that we would be using much in our critically ill population. While I would accept that adrenergic stimulation has a maladaptive role in chronic heart failure, and that trials of beta blockade (orally and in gradually escalating doses) have reported beneficial effects in clinically stable patients, in critically ill patients who have severe systolic heart failure, beta adrenergic receptor blockade can be hazardous.

Later that day I wandered back to my office and logged onto [www.nejm.org](http://www.nejm.org) and found the article in question which appeared in the May 31<sup>st</sup>, 2001 edition.<sup>1</sup> The patient who was admitted to the ICU would have been excluded from that trial for many reasons, including being a hospitalised patient with an acute cardiac illness requiring continuous inpatient care, severe peripheral oedema, serum creatinine > 0.248 mmol/L and receiving a calcium channel blocker.

Such broad interpretations of various 'landmark' articles with little consideration given to the exclusion criteria (i.e. failure to read the fine print) are not necessarily rare. Some clinicians do not restore a haemoglobin level beyond 70 g/L in acutely ill patients because 'mortality was not improved with transfusion in a recent study reported in the *New England Journal of Medicine*' (ignoring the exclusion criteria of a decrease in haemoglobin of 30 g/L in the preceding 12 hr, requirement of 3 units of packed cells in the preceding 12 hr and postoperative cardiac surgery).<sup>2</sup> Moreover, patients with acute respiratory failure will be given glucocorticoids, CPAP, nitric oxide, ketoconazole, N-acetylcysteine and a whole range of therapies without due consideration being given to the underlying aetiology (and therefore the exclusion criteria), with cursory consideration of the results of various studies appearing to support their use.

To convert the reported benefit of any trial to something that is relevant to clinical practice, it is usually recommended that the clinician estimate the susceptibility of his or her untreated patient in relation to the control group described in the report, so that the likelihood of effectiveness of therapy (e.g. assessment of number needed to treat) can be judged appropriately.<sup>3,4</sup> However, it is often forgotten that there are many criteria within the report that may have excluded the patient from the trial in the first place, and thus exclude the conclusions reached being valid for that patient.

Although the treatment in question is not evaluated in the 'exclusion group' and therefore does not mean that it won't be beneficial or will be harmful, blind application of the results of any clinical study can be hazardous, as there are usually good reasons why a particular study excludes patients from the 'treatment' group (e.g. previous studies have found treatment of no use or even dangerous).

There is no substitute for thinking. When managing a patient with an acute clinical problem, an intelligent and alert clinician is still required.<sup>5</sup>

"Learning without thought is labour lost; thought without learning is perilous"  
Confucius

L. I.G. WORTHLEY

*Department of Critical Care Medicine, Flinders Medical Centre, Adelaide, SOUTH AUSTRALIA*

#### REFERENCES

1. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-1658.
2. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomised, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340:409-417.
3. Sackett DL Haynes RB. Summarising the effects of therapy: a new table and some more terms. *Evidence-based Medicine* 1997;2:103-104.
4. Sackett DL, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based medicine. How to practice & teach EBM.* Edinburgh:Churchill Livingstone. 1997.
5. Naylor CD. Clinical decisions: from art to science and back again. *Lancet* 2001;358:523-524.