**Editorials**

**Selective digestive decontamination: once again**

It is nearly 20 years since the first paper describing the implementation of selective digestive decontamination (SDD) was published, and neither the enthusiasm for testing the hypothesis of SDD efficacy nor the attendant controversy over this technique appear to have waned.

The recent publication of the largest (positive outcome) prospective randomised trial of SDD by de Jonge et al. and the claims, primarily based upon two recent meta-analyses, that i) SDD reduces mortality and, ii) “the main reason for SDD not being widely used is the primacy of opinion over evidence”, would appear to warrant close scrutiny. This requirement appears all the more justified as the recent critiques of SDD by seemingly accept the reduction in rates of mortality and respiratory tract infection, but base their repudiation of SDD upon arguments regarding real or anticipated rates of antibiotic resistant bacteria, a concern also reiterated by the editorial accompanying the de Jonge et al study.

**Meta-analysis overview**

1. The Nathens and Marshall meta-analysis, described a number of patient groups in which SDD had been compared with no prophylaxis. For example, critically ill surgical patients, critically ill medical patients, transplantation, major elective surgery, thermal injury and acute pancreatitis. However, consideration will only be given to the first two groups: “surgical”, comprising 11 individual studies, and “medical”, with 10 studies. The “surgical” group was defined when ≥ 75% of subjects evaluated had been admitted following trauma or surgery (although the Cochrane Database identified the Unertl et al trial, as having 52% medical “admission diagnosis”), and the “medical” group was defined when < 25% met this criterion. Studies using both topical and systemic component SDD and topical component only SDD were combined. No further justification was given for the characterisation of these groups and no primary trial results were reported. Nathens and Marshall claimed that SDD effectively reduced intensive care unit (ICU) mortality in the “surgical” group (odds ratio: 0.70; 95% CI: 0.52 to 0.93) as opposed to “medical” patients, where no mortality effect was apparent (odds ratio: 0.91; 95% CI: 0.71 to 1.18). Within the “surgical” group only topical and systemic component SDD was effective (odds ratio: 0.60; 95% CI: 0.41 to 0.88). Of the nosocomial infections identified, SDD effectively reduced the rate of pneumonia and urinary tract infection in both “surgical” and “medical” patients, but bacteremia was reduced in the “surgical” group only. Of interest, SDD had no impact upon wound infection.

2. The D’Amico et al meta-analysis, identified 34 individual studies or sub-studies and was originally reported in the Cochrane Database in 1997 and updated in July 2001, although no new studies were identified as of that date. In addition to the background trial information provided in the Cochrane Database, the grouped data used in the standard meta-analytic analyses was intention-to-treat (provided by contact with original authors) not per-protocol as reported in published original trials, a notable difference from that presumably used by Nathens and Marshall. The underlying strategy of analysis was to consider studies (n = 17) comparing topical and systemic component SDD with no prophylaxis separately from topical component only SDD (n = 10); a further subgroup of seven trials was also identified where systemic antibiotics had been given to the control group.

A significant reduction in ICU mortality was apparent only for topical and systemic component SDD (17 studies: odds ratio: 0.80, 95% CI: 0.69 to 0.93; p = 0.007), but interestingly not when topical and systemic component SDD was compared with systemic prophylaxis given to the control groups (odds ratio = 0.98; 95% CI: 0.73 to 1.32). Individual patient data (IPD) were also available from 25 of 33 trials. When analysis was performed using IPD, the treatment effect of topical and systemic component SDD was consistent across the three patient groups identified on admission diagnosis; medical, surgical and trauma, but could not be identified in the (small number of) patients in each group with APACHE II scores > 30. No substantive difference was noted in the results of grouped versus IPD analyses.

Only nosocomial respiratory infections were considered by D’Amico et al, and they reported a significant protective effect of both topical and systemic component (odds ratio = 0.35, 95% CI: 0.29 to 0.41) and topical component SDD (odds ratio = 0.56; 95% CI: 0.46 to 0.68), but not when topical and systemic component SDD was compared with systemic component only SDD (odds ratio = 0.81; 95% CI: 0.61 to 1.08).
Critique

The studies identified by Nathens and Marshall were the same as those used by D’Amico et al, with the exception of a non-randomised trial by Godard et al, not included in the D’Amico et al meta-analysis. The utilisation of intention-to-treat data versus per-protocol published trial data overcomes potential bias due to under-reporting of patient numbers, a problem identified by D’Amico et al, and, in a meta-analysis on immunonutrition, by Beale et al. Using the intention-to-treat data provided by D’Amico et al, (quantitative analysis performed by the “metan” routine, using Stata statistical package, version 8.1, 2003; College Station, Tx) there was no significant mortality effect of SDD in the “surgical” group of Nathens and Marshall, with (odds ratio: 0.79; 95% CI: 0.62 to 1.02, p = 0.07) or without (odds ratio: 0.79; 95% CI: 0.611 to 1.02; p = 0.07) the Unertl et al data (see above). This finding is consistent with the results presented by D’Amico et al, using individual patient data.

Primary mortality end-points of the SDD trials considered in both meta-analyses were invariably that in the ICU. Given recent recommendations for prolonged follow-up in clinical sepsis trials, the translation of this to improved hospital or post hospital mortality is uncertain. More importantly, in both meta-analyses, only the use of combined topical and systemic therapy in SDD was advantageous with respect to mortality and, as indicated by D’Amico et al (and discussed in three recent over-views of SDD), the parenteral broad spectrum antibiotic (usually cefotaxime) would appear to be the critical factor in SDD.

This can be demonstrated (albeit only in a “suggestive” non-weighted analysis) by combining the data from D’Amico et al. For example,

a) 24 studies reported the use of topical plus systemic SDD, with a mortality of 23.3% (539 deaths in 2313 patients), as opposed to a mortality of 18.6% in the sub-group of studies (n = 7, see above) where systemic antibiotics were administered to the control group (130 deaths in 699 patients); a significant difference (p = 0.009; two-sided Fisher’s exact test), and

b) 29 studies reported no prophylaxis, with a mortality of 28.62% (705 deaths in 2463 patients), as opposed to the mortality of 18.6%, where systemic antibiotics only were administered to the control group; p = 0.001.

Although D’Amico et al, considered that a trial comparison of combined topical and systemic therapy with systemic therapy alone would be a “logical next step”, Silvestri et al, resiled from this position to claim that “…the efficacy of SDD, rather than the addition of cefotaxime, determines outcome…..”. The latter authors cited evidence from a study of traumatic and medical head injury, where “previous (short-term) antibiotics” were a risk factor (odds ratio 0.2; 95% CI: 0.05 to 0.86) for Gram-negative enteric bacilli and Pseudomonas spp colonisation within 24 hours of ICU admission. However, “short-term” was defined in the study as “any dose of any antibiotic prior to first sampling” and the CI of the estimate were wide, as were other CI in the study, up to an odds ratio of 128, suggesting unstable or implausible estimates, presumably due to the small sample size (n = 48) and the multiple statistical comparisons.

The mechanism for the SDD protective effect has not been well characterised. The relationship between respiratory infections and subsequent ICU death has been described by SDD protagonists as “weak”; Kollef suggested that “Trauma and surgical patients have previously been shown to benefit from the use of systemic antibiotic prophylaxis, including reduced rates of nosocomial infection and improved hospital survival”, but the two references offered in proof refer only to prevention of surgical wound infection by antibiotic prophylaxis and contained no analysis of mortality. Silvestri et al, noted experimental and cardiovascular by-pass patient evidence of reduction in gut endotoxin and its absorption leading to “recovery of systemic immunity”. Nathens and Marshall, reported a reduction of bacteraemia, as opposed to other infections, pneumonia and urinary tract, in their “surgical” group compared with the “medical”, but offered no pathophysiological explanation as to why this should be. Furthermore, the definitions of the two categories of patients would appear to be ad hoc and problematic from an inference point of view.

Thus there appears to be a paradox within the SDD paradigm; topical component SDD appears to impact upon nosocomial respiratory infection, which has no direct impact upon mortality, as systemic prophylaxis alone reduces mortality, but has no effect upon nosocomial respiratory infection.

The reduction of nosocomial infection by SDD would have been expected to be translated into favourable differences for SDD in proxy outcome measures, such as mechanical ventilation time and/or ICU length of stay. A previous meta-analysis, by Heyland et al, found no difference in ICU length of stay; 15.5 days versus 17.0 days, p = 0.48. In their “surgical” group, Nathens and Marshall, found a reduction in ICU length of stay (8 studies only; 16.9 ± 13 vs 15.2 ± 12.5 days, t-test, p < 0.05), which may be expressed as a weighted mean difference (WND): -1.8 days (favouring SDD); 95% CI: -3.4 to -0.2 days; p = 0.03. However, mechanical ventilation time was not reduced by SDD in the “surgical” group (WND: -0.8 days; 95% CI: -2.1 to 0.4 days, p = 0.2) and in the larger
D’Amico et al., analysis of topical and systemic SDD vs no prophylaxis, where the mean percentage of surgical patients was 25%, neither ICU length of stay (WMD: -0.9 days; 95% CI: -2.4 to 0.5 days; p = 0.21) nor mechanical ventilation time (WMD: -1.5 days, 95% CI: -3.0 to 0.1 days; p = 0.06) demonstrated reduction in the SDD arm.

However, as noted by Beale et al., differences in mortality rates and increased early death rates, when overall mortality rates are the same, may confound the interpretation of time-dependent variables such as ventilator days and length of stay. Beal et al., addressed this potential problem by the use of individual patient data in their analysis and censored for non-survivors. Such an analytic approach has not been repeated within the SDD paradigm, despite individual patient data being available. In individual trials, contradictory results have been found for the impact of SDD upon ICU length of stay for survivors; no influence in two studies and favourable in one.

The impact of the costs of SDD has been addressed in a minority of papers; both surveys of SDD practice from SDD protagonists cite the low costs of all non-patent SDD drugs and four studies which have demonstrated reduced costs per survivor with SDD. However, studies may be cited which show increase in costs with SDD, and a comparison of these two cohorts is instructive (Table 1). The studies associated with decreased costs for SDD displayed higher control rates of pneumonia (compared also with the overall control rate of 32% in the D’Amico et al. meta-analysis) and longer ICU length of stay and mechanical ventilation time than the studies with increased SDD costs. Comparison with the large prospective international cohort study of ventilated ICU patients of Esteban et al., is also informative; mean ICU length of stay and mechanical ventilation time is better approximated to the comparator patients of Esteban et al. by those studies showing increased SDD costs. As no difference in ICU length of stay and mechanical ventilation time has been demonstrated between SDD and control patients (see above), any cost difference must be assumed to reflect costs of both SDD and the diagnosis and treatment of acquired infections. Thus costs and cost differentials are not fixed by the use of SDD per se, but are functions of variables such as the underlying control rate of pneumonia (and other infections) and length of ventilation.

Uncertainty has also been expressed regarding two fundamental aspects of SDD. Firstly, the individual constituents of the “package”, whether this be the topical and systemic antibiotics or topical alone. Bonten et al., further note that a “head-to-head comparison of the complete SDD package vs oropharyngeal decontamination in a randomised fashion has never been performed”. Secondly, the diagnosis of pneumonia has been clinically based with a variable and uncontrolled use of protected specimens; the latter technique may vary the study diagnosis sensitivity. More disquieting was the reported inverse relationship between the methodological quality score of the SDD studies and the rates of pneumonia (but not mortality), suggesting overly optimistic estimates of SDD benefit with respect to nosocomial infection.

De Jonge et al. study

What then may be said of the latest large study of SDD? Firstly, this was an un-blinded study which showed odds ratio for ICU mortality of 0.59 (95% CI: 0.42 to 0.82) and hospital mortality of 0.71 (95% CI:

Table 1. Demographic comparisons for costing studies and selective digestive decontamination

<table>
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<tr>
<th>Study</th>
<th>N</th>
<th>Year</th>
<th>AP II</th>
<th>CPn rate (%)</th>
<th>LOS: SDD</th>
<th>LOS: control</th>
<th>MVtime: SDD</th>
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N = total study number, Year = year of publication, AP II = APACHE II score, CPn rate = control arm rate of pneumonia, LOS:SDD = mean intensive care unit length of stay for selective digestive decontamination (SDD) patients (days), LOS:control = mean intensive care unit length of stay for control patients (days), MV time:SDD = mean mechanical ventilation time for SDD patients (days), MV time:control = mean mechanical ventilation time for control patients (days), NA = not available.
The authors noted the magnitude of improvement in outcome compared with the D'Amico et al\textsuperscript{a} meta-analysis (odds ratio for ICU mortality, 0.8, 95% CI: 0.69 to 0.93) and suggested that various modifications of their SDD regimen may have been responsible. Discordance between meta-analyses and (subsequent) large trials are well described,\textsuperscript{33,34} with overall correlation of treatment effects varying between -0.12 to 0.76 and for primary end-points, 0.50 to 0.76. Un-blinded studies are known to yield exaggerated treatment effects\textsuperscript{35} and this factor cannot be excluded, given that the two ICUs where the study was performed were co-located and shared staff. Paradoxically and almost counter-intuitively, in the Cochrane Database update of the D'Amico et al meta-analysis,\textsuperscript{36} there was no effect of SDD (topical plus systemic) in un-blinded studies (total number of patients = 2568; odds ratio 0.90, 95% CI: 0.74 to 1.08; p = 0.2) compared with double-blind (total number of patients = 1013; odds ratio 0.63, 95% CI: 0.48 to 0.83; p = 0.0009).

However, the calculation of the trial sample size for mortality needs further comment. Sample size for what appeared to be the “dominant” primary endpoint, anticipated incidence of colonisation with certain prescribed resistant bacteria, yielded “at least 503 patients….in each group”\textsuperscript{2}. With this sample size, the 95% CI for the effect on mortality, about a target odds ratio of 0.8 (the odds ratio point estimate of the D’Amico et al meta-analysis,\textsuperscript{6} above) and 25% mortality in the control group (less than the control mortality of D’amico et al, at 28.2%), extends from 0.60 to 1.07; that is, a significant mortality effect cannot be declared. By way of clarification, as the odds ratio metric is not transparent,\textsuperscript{37} the above trial set-up corresponds to proportions (π) of 25% in the control group (π\textsubscript{c}) and 21% in the treatment group (π\textsubscript{t}), as odds ratio = [π\textsubscript{t}/(1-π\textsubscript{t})] / [π\textsubscript{c}/(1-π\textsubscript{c})]. A sample size of 875 per group would give a 95% two-sided CI of 0.64 to 1.00 about an odds ratio of 0.8 (computations are based upon the statistical package nQuery Advisor\textsuperscript{©} Release 4.0).\textsuperscript{38} thus > 1750 patients in total would be needed to detect a significant mortality effect at the 0.8 odds ratio level.

Following a suggestion of Flather et al,\textsuperscript{39} the power for the D’Amico et al\textsuperscript{a} meta-analysis, calculated by conventional means, is 0.79. The odds ratio observed in the de Jonge et al, study of ICU mortality was 0.59 (95% CI: 0.42 to 0.82) and a sample size of 420 per group would give 95% CI about an odds ratio of 0.42 to 0.83.\textsuperscript{38} However, these are post hoc calculations which are known to be flawed from a methodological viewpoint.\textsuperscript{40,41} Thus it is perhaps surprising that the observed mortality treatment effect of a trial that was under-powered for one of its primary endpoints was substantially greater than that of a large meta-analysis.

The perspective of de Jonge et al,\textsuperscript{2} was presumably to conduct their trial based upon all cause mortality. However, some degree of uncertainty would appear to exist regarding the pathophysiological basis this of SDD (see above). Silvestri et al,\textsuperscript{19} assuming an “association between pneumonia and mortality”, a baseline mortality of 30% in a mixed ICU population and 27% of deaths in the ICU being “directly attributable to pneumonia”, calculated that 2000 to 3000 patients were needed to detect a 10% to 20% mortality reduction; the presumption being that SDD reduced mortality (primarily) via reduction in antecedent respiratory infection.

If the mortality effects of de Jonge et al trial are accepted, an alternative estimate of treatment efficacy may be exploited; the Mann-Whitney statistic, which estimates the probability (0 to 1.0) that a randomly selected patient given an innovative therapy will respond better than a randomly selected patient given “standard” treatment.\textsuperscript{42} For both ICU and hospital mortality, the Mann-Whitney statistic is 0.54, the interpretation being that there is a 54 % probability that the next randomly selected patient (or, more correctly, one of a pair of patients) on therapy will improve compared with no therapy.\textsuperscript{41} In the context of un-blinded trials, it is recommended that the Mann-Whitney statistic be reduced by 0.11,\textsuperscript{42} which would suggest a less than 50% overall probability of improvement for SDD.

With respect to sub-groups, for ICU mortality SDD improved (statistically significant) outcome only in the “urgent surgery” group (p = 0.02), whereas for hospital mortality, SDD did not improve outcome in any (“medical” group, p = 0.07), albeit the overall point estimates for all groups demonstrated a favourable impact of SDD. Again, no information regarding potential pathophysiologic mechanisms underlying the observed treatment effect (incidence of bacteraemia, respiratory infection) were offered and although ICU length of stay was decreased by SDD, mechanical ventilation time was not reported.

The primary end-points of the study were three: acquired colonisation by any resistant strain (p = 0.001), ICU (p = 0.002) and hospital mortality (p = 0.02). These end-points were reported simultaneously without statistical adjustment; this is problematic.\textsuperscript{44,45} A number of adjustment procedures are available; the most well-known and simple (but conservative), the Bonferroni, would yield adjusted p values (above) of 0.003, 0.006 and 0.06 respectively.

Conclusions

A number of substantive paradoxes and contradictions have been exhibited within the SDD paradigm. The problematic question of the increase in the incidence of resistant organisms due to SDD has not been canvassed, but recent critiques\textsuperscript{3,4,8} and cautions\textsuperscript{9} regarding SDD,
and a primary end-point of the de Jonge et al trial,2 proceeded from this perspective. The accompanying editorial3 to the de Jonge et al trial, posed the question: “SDD: for everyone, everywhere?” and replied that SDD “worked” (i.e. reduced mortality) but was less certain about its application to “all environments”. An alternate question may be: “What is the future of SDD”, to which a reasoned response may be: “Still uncertain”.

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Immunonutrition - a proven treatment for perioperative patients or an interesting idea in search of data?

There is evidence that immunonutrition (i.e. nutrition designed to modulate or enhance immune function) might confer benefit to major surgery patients, especially when it is administered pre-operatively. Two recent clinical trials1,2 and a meta-analysis3 support this conclusion. It can decrease the incidence of infective complications and may reduce the post-operative length of stay. Unfortunately, its effect on reducing mortality has yet to be proven. The issue is also confounded by a concern that the inclusion of arginine in the immunonutrition formulation may be detrimental in some patients (particularly those with established sepsis)4 a factor that has caused the Canadian Critical Care Clinical Practice Guidelines Committee to advise against the use of arginine rich immunonutrition for critically ill patients.5

Our understanding of the immune system remains limited, but we do know that the immune response is immensely complex and interrelated. We have very few drugs with which to influence the system (with the exception of immunosuppressives) and consequently clinicians have little appreciation of the possibilities and complexities associated with its modulation. If immune dysfunction is of such great importance it is reasonable...
to wonder why pharmaceutical companies have not marketed drugs designed to enhance this system.

We are confronted by two fundamental questions;
1) which changes in the immune system are clinically important, and
2) what additives should be used to alter the immune system to benefit the patient?

Into this void has entered dietary immunomodulation, not only for humans but for aging cats (Eukanuba Senior Cat Formula claims that it 'provides nutritional support against the effects of the natural aging process on the immune system'). Given this background it is not surprising that clinicians have been cautious in their adoption of this therapy. Moreover, as nutritional products do not come with the price tag of many of the recently marketed pharmaceuticals, it is unlikely that there will be significant commercial backing for major research in this area. Indeed, one company (Nutricia) has discontinued its immune modulating product (Stresson), suggesting that nutritional modulation of the immune system is not, or is no longer, an area of high interest.

However the story is far from over, a functioning immune system is important and interest will return. In the interim we need to reflect on exactly what we are trying to achieve. Questions of mechanism are seen to be peripheral in the context of evidence-based medicine where efficacy in clinical trials is the goal. However, failure to appreciate exactly what one is trying to achieve, or failure to select a patient group in which an immune change is likely to deliver benefit, will generate trials that are doomed to deliver confusing or negative results.

In this issue of Critical Care and Resuscitation O’Callaghan and Beale explore immunological effects that occur after major surgery, and which immunonutrition products have been reported to influence outcomes. Inevitably, they raise more questions than they answer. For example,

1. What are the immunological changes provoked by surgery we wish to alter by dietary means?
2. What degree of change is clinically significant (rather than statistically significant)?
3. What immunological changes are normal adaptations to stress (and thus are potentially beneficial) and what changes are detrimental?
4. Are the undesirable immunological changes (as surrogate endpoints) clearly associated with morbidity or mortality?
5. Are the important changes similar in all patients or are some patients more predisposed (e.g. the malnourished patient)?
6. What is the dose effect of treatment (i.e. is there a minimum effective dose, do some patients exhibit resistance to whatever dose is administered)?

We fall at the first fence. What is, or are, the immunological changes we wish to alter? Is it preservation of gut lymphoid tissue, or is it IgA secretion, or phagocytosis, or respiratory burst, or IL-2 receptor levels or delayed hypersensitivity or lymphocyte count or CD4/CD8 ratios? With a better understanding of the basic immune processes, the design of a clinical trial would be relatively straightforward and, following decisive results, widespread clinical application of a valuable treatment would be swift.

However, we should not be too critical, failure to identify a group that can be clearly predicted to show most benefit with treatment has probably confounded numerous intensive care trials, including major sepsis and mechanical ventilation studies.

For the moment it is reasonable for surgeons and peri-operative services to consider pre-operative immunonutrition for unwell patients listed for high risk surgery, particularly those who are identified as malnourished. This approach is unlikely to be associated with harm and may result in benefit. It may also reduce subsequent intensive care complications and lead to a shorter hospital stay.

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Illicit drugs – The dark before an Australian DAWN?

The social, economic and health costs associated with alcohol and other drug use in Australia are profound. Each year, the use of alcohol, tobacco and illicit drugs accounts for more than one in six deaths. It was estimated in 1998 that, either directly or indirectly as a result of harmful drug use, approximately 22,500 Australians would die and over 175,000 would require hospitalisation. Despite this, there are surprisingly little data collected on the impact of illicit drugs on the health system, and no comprehensive mechanism for the recording of information concerning drug-related attendances and admissions to hospitals in Australia.

Historically, the ‘war on (illicit) drugs’ has tended to focus on limiting the drug supply through measures such as reducing access to raw materials or law enforcement. The National Illicit Drug Strategy was launched in 1997, with a significant proportion of the subsequent $1 billion in Australian Commonwealth funding being committed to supply reduction initiatives. Despite this, it is estimated that these measures stop only 10% of the supply, with enforcement efforts having little impact on the street availability of illicit drugs in the major cities of Australia. As expressed by Milton Friedman, ‘market forces will inevitably overcome prohibition when dealing with substances for which there is a plentiful supply and a willing market’. Television footage of illicit drug seizures are interesting and politically rewarding, but give us little scientific evidence to the extent of the problem in Australia and the impact upon individuals and the health system.

More recently, increasing attention has been paid to demand-reduction strategies, with the need to address underlying social and cultural risk factors for illicit drug use, as well as the development of targeted, credible and relevant education campaigns for those at risk. However, it has become increasingly apparent that, despite the importance of measures addressing supply and demand, illicit drugs have continued to have an enormous impact on our society.

In 2001, Australia was reported to have the highest level of abuse of the amphetamine, ecstasy, in the world, as well as ranking second only to Thailand in the use of methamphetamine. Accordingly, as recognised in the National Drug Strategic Framework (1998/9 to 2003/4) and a subsequent commissioned evaluation, we need to develop a range of targeted harm-reduction strategies designed to reduce the impact of drug-taking on the individual and the community. While not condoning an intrinsically dangerous practice, if we accept that individuals are going to continue to use illicit drugs for recreational purposes, we need to look at ways in which this may be done safely, reducing the harm that these individuals do to themselves and the community.

In order to effectively target and employ such harm minimisation techniques, it is important to obtain accurate epidemiological information and identify patterns and trends in drug usage. However, Australian data relating to the use of illicit drugs are limited, and much that is available is based on self-report and personal interview. It is worth noting that the major sources of information on illicit drug use cited by the National Drug and Alcohol Research Centre in their Australian Drug Trends annual reports, are through the Illicit Drug Reporting System, of which there are three components; 1) interviews with injecting drug users, 2) interviews with key informants and, 3) analysis of indicator data sources such as the National Drug Strategy Household (NDSH) Survey and data derived from Police seizures and arrests, and from opioid-related deaths.

The 2001 NDSH Survey reported that 16.9% of Australians interviewed admitted to using illicit substances in the past 12 months, including over 35% of those between 20 and 29 years of age. Among the individuals over 13 years of age, 3.9% admitted to having driven a motor vehicle while under the influence of illicit drugs in the past 12 months, while 2.3% had attended work. The survey also reported that approximately 6% of interviewees had suffered an injury (non-self-inflicted) as a result of an alcohol or other drug-related incident in the preceding year.

The limitations of data such as these, which rely heavily upon self-report, are obvious. Of concern, there are relatively few other data sources available to help us understand drug abuse and, in particular, the impact on the individual and public health. The new phase of the National Illicit Drug Strategy ‘Tough on Drugs’ campaign announced in the 2003/4 Federal Budget, included funding for the ‘establishment of illicit drug reporting and information databases to create a system for monitoring demand for, and usage of, illicit drugs in Australia, and the harms arising from use’. It is envisaged that they will ‘facilitate evidence-based decision making and act as a strategic early warning system to alert governments to emerging drug problems’. However, the databases that are used as examples, are the National Drug Household Survey, the National Coronial Information System, and the National Illicit Drug Reporting System.

The paper by Crétitos and Parr in this issue of Critical Care and Resuscitation is a useful analysis of drug-related admissions to an Intensive Care Unit in...
single hospital in New South Wales. They conclude from their data that drug-related problems, whether related to the recreational use of illicit drugs or self-poisoning, not only account for a significant number of admissions to their Unit, but that this cohort have a high rate of subsequent functional impairment and dependence upon medical care on discharge.\textsuperscript{13} Although providing an interesting snapshot for one Unit, there is a clear need to collect data exploring the issue on a grander scale to enable us to accurately define the scale of the problem, and the specific areas towards which we should be directing our limited health resources.

In the United States, a national data system that collects information on drug-related visits to emergency departments was established in 1972. For the past eleven years, responsibility for the operation of this Drug Abuse Warning Network (DAWN) has been taken by the Substance Abuse and Mental Health Services Administration of the US Department of Health and Human Services. A broad range of epidemiological and health data and trends are collected, and published biannually. It does not measure the prevalence of drug use in the community, the untreated health consequences of drug use, or the impact of such use on health care settings other than hospital emergency departments, but at least it provides valuable information on some of the health consequences as well as identifying emerging problems. It now uses a probability sample of hospitals, and in 2002, 437 hospitals participated, with data submitted on 189,616 drug abuse episodes. In that year, it estimated that just over 670,000 emergency department visits related to drug use across the country.\textsuperscript{12}

It is far more likely that people using illicit drugs will access primary health care or acute care in a hospital setting at some point, either as a direct result of their drug use or for a non-drug related reason, rather than using the specialist drug treatment sector.\textsuperscript{13} Cretikos and Parr highlight the unique opportunity that a hospital admission, and particularly one to an intensive care unit, presents to affect perceptual or behavioural change when an individual is perhaps at their most receptive. In a prospective, randomised, controlled trial in a population of patients treated in a Level 1 trauma centre, Gentilello et al, demonstrated significant decreases in drinking at 12-month follow-up in those patients receiving a single in-hospital motivational intervention, compared with controls. In addition, they had a 47% reduction in injury episodes requiring medical care, and fewer traffic violations, including impaired-driving violations.\textsuperscript{14} In a review of alcohol interventions in trauma centres, Gentilello et al, concluded that these centres should become ‘major sites for the incorporation and integration of community agencies available for treating patients with alcohol problems, and screening, intervention and referral should be routine’.\textsuperscript{15} It would appear appropriate and desirable that this philosophy be applied to all patients presenting to hospital with drug-related problems.

Although it is only one aspect of the health response to the issue of illicit drug use, the hospital system has a crucial role. It would appear most unlikely that a ‘war on drugs’ will ever be won. As a profession, we need to ensure that we continue to explore and improve harm minimisation and intervention techniques in which we may play an important part. To assist that process, we need to have ready access to useful and current data on the impact that illicit drugs are having, not only on the health of individuals, but also on the hospital and health systems. The Commonwealth Government needs to make a commitment to the establishment of a process by which these data can be collected, analysed and acted upon in a timely fashion.

It is difficult to fight a war without knowing what you are aiming at.

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Although we understand that transplanting health care from primary to secondary care makes economic sense, the hope is that earlier presentation of patients to hospital emergency departments who present with acute coronary syndrome will lead to improved outcomes for patients, the gain from which will be realised in the longer term through the expected reduction in mortality and nonfatal events.

Mortality and nonfatal events following acute myocardial infarction: beyond concept and into practice

The societal burden of coronary heart disease remains high, despite improvements in our understanding of the pathogenesis of acute coronary syndromes. Approximately 40% of all people in Western society will die as a consequence of atherosclerotic diseases. Much of this mortality in due to acute myocardial infarction, and one of our main goals in this setting to obtain rapid restoration of normal flow in what is usually an occluded epicardial coronary artery due to atherothrombosis. Although we understand that the final pathway in coronary occlusion of acute myocardial infarction is usually thrombotic, even our best thrombolytic regimes have been imperfect in restoring coronary flow in all patients. Immediate percutaneous coronary intervention (PCI) now emerges as a potential new “gold-standard” in the management of acute myocardial infarction. A recent meta-analysis of 23 randomised controlled trials confirmed that immediate PCI versus thrombolytic therapy was associated with statistically significant reductions in mortality (7% vs 9%), nonfatal reinfarction (3% vs 7%), stroke (1% vs 2%), and the combined end point of death, nonfatal reinfarction, and stroke (8% vs 14%).

However, a number of important caveats require consideration before we can extrapolate such data to all patients with acute myocardial infarction. In brief, there remain at least 5 active issues that require careful consideration in identifying the best revascularisation strategy.

One, time from onset of symptoms. Although there is a clear incremental benefit of reduced “door-to-needle” times of thrombolytic therapy in acute myocardial infarction, this benefit seems less clear with PCI. Indeed, the benefits of PCI over thrombolytic therapy emerged when symptoms had lasted for longer than 3 hours in one study, and comparable results were noted for each treatment group within this 3 hour window. This may reflect the crucial period post coronary occlusion whereby the occluding coronary thrombus is most amenable to revascularisation with thrombolytic therapy and rapidly organises such that it is less readily lysed with passing time. Infarct PCI, on the other hand, appears to be less influenced by time since coronary occlusion in restoring coronary flow. However, a more recent trial has shown a consistent benefit of PCI versus thrombolytic therapy, irrespective of the time from onset of symptoms.

Two, options available at hospital of initial presentation. There are obviously going to be greater delays in accessing a cardiac catheterisation lab if a patient presents to a hospital at a regional centre without such facilities initially. Studies to date have lent support to the concept that when a well designed network is established that allows rapid transfer of patients with acute myocardial infarction to tertiary referral centres with cardiac catheterisation facilities, that primary PCI is superior to thrombolytic therapy. A recent meta-analysis of 6 trials with over 3,700 patients showed that there was a statistically significant reduction in reinfarction by 68%, in stroke by 56% and a trend toward reduction in all-cause mortality of 19% (p = 0.08) with transfer for PCI versus thrombolytic therapy. It is important to remember that most patients were transferred in under 2 hours.

Three, interventional operator and centre experience. There is data to support the concept that both operator
and referral centre experience are important determinants of outcome in PCI in both the elective and acute myocardial infarction setting, and it is considered by some that establishment of dedicated “infarct centres” should be utilised to optimise patient care. A

Four, patients with haemodynamic compromise. Most of the trials to date comparing primary PCI and thrombolytic therapy in patients with acute myocardial infarction have excluded patients with haemodynamic compromise. However, a recently published aspect of the SHOCK trial reported that patients randomised to early revascularisation with early PCI or coronary artery bypass surgery in the setting of AMI and haemodynamic compromise had improved mortality only if the revascularisation was successful in restoring normal coronary artery flow. 7

Five, appropriate adjunctive therapy. We now have significant data to support the role of aggressive antiplatelet therapy in the form of IIb/IIIa receptor inhibitors in patients undergoing primary PCI for acute myocardial infarction. A 9 However, the role of other adjunctive management strategies beyond this, such as the role of the Intensive Care Unit and haemodynamic support measures have not been significantly investigated.

The article by Delaney et al., 10 in this edition of Critical Care and Resuscitation addresses a number of these active issues. They present observational data from their single centre experience of an invasive approach to the management of acute myocardial infarction. Different groups included patients presenting primarily to their institution as well as patients transferred from elsewhere, and included patients being treated with PCI as a “primary” therapy and as a “rescue” procedure for presumed failed thrombolysis. Only patients with pulmonary oedema or cardiogenic shock were selected. The authors conclude from their results that “an early invasive revascularisation strategy for critically ill patients with acute myocardial infarction is associated with good outcomes, although this requires the input of specialist ICU resources.” Although, the many limitations of a non-randomised database analysis of a single centre’s experience are acknowledged by the authors, they do provide a local framework by which such aforementioned “infarct centres” can be fashioned.

However many questions remain unanswered and clearly more data is required. It is unclear what role the Intensive Care support played in improving outcomes in this heterogeneous patient group. Although an obvious and plausible rationale exists for the involvement of the Intensive Care Unit it requires further investigation to tease out the component inputs of the whole invasive management strategy on patient outcomes. Still to date, no clear evidence exists that definitively supports the concept of “rescue” PCI for failed thrombolysis, although a few small studies seem supportive. 11 This in part reflects the limitations of clinical and electrocardiographic indices for defining “reperfusion”. The concept of “facilitated” PCI, whereby early administration of a thrombolytic and/or a IIb/IIa receptor inhibitor is immediately followed by invasive coronary angiography with a view to angioplasty and stenting, is being actively studied, and may be a future framework for managing acute myocardial infarction. A 8 We also still have no local data on the cost effectiveness of these early invasive strategies.

As time passes, evidence is mounting that PCI should be a central strategy in the management of acute myocardial infarction and that this concept is relevant to both metropolitan and regional centres within appropriate limits. What we now require is a clearer picture of exactly how, rather than if, we should be implementing such services, and multi-disciplinary approaches coordinating the services of many different teams as described by Delaney et al., 10 will be crucial to the success of such programs.

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