

# A new paradigm for treating infections: “go hard and go home”

Jeffrey Lipman and Rob Boots

The incidence of sepsis exceeds that of colon cancer, breast cancer, and AIDS, with mortality rates of 30% for mild to moderate sepsis and up to 82% for severe sepsis and septic shock.<sup>1</sup> In a prospective, 3-month study conducted by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), 12% of patients admitted to intensive care units in Australia and New Zealand had sepsis.<sup>2</sup> Other countries seem to have a higher incidence than Australasia.<sup>3,4</sup> Many more patients develop sepsis while in the ICU, especially those with multiple trauma.

ICUs often harbour the most resistant organisms.<sup>5</sup> In many ICUs around the world, serious infections with gram-negative bacteria resistant to most, if not all, antibiotics are occurring. Typical organisms responsible are *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and occasionally *Stenotrophomonas maltophilia*. However, even other commonly isolated organisms, such as *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae*, are being found to have multiple resistance mechanisms, including some that lead to resistance to all antibiotics, including the carbapenems. We have referred to these strains as “XDR” (extreme drug resistance).<sup>5</sup>

The pharmaceutical industry has not responded to the threat of XDR gram-negative bacilli. Organisms such as *P. aeruginosa* are an intrinsically more difficult target for drug discovery teams than gram-positive organisms. Furthermore, novel agents may have unforeseen toxicities or pharmacokinetic hurdles that may make commercialisation more difficult. Therefore, it is not certain that the costs of discovering new antibiotics active against the most resistant hospital pathogens will be recouped in sales, and antibiotic development has dried up.<sup>6</sup> This is illustrated by the Infectious Diseases Society of America embarking on a campaign of “Bad bugs, no drugs”.<sup>7</sup>

It behoves us to use antibiotics judiciously and appropriately.

## Getting it right the first time

There is now significant evidence that correct antibiotic choices will save more lives than virtually all other ICU therapies.<sup>8-19</sup>

Examining ventilator-associated pneumonia, Rello et al determined that inadequate initial therapy was associated

## ABSTRACT

There is now significant evidence that initial use of the correct antibiotic saves more lives than virtually all other intensive care therapy. This means covering all possible causative organisms with the initial empirical choice. For nosocomial sepsis, broad-spectrum antibiotics must be started as soon as the relevant samples have been taken for culture, with de-escalation of therapy targeted to the causative organisms when results and susceptibilities are available.

There is an international trend to use shorter antibiotic courses. *Pseudomonas pneumonia* probably needs a 7–10 day course. In our ICU, provided the infection source is controlled, we seldom use antibiotic courses longer than 7 days.

Evaluation of the kill characteristics of antibiotics in experimental models suggests that different classes of antibiotics should have different dosing regimens. For  $\beta$ -lactam antibiotics, the kill characteristic is almost entirely related to the time that tissue and plasma levels exceed a certain threshold, with no significant post-antibiotic effect, particularly against gram-negative organisms. Kill characteristics of other antibiotics, such as aminoglycosides, relate to adequate peak concentrations and a significant post-antibiotic effect.

Clinically, these kill characteristics translate into the need for appropriate doses of the various antibiotics in patients with sepsis. We have shown that some patients with normal serum creatinine levels have very high creatinine clearance rates; in ICU patients with sepsis, blood pressure and tissue perfusion are maintained with large fluid loads and inotropic agents, thereby raising creatinine clearance. High clearances produce low trough concentrations of antibiotic, with important implications for underdosing and the development of antibiotic resistance.

The new paradigm for treating sepsis, particularly nosocomial sepsis, is: get it right the first time, hit hard up front, and use large doses of broad-spectrum antibiotics for a short period.

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with a mortality of 37% versus 15% in patients who received appropriate initial antibiotic cover.<sup>10</sup> In a study of 132 mechanically ventilated patients, Luna et al showed

that patients who received inadequate treatment, as determined by bronchial alveolar lavage (BAL) culture, had a mortality of 91%, compared with 38% in the adequately treated group.<sup>11</sup> Late adoption of adequate therapy did not decrease the mortality rate, suggesting that early treatment was a key factor. Similarly, a study from Spain found an attributable mortality of 24.7% in patients with ventilator-associated pneumonia managed initially with inadequate antibiotics, compared with 16.2% in those whose initial treatment was adequate.<sup>12</sup>

Garnacho-Montero et al examined 406 patients who were admitted to their ICU with a diagnosis of sepsis, and determined that the risk of death in medical patients who received initial inadequate antimicrobial cover was eight times higher than the risk in those who received adequate cover.<sup>13</sup> Valles et al studied 339 patients from 30 ICUs, finding a 30% mortality reduction with adequate (expressed as “correct”) antibiotics in bloodstream infections and almost a 60% reduction in patients with APACHE scores > 24.<sup>14</sup>

Kollef and colleagues showed that adequate antibiotic therapy could decrease hospital mortality from 52% (inadequate therapy) to 12%.<sup>15</sup> In another study by this group, Ibrahim et al showed a decrease in hospital mortality among patients with bloodstream infections from 62% to 28% with adequate antimicrobial treatment.<sup>16</sup> MacArthur et al and Harbarth et al retrospectively investigated “adequate” and “inadequate” antibiotic therapy in two large mediator trials in 2614 patients and 900 patients, respectively.<sup>17,18</sup> The first trial showed a 10% absolute crude mortality difference between the two groups, and the second reported a 15% decrease in 28-day mortality with adequate antibiotic coverage.

A prospectively designed trial of 920 patients from hospitals in Israel, Germany and Italy used a priori definitions of adequate versus inadequate therapy; 319 patients received inappropriate therapy, for a mortality rate of 20%.<sup>19</sup> In the group who received adequate therapy, mortality was 11%.

These data all strongly suggest that early correct antibiotic treatment may have a greater impact on mortality than therapies such as activated protein C, low tidal volume ventilation, and tight glucose control.

Not only is it important to administer the “correct” antibiotic, it is also important to administer it as soon as possible. Kumar et al showed a linear increase in mortality when antibiotic administration was delayed in patients with septic shock.<sup>20</sup> Lodise et al showed a less pronounced, but still marked, effect when antipseudomonal therapy was delayed after blood had been taken for culture in patients with *Pseudomonas* bloodstream infections.<sup>21</sup>

To allow rational antibiotic choices without automatically always starting with the broadest antibiotic cover available, it can be useful to know which organisms colonise the local clinical environment and their antibiotic sensitivities.<sup>22</sup> ICUs differ in their commonly grown organisms, which in turn differ in their antibiotic sensitivities, even within the same hospital.<sup>23</sup>

Implicit in this strategy of starting broad-spectrum antibiotics up front is the concept of de-escalation to narrower spectrum antibiotics as soon as culture results and sensitivities are available. We will not specifically discuss this here but refer readers to two recent reviews on de-escalation.<sup>24,25</sup>

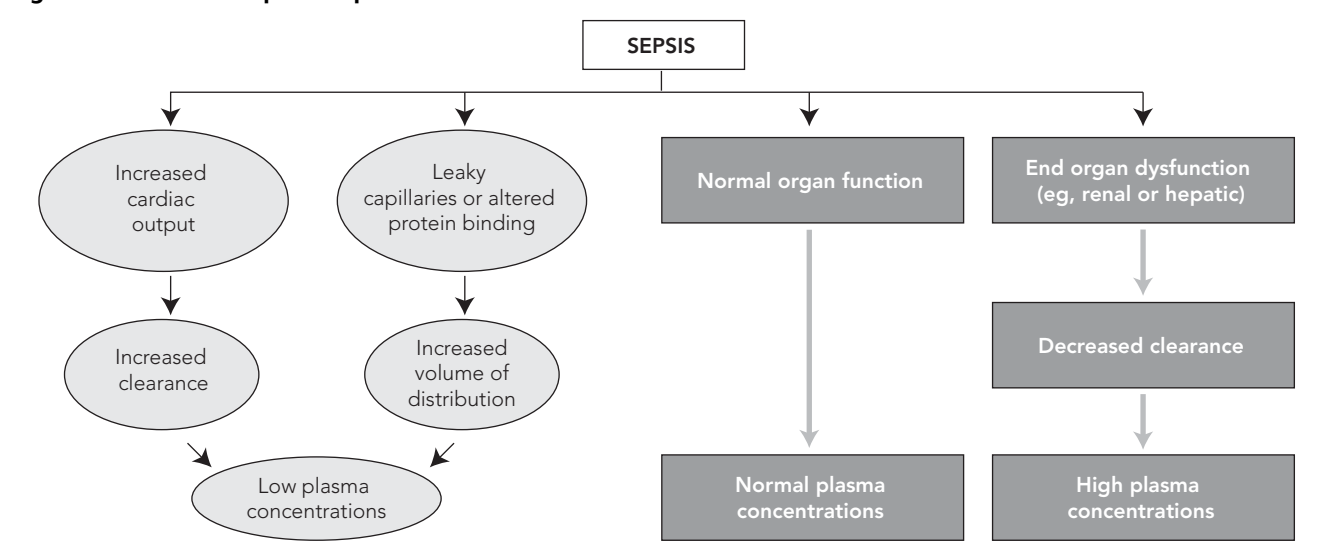
### Duration of antibiotic therapy

Dennesen et al investigated the time to resolution of signs of infection in a group of 27 patients receiving antibiotics for ventilator-associated pneumonia.<sup>26</sup> They found that patients’ temperature, white cell count and oxygenation had all improved by Day 6–8 of therapy.

In a single-centre study by Singh et al, a short course of ciprofloxacin was compared with prolonged antibiotic use.<sup>27</sup> Patients with a Clinical Pulmonary Infection Score (CPIS) ≤ 6 (implying low likelihood of pneumonia) were randomly allocated to receive either ciprofloxacin monotherapy or other standard antibiotic therapy, with re-evaluation after 3 days. Ciprofloxacin was discontinued if CPIS remained ≤ 6. Antibiotics were continued beyond 3 days in 90% (38 of 42) of the patients in the standard antibiotic therapy group compared with 28% (11 of 39) in the ciprofloxacin group. Mortality and length of ICU stay did not differ despite the shorter duration of antimicrobial therapy. Antimicrobial resistance, superinfections, or both, developed in 15% (5 of 37) of patients in the “short course” group versus 35% (14 of 37) in the “prolonged” arm.

Such data prompted Chastre et al to compare the outcome of therapy of a “short” (8-day) versus “long” (15-day) course of antibiotics.<sup>28</sup> Their prospective, randomised, multicentre trial enrolled patients with microbiologically proven ventilator-associated pneumonia (by BAL, protected specimen brush or sampling catheter) who were receiving appropriate initial empirical treatment. They unblinded the study at Day 8 to stop therapy in the “short” arm. Endpoints were mortality at Day 28, recurrence of pulmonary infection and antibiotic use. There were no differences in outcomes. However, if patients did have a recurrence of pneumonia, *Pseudomonas* spp. were the most common causative organisms.

**Figure 1. Effects of sepsis on plasma antibiotic concentrations**



Although many intensive care patients have normal or decreased clearance of drugs (right side of figure), some with the pathophysiological changes of sepsis, such as increased cardiac output and increased volume of distribution, have low plasma drug concentrations. (Adapted from Roberts and Lipman.<sup>32</sup>)

## Antibiotic dosing and underdosing

### Kill characteristics

Evaluation of the way in which antibiotics kill bacteria (kill characteristics) in experimental models suggests different dosing intervals for different classes of antibiotics.<sup>29</sup>

For example,  $\beta$ -lactams have a slow continuous kill characteristic.<sup>29,30</sup> This contrasts with the concentration-dependent kill of aminoglycosides:<sup>29,31-33</sup> experimentally, a high peak concentration of an aminoglycoside antibiotic provides a better, faster killing effect on standard bacterial inocula. This has now been clinically translated into single daily dosing, more correctly termed extended-interval dosing.<sup>31-34</sup>

In-vivo animal experiments have shown that the killing effect of  $\beta$ -lactam antibiotics is almost entirely related to the time for which levels in tissue and plasma exceed a certain threshold.<sup>29,30</sup> These antibiotics lack a significant post-antibiotic effect, particularly against gram-negative organisms. Furthermore, once the concentration of antibiotic falls too low, any bacteria remaining in the inoculum proliferate almost immediately.<sup>29,30,35-38</sup>

It is argued that maintaining serum levels above the minimum inhibitory concentration (MIC) for only 60% of the dosing interval may not be ideal for two reasons. Experimental studies showed that maximum killing of bacteria occurred at antibiotic concentrations 4–5 times the MIC.<sup>36,37</sup> When antibiotic concentrations fell below this threshold, bacterial growth immediately resumed.<sup>36-38</sup> Mouton et al showed experimentally that a sustained level of

ceftazidime around or slightly above the MIC is not high enough to maintain efficacy any better than one (8h) dosing interval.<sup>36</sup> When sustained concentrations more than four times the MIC are used, continuous administration becomes more efficacious than intermittent dosing. Although this result may a function of continuous infusions not having high concentrations, most believe it supports the conclusion that low doses for a prolonged time are problematic.

Our view is that, in the absence of any post-antibiotic effect, the plasma concentration of a  $\beta$ -lactam antibiotic should exceed the MIC for the respective organism for 100% of the dosing interval. It is not surprising that dosing regimens of  $\beta$ -lactam antibiotics are currently being re-evaluated.<sup>30,39,40</sup>

### Low antibiotic levels and bacterial exposure

In-vitro and in-vivo data are now emerging that suggest inappropriate antibiotic dosing may be contributing to the increasing rate of antibiotic resistance. This is particularly the case for fluoroquinolones, although data on other antibiotic classes are emerging.

Fantin et al used an experimental model of *P. aeruginosa* aortic endocarditis in rabbits treated with ceftazidime and ceftazidime to propose that bacterial resistance to  $\beta$ -lactams can develop when antibiotic concentrations fall below the MIC for more than half the dosing interval.<sup>35</sup>

Tam et al used an in-vitro hollow-fibre infection model to show that a ratio of trough concentration to MIC >6.2

could suppress the development of resistant *P. aeruginosa* subpopulations.<sup>41</sup>

### Increased creatinine clearance

Typically, acute elevations in serum creatinine concentration are interpreted as renal dysfunction, particularly when combined with oliguria, suggesting a reduced glomerular filtration rate. The need to reduce the dose of many drugs in this setting to avoid toxicity is generally accepted, particularly for renally eliminated drugs with a narrow therapeutic index, such as aminoglycosides. A raised serum creatinine concentration commonly triggers the clinician to decrease the dose of these renally eliminated drugs.

On the other hand, a “normal” serum creatinine concentration is generally assumed to equate to normal renal function, and little attention is paid in this setting to modifying drug dosages from those routinely recommended. However, this interpretation of renal function may not always be correct. Some patients with a normal serum creatinine concentration have some renal dysfunction, notably the elderly or malnourished. To further complicate interpretation, a normal serum creatinine concentration may represent higher than expected glomerular filtration rates. In this setting, readjustment of standard dosing regimens to include more frequent or higher doses of renally cleared drugs will be necessary.

Currently, this phenomenon (which we recently termed augmented renal clearance [ARC]) is poorly described, and increasing drug doses in response to higher clearances is seldom considered<sup>42,43</sup> (Figure 1 and Figure 2). However, in terms of maintaining therapeutic concentrations, an increase in dose or frequency may be clinically appropriate.<sup>43</sup>

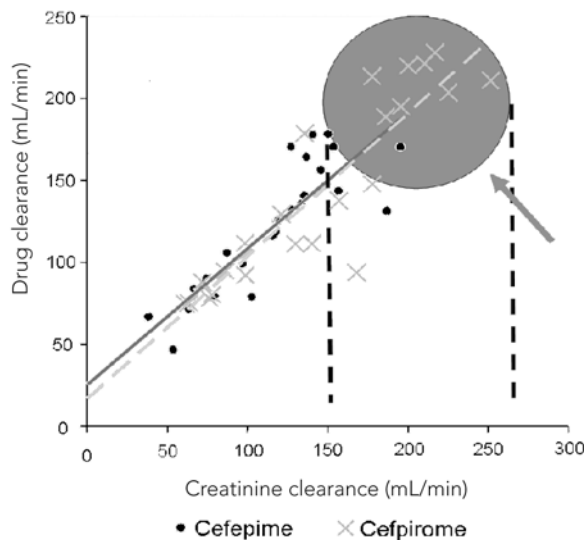
Fuster-Lluch et al reported increased creatinine clearance (defined as  $>20\text{ mL/min}/1.73\text{ m}^2$ ) in 17.9% of patients on the first morning of admission to the ICU, and in 30% during the first week in the ICU.<sup>45</sup> Patients with ARC were primarily postoperative or had multiple trauma. In these settings, volume loading, use of vasoactive agents, and the underlying systemic inflammatory response syndrome are likely to result in high cardiac output, which contributes to elevated renal blood flow.<sup>46,47</sup> Animal data also suggest increased clearances in the setting of experimental sepsis.<sup>48</sup>

The impact of noradrenaline on renal blood flow has been debated in the literature,<sup>49-52</sup> with recent experimental animal data showing that it increases renal blood flow,<sup>53</sup> particularly in states of generalised vasodilation.<sup>54</sup>

It is not surprising then to find low trough concentrations of renally cleared antibiotics in such circumstances. In fact, we have demonstrated the close correlation of increased renal clearance and low trough concentrations of cefepime and ceftazidime<sup>44</sup> (Figure 2).

Antibiotic dosing must aim to address not only the bacteria isolated, but also the most resistant subpopulation,

**Figure 2. Drug clearance and effect of creatinine clearance**



The relationship between renally excreted drugs (cefepime and ceftazidime) and creatinine clearance is linear, from low creatinine clearances (left) to high clearances (right). When creatinine clearance is low, renally excreted drugs have low clearances and hence accumulate, necessitating diminishing doses. The important part of this graph is ringed — some intensive care patients have much higher than normal creatinine clearances, up to 250 mL/min. These patients have very high drug clearances, and hence low plasma levels at the end of any dosing period, and require increased antibiotic doses. (Adapted from Lipman et al.<sup>44</sup>)

to prevent the advent of further resistant infections through inadvertent selection pressure of current dosing regimens. Dosing of drugs with time-dependent kill characteristics needs high troughs to avoid poor outcomes and the development of resistance. These data serve to underline the importance of ARC in dosing  $\beta$ -lactam antibiotics in the critically ill, and raises important questions as to the optimal strategy in this setting. Given the time-dependent kill characteristics of this class of antimicrobials and the increased clearances documented in the critically ill, maintaining adequate drug concentrations through more frequent dosing or prolonged infusions is required.

### Conclusions

The new treatment paradigm is summarised in Figure 3. Years ago, we were told to start with penicillin and to keep broad-spectrum drugs for demonstrated treatment failure. Counsel also was for low doses of antibiotics, as they were cost-effective and caused fewer side effects. Lastly, it was emphasised that patients should always finish a 2-week course of antibiotics.

**Figure 3. Change in paradigm for antibiotic use**

Old	New
Start with penicillin	Get it right first time
Cost-efficient low dose	Hit hard up front
Low doses = less side effects	Low dose = resistance
Long courses $\geq$ 2 weeks	Seldom longer than 7 days
<b>Go hard and go home</b>	

The new paradigm for antibiotic treatment, particularly of nosocomial infections, is:

- Cover all (or certainly most) organisms initially — *get it right the first time*;
- Give large doses to prevent underdosing — *hit hard up front*;
- Avoid low doses of antibiotics, which predispose to resistance; and
- With a few exceptions, and provided there is source control, recognise it is seldom necessary to give more than a 5–7-day course.

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