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Global personalization of antibiotic therapy in critically ill patients

Dagan O Lonsdale [ID][a,b] and Jeffrey Lipman[c,d,e]

aDepartment of Clinical Pharmacology, St George's, University of London, London, UK; bDepartment of Critical Care, St George's University Hospitals NHS Foundation Trust, London, UK; cDepartment of Intensive Care, Royal Brisbane and Women's Hospital, Brisbane, Australia; dUniversity of Queensland Centre for Clinical Research, The University of Queensland, Brisbane, Australia; eDivision of Anaesthesiology Critical Care Emergency and Pain Medicine, Nîmes University Hospital, University of Montpellier, Nîmes, France

ABSTRACT

Introduction: Sepsis from bacterial infection remains a significant cause of morbidity and mortality. Antibiotic use continues to increase in the community and secondary care. This is driven by the potential benefits to the individual patient of a course of antibiotics. Far less attention is given to the potential adverse effects of antibiotic use in our view. These costs may be significant to both the individual and society.

Areas covered: We review the evidence underpinning the costs and benefits of antibiotic use. We also discuss strategies to personalize medicine in this area that maximize the benefit to cost ratio for patients and society.

Expert opinion: The body's innate immune response to infection is similar to that of other inflammatory insults. Our view is as clinicians we need to differentiate these responses and hence require an accurate method to determine a diagnosis of a bacterial infection and monitor illness severity. Without this, clinicians will continue to prescribe significant volumes of unnecessary antibiotics in cases of non-bacterial inflammatory states.

1. Introduction

Infection in the ICU is common, and 25–30% of adult and up to 12% of pediatric critical care admissions are infection related [1–5]. At any one time, 50% of patients on an adult unit are considered to have an infection and the majority of patients will receive at least one course of antibiotics during a critical care admission, regardless of age [6,7]. Alongside their use in secondary care, antimicrobials are commonly used in the community. In the UK, there are 25 million community prescriptions of beta-lactams and macrolide antibiotics annually, globally this number is in the billions [8,9].

Antimicrobials, as a drug class, have the unique property of an adverse effect that can impact on whole populations who have not taken the drug – the emergence of resistant organisms. Indeed, the ubiquitous use of antimicrobials across the world has led to such widespread drug resistance that the World Health Organization describes the situation as a 'threat to the very core of modern medicine' [10]. There is a need, therefore, to consider both individual and population effects of each antibiotic prescription.

2. Antibiotic effects: benefits and costs

There is little doubt about the potential benefits of antibiotics to the individual with a bacterial infection. Estimates of the impact of penicillin in the 1940s alone are considerable, with reduction in the mortality of pneumonia from 18% to 1% and the drug contributing to a 10-fold increase in survival of wounded

soldiers between the two world wars [11]. Case series of treatment of pneumococcal meningitis reported reduction of mortality from 90% to 3–40% [12–14] following the introduction of penicillin, with similar results for surgical infection [15] and downgrading of pneumonia as a major public health concern [16]. Antibiotic use retains the strongest recommendation for use and highest level of evidence presented for any drug in the most recent surviving sepsis guidelines, alongside fluid resuscitation and vasopressors for refractory shock [17]. Contemporaneous evidence continues to support the mortality benefit of early antimicrobial therapy in the setting of septic shock secondary to bacterial infection [18–20].

Contrary to the emphasis placed on the benefits of antibiotics, far less weight is placed by clinicians on the potential costs of antibiotic use in our view. With rationalization more firmly wedded to the benefits to the wider population than to the individual [21]. This is despite the fact that the impact of resistant organisms on the individual was apparent almost contemporaneously with evidence of antibiotic efficacy. With evidence from the early 1940s establishing failure of prophylactic use of sulfa-drugs in pneumonia, emergence of resistance from under-dosing and treatment failure in individuals in whom resistance developed [16,22,23]. In current practice, infections secondary to multidrug-resistant pathogens are associated with increased hospital length of stay and mortality [24,25]. Infection with multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and extended beta-lactamase and carbapenem-

resistant gram-negative organisms are associated with prior use of antibiotics in individuals [26–29]. Further risk of hospital-acquired infection arises from disruption of commensal flora resulting from antibiotic use, with an increase in the colonization with multidrug-resistant organisms such as *Enterococcus faecium, MRSA, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa,* and *Enterobacter* species (the ESKAPE organisms) [21,30–32]. These findings are not exclusive to adult populations, with similar associations identified in children [33]. Alteration of bacterial flora is rapid. In one study, the emergency of resistant pathogens in intestinal flora occurred after 1 day of antibiotic exposure to imipenem [34]. Direct adverse effects of antibiotics should also be considered. Nephrotoxicity associated with aminoglycosides and glycopeptides are well recognized and countered by clinicians with therapeutic drug monitoring to minimize harm. Other recognized direct toxicities include hepatotoxicity (particularly amoxicillin-clavulanic acid and ceftriaxone) [35], cardiac toxicity (macrolides and quinolones) [36,37] and neurotoxicity (beta-lactams) [38]. Drug-induced fever from antibiotics may confuse the clinical picture in infection [39].

2.1. Global cost

The cost of antimicrobial resistance (AMR) to society is of course considerable. The UK government projects that by 2050, without intervention, ten-million deaths will be attributable to AMR each year around the world. This is more than cancer and diabetes mellitus combined [40]. The projected global economic cost of inaction is 100 trillion US dollars [41]. Physician- and patient-initiated antibiotic use is a significant contributor and antibiotic use continues to rise. In their review of trends in the twenty-first century, Klein et al. identified a 65% increase in antibiotic use globally (2000–2015). While the increase in consumption over this period was more marked in low- and middle-income countries, high-income countries still account for the majority of antibiotic use in humans [42]. Alongside this increase in use is an increase in global prevalence of antibiotic resistance. The World Health Organization particularly highlights *Klebsiella pneumoniae, Escherichia coli, Neisseria gonorrhoeae*, tuberculosis, MRSA and colistin resistant *Enterobacteriaceae* as particular issues in current practice. Noting also that non-bacterial infections such as malaria and HIV are also of concern [43]. The other key issue is antibiotic use in animal and plant species. Drugs used in humans are also used in the production of meat, poultry, fish, and even in the production of fruit [44]. In these sectors, drugs are seldom used for the treatment of a specific infection in a specific animal, but are more likely to be given to a whole herd or population. Either as prophylaxis or treating the herd when one animal is infected. As drug is often administered in feed, variable drug concentrations are achieved in each animal and there is potential for sub-therapeutic dosing and consequent emergence of resistance. Other postulated drivers of AMR include high population density, waste disposal and sanitation methods, and international travel [45,46].

3. Personalization of antimicrobials for the individual

Given the complexities of the cost–benefit relationship of an antibiotic prescription for an individual, there is a strong argument to move toward a more personalized approach. Indeed, our view is that the management of bacterial infection in secondary care has fallen behind colleagues in other fields in this regard. The treatment of cancer has been revolutionized by the more personalized approach of oncologists. Genetic screening identifies at-risk patients, allowing surveillance or prophylactic treatment. The choice of therapeutic drug monitoring is determined by the tumor subtype to maximize efficacy and patient factors to minimize toxicity [47]. HIV is perhaps the most obvious comparator for infectious diseases here, with treatment regimens based on HIV subtype and genetic screening to identify individuals at risk of adverse drug reactions [48].

3.1. Optimizing dose

With the drive to reduce sepsis mortality, it is perhaps unsurprising that the evidence in favor of a personalized approach is most established in critical care. The effect of severe infection on antibiotic pharmacokinetics may have significant consequences for the individual. For example, changes in volume status are common in sepsis. Altered vascular tone and endothelial dysfunction shifts fluid from the vascular to extravascular space [49]. Fluid resuscitation and acute kidney injury may increase total body water content. Therapies such as vasopressors, mechanical ventilation and extra-corporeal circuits will also influence the movement of water.

Hydrophilic antibiotics (Table 1) are particularly sensitive to this shifting fluid, resulting in an increased volume of distribution which may result in plasma concentrations below therapeutic levels [50–54]. Altered organ function may impact clearance pathways. This may lead to reduced clearance in acute kidney injury or augmented clearance in patients with high cardiac output secondary to sepsis [55–57]. Again, this can lead to subtherapeutic antibiotic concentrations for some patients [58]. An international study of serum antimicrobial concentrations in critically ill adults demonstrated that one in seven adult patients fails to achieve therapeutic drug concentrations during therapy, and that failure to achieve these targets reduced chances of successful antibiotic treatment [59]. There are similar findings in studies of antibiotics in children [60].

Once a decision has been made to initiate antibiotics, optimizing dose for efficacy should be as second nature as therapeutic drug monitoring is for safety of antibiotics like the aminoglycosides. Successful treatment with a right dose first-time approach has the potential to minimize exposure to

Table 1. Commonly used antimicrobials and their solubility characteristics.

Hydrophilic antibiotics	Lipophilic antibiotics
Aminoglycosides	Fluoroquinolones
β-Lactams	Macrolides
Glycopeptides	Rifampicin
	Licosamides

Table adapted from McKenzie [61] and Roberts and Lipman [52].

other antibiotics (no need for a second antibiotic) and duration of therapy.

One approach is to optimize drug concentrations in a one size fits all approach, such as the use of prolonged infusions for beta-lactams [62]. The alternative is to optimize for the individual both to improve efficacy (bacterial kill) and prevent emergence of resistance. The widespread utility of computers at the bedside makes this a near rather than remote possibility – for example linking dynamic organ changes and therapeutic drug monitoring data to e-prescriptions or auto-generating warnings to clinicians. Proprietary software continues to be developed to this end [63].

Although this approach is appealing from a theoretical scientific and physiological perspective, there remains a challenge of what the most appropriate pharmacokinetic–pharmacodynamic (PKPD) target is and how to prove personalized PKPD optimization improves clinical outcomes for patients. Most PKPD studies use serum drug concentration as a surrogate for tissue concentrations at the site of infection, a situation that has significant limitations. Alternative sampling techniques such as tissue micro-dialysis catheters or bronchial sampling are appealing from a research perspective but are not practical for implementation into widespread clinical practice.

The question of what antibiotic concentration is efficacious is also of interest. Many PKPD studies target a 'worst-case' scenario, where the causative pathogen has a minimum inhibitory concentration (MIC) at the borderline of what is considered susceptible to treatment with the antibiotic studied. However, in both the community and health-care settings, there will be a range of MICs and the majority of isolates will be well below this PKPD target. For example, amoxicillin/clavulanate has a breakpoint MIC of 8 mg/L (of amoxicillin) for isolates of *Enterobacteriaceae* (i.e. isolates with MICs above this are considered resistant) [64]. PKPD studies of amoxicillin/clavulanate have identified that doses higher than those licensed in the British National Formulary are required to achieve sustained serum concentrations above 8 mg/L for some patients [60,65]. In a recent study by Delgado-Valverde et al. in Spain, approximately 70% of isolates of *Enterobacteriaceae* had an MIC of 4 mg/L or less [66]. Targeting the breakpoint MIC of 8 mg/L is therefore unnecessary for the majority of patients. Clinicians will not know for whom it is necessary until cultured isolates are available so we would argue this remains the most appropriate and pragmatic approach. This strategy makes it challenging to undertake interventional studies of personalized antibiotic PKPD optimization as sufficient numbers of those with higher MIC isolates must be recruited.

3.2. Optimizing duration

Alongside optimizing the dose for an individual, the duration of therapy should be considered. The most recent surviving sepsis guidelines point to a lack of consensus of how and when to de-escalate antibiotics [17]. Evidence from individual infection types points toward favoring shorter rather than longer courses. For lower respiratory tract infection (hospital

and community acquired), 7-day courses appear as efficacious as longer courses [67,68]. A meta-analysis of trials of treatment of pyelonephritis and complicated UTI in adults found that 7-days was equivalent to longer treatment [69] and these findings are replicated in children [70]. Shorter courses also appear as efficacious in intra-abdominal infections where adequate source control is achieved [71].

These all represent population-level approaches, rather than personalized care. It is perhaps unremarkable then that clinicians deviate from guidelines as they manage the individual. A review of therapy duration in primary care in the UK found that a significant proportion of prescriptions for antibiotics have a duration that exceeds those recommended in guidelines [72]. These findings are replicated in reviews of hospital prescribing [73]. This again points toward a systemic bias toward the potential benefits of an antibiotic for the individual ('longer courses *must* be better') over the potential harms to both the individual and society.

There is clearly a need for a more objective method by which clinicians can make decisions on de-escalating care. The potential for biomarkers has been lauded in this regard and they probably remain the most likely route toward an independent measure of the degree of sepsis/severity of infection, thereby affording a clear stopping criterion. Procalcitonin, with or without C-reactive protein, is the most likely, and well-studied, candidate. A recent review by Pepper et al. identified 16 randomized controlled trials (over 5000 patients) that addressed the question of whether procalcitonin-guided de-escalation had an impact on mortality or antibiotic duration [74]. Their meta-analysis found reduced mortality and decreased antibiotic use when procalcitonin guided decision-making but highlighted high risk of bias of this finding. They point to the need for further well-designed research to answer the question as to whether procalcitonin-guided treatment confers a mortality benefit. While it would of course be advantageous to the individual were procalcitonin to improve mortality from an individual sepsis or infection episode, we might argue that there is benefit enough in simply reducing antibiotic exposure with this approach. For both the individual and society. It should be acknowledged that the use of procalcitonin as a biomarker may just provide a prompt to think about antimicrobial de-escalation [17] and studies are not universally positive. In one multi-center study of COPD exacerbations, the use of procalcitonin to guide antibiotic therapy *increased* mortality [75].

4. Personalization of antimicrobials for society

Perhaps the biggest area of conflict between society and individual is in the choice of agent used at the outset of managing an infection. The current surviving sepsis guidelines recommend the use of drugs with a broad-spectrum of activity to cover all likely pathogens in patients with sepsis [17]. The rationale is sound at face value, with evidence that inappropriate antibiotics increase mortality and morbidity [76,77]. One single-center study suggested the number needed to treat with appropriate antibiotics to prevent patient death is 4 [78]. In this retrospective study, as with many others, the determination of whether an antibiotic was appropriate used

the susceptibility patterns of the isolated pathogen. This information is not available to the initiating clinician, highlighting the inherent challenge in selecting an antibiotic to cover all likely pathogens. In addition, studies in sepsis repeatedly demonstrate high 'culture-negative' rates of at least one in three cases [79,80]. In addition, the surviving sepsis guidelines do not define how 'likely' it needs to be for a pathogen to be the causative organism to prompt antibiotic selection to cover it. The cost of inappropriate broad-spectrum antibiotics is similar to the harms associated with antibiotic use discussed previously. Local experience of infective pathogens and antimicrobial susceptibility patterns therefore drives drug choice for patients, with individual patient factors considered (immunodeficiency, age, etc.). Again, the focus here is favored toward greatest efficacy for the most patients. Without a more accurate and rapid way of determining causative pathogens than microbiological sampling and culture, it is difficult to imagine how this methodology could be adapted to reduce population exposure to broad-spectrum antibiotics. With such a high negative culture rate in sepsis (let alone non-severe infection) it is difficult to know how accurate predictions on the likelihood of a particular pathogen are.

Antibiotics are of course only one part of the picture. The sepsis-3 definition of 'life-threatening organ dysfunction caused by a dysregulated host response to infection', does not define how infection should be diagnosed, noting an infection should be 'suspected' to diagnose sepsis [81]. This leaves the clinician with the challenge of determining sepsis from inflammatory response to other pathologies (e.g. trauma or burns) and bacterial from other infections.

5. Diagnostics

The key to unlocking global personalization may therefore lie in improved diagnostics. If we can accurately determine those patients with infection and identify whether this is bacterial or another pathogen, we will be ideally positioned to optimize treatment for the individual and reduce antibiotic exposure for the population. This requires an accurate way to determine whether a pathogen is present, versus an alternative inflammatory condition and whether the pathogen is invasive and infection causing, rather than simply colonizing.

It seems clear that clinicians cannot undertake this task without additional diagnostics. Stevens et al. circulated clinical case vignettes to 43 US hospitals to investigate variability in diagnosis of ventilator-acquired pneumonia [82]. Some hospitals identified 0 cases of pneumonia, others 100%. These findings of significant inter-clinician variability in diagnosing infection are replicated in other infection types in adults and children [83,84].

Procalcitonin is again perhaps the most widely studied biomarker for the diagnosis of infection. One meta-analysis of 30 studies found a sensitivity of 0.77 and specificity of 0.79, with the area under receiver-operator-curve of 0.85 [85]. A recent consensus guide concluded that procalcitonin should be used for the diagnosis of infection. However, their conclusion that likelihood of bacterial infection and illness severity should be incorporated into algorithms suggests procalcitonin remains imperfect as a standalone biomarker [86].

Like other single biomarkers such as CRP, procalcitonin is raised in numerous other conditions, including burns, trauma, surgery, and thyroid carcinoma. The answer may lie in the use of biomarker arrays, where multiple molecules are screened and algorithms used to identify infection [87]. A number of proprietary technologies are in development to this end [88]. Rapid identification of bacterial pathogens would also assist clinicians. Evidence from clinical studies is encouraging. Combined polymerase-chain reaction-mass spectrometry analysis of specimens provides a rapid identification of bacterial pathogens (within 6 h). However, the technique remains imperfect with one in five cases missed in one international study [89], although ongoing development of the technology may improve these results [90].

6. Conclusion and expert opinion

Sepsis remains a significant cause of morbidity and mortality. Understandably, there is a drive to maximize survival for the individual and in critical illness, there is perhaps a tendency to place less value on the long-term consequences of an intervention. For antibiotics, these consequences are significant for both the individual and society. The human body's innate immune response to infection is similar to that of other inflammatory insults. Our view is as clinicians we need to differentiate these responses. There is, therefore, a pressing need for an accurate method to determine a diagnosis of a bacterial infection and monitor illness severity. Without this, clinicians will continue to prescribe significant volumes of unnecessary antibiotics in cases of non-bacterial inflammatory states.

Evolving technology provides us with an opportunity to address these issues. The explosion of research into novel biomarkers of sepsis will hopefully yield a suitable candidate. Presepsin, interleukins (27/6), or CD 64 perhaps show the most promise as stand-alone metrics [91–93]. Although greater accuracy may be found through the use of multiple metrics, with a machine learning approach [94]. This methodology seems to more closely resemble the physician's approach to medicine – diagnosis by looking at the patient and the history of their problem as a whole rather than decision-making based on one symptom. Integrating such advanced diagnostics with electronic health records and prescribing systems has the potential to not only provide precision medicine to the individual but also much more easily allow integration and cross-talk across health-care systems.

Crucial to the adoption of new technologies is the need for clinicians to trust the science behind them [95]. One way to improve confidence is to place technology at the bedside, allowing clinicians to interact directly with the tools that support the decisions they are making for the patient in front of them. This is not a remote possibility. Nearside patient testing of blood is now routine and allows rapid alteration of therapies – glucose monitoring and insulin control perhaps being the most widely adopted. The use of more complex technologies is expanding. Point of care dynamic coagulation analysis is becoming routine, with thromboelastography in emergency and critical care departments across the globe. Miniaturization

of mass-spectroscopy, polymerase chain reaction (PCR) and chromatography technologies offers the potential for more complex nearside testing [96]. Clinicians today take blood samples to nearside technology that gives data on electrolytes, glucose, gas exchange and pH homeostasis. These tests have become central to the decision-making process for patient care. Clinicians of the future will measure biomarkers with bedside mass-spectrometry to diagnose sepsis and predict risk, PCR to identify organisms and antimicrobial susceptibility and patient factors to determine suitable therapies. During treatment, bedside measurements of serum drug concentrations will allow rapid and widespread therapeutic drug monitoring for a greater range of medicines. Integration with prescribing software will then allow dynamic, real-time dose adjustment. This level of precision medicine will benefit the patient by maximizing treatment benefits and, by minimizing overexposure to unneeded antibiotics, will benefit society.

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DL and JL contributed equally to the drafting of the manuscript.

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ORCID

Dagan O Lonsdale 🆔 http://orcid.org/0000-0003-0838-921X

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