# ­­Global personalisation of antibiotic therapy in critically ill patients

## 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 personalise medicine in this area that maximise 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.

## Introduction

Infection in the ICU is common. 25–30% of adult and up to 12% of paediatric 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 Organisation 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.

## Antibiotic effects: benefits and costs

There is little doubt of 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 ten-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 rationalisation 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 multi-drug resistant pathogens are associated with increased hospital length of stay and mortality [24, 25]. Infection with multi-drug 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 colonisation with multi-drug 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 one day of antibiotic exposure to imipenem [34]. Direct adverse effects of antibiotics should also be considered. Nephrotoxicity associated with aminoglycosides and glycopeptides are well recognised and countered by clinicians with therapeutic drug monitoring to minimise harm. Other recognised 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].

### 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 21st century, Klein et al. identified a 65% increase in antibiotic use globally (2000­–2015). Whilst 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 Organisation 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 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].

## Personalisation 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 personalised 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 revolutionised by the more personalised approach of oncologists. Genetic screening identifies at-risk patients, allowing surveillance or prophylactic treatment. The choice of therapeutic is determined by the tumour sub type to maximise efficacy and patient factors to minimise 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].

### Optimising dose

With the drive to reduce sepsis mortality, it is perhaps unsurprising that the evidence in favour of a personalised 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 on 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 1 in 7 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, optimising 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 minimise exposure to other antibiotics (no need for a second antibiotics) and duration of therapy.

One approach is to optimise drug concentrations in a one size fits all approach, such as the use of prolonged infusions for beta-lactams [61]. The alternative is to optimise 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 [62].

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 personalised PKPD optimisation 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 healthcare 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) [63]. 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, 64]. 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 [65]. 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 personalised antibiotic PKPD optimisation as sufficient numbers of those with higher MIC isolates must be recruited.

### Optimising duration

Alongside optimising 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 favouring shorter rather than longer courses. For lower respiratory tract infection (hospital and community acquired), 7–day courses appear as efficacious as longer courses [66, 67]. A meta-analysis of trials of treatment of pyelonephritis and complicated UTI in adults found that 7-days was equivalent to longer treatment [68] and these findings are replicated in children [69]. Shorter courses also appear as efficacious in intra-abdominal infections where adequate source control is achieved [70].

These all represent population level approaches, rather than personalised 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 duration that exceed those recommended in guidelines [71]. These findings are replicated in reviews of hospital prescribing [72]. 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 randomised controlled trials (over 5000 patients) that addressed the question of whether procalcitonin-guided de-escalation had an impact on mortality or antibiotic duration [73]. 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. Whilst 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 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-centre study of COPD exacerbations, the use of procalcitonin to guide antibiotic therapy *increased* mortality [74].

## Personalisation 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 recommends the use of drugs with a broad-spectrum of activity to cover all likely pathogens in patients with sepsis [17]. The rational is sound at face value, with evidence that inappropriate antibiotics increases mortality and morbidity [75, 76]. One single-centre study suggested the number needed to treat with appropriate antibiotics to prevent on patient death is 4 [77]. 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 1 in 3 cases [78, 79]. 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 favoured 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 [80]. 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.

## Diagnostics

The key to unlocking global personalisation 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 optimise 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 colonising.

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 [81]. 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 [82, 83].

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 area under receiver-operator-curve of 0.85 [84]. 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 [85]. 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 biomarker arrays, where multiple molecules are screened and algorithms used to identify infection [86]. A number of proprietary technologies are in development to this end [87]. 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-hours). However, the technique remains imperfect with 1 in 5 cases missed in one international study [88], although ongoing development of the technology may improve these results [89].

## Conclusion and expert opinion

Sepsis remains a significant cause of morbidity and mortality. Understandably, there is a drive to maximise 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 [90-92]. Although greater accuracy may be found through the use of multiple metrics, with a machine learning approach [93]. 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 healthcare systems.

Crucial to the adoption of new technologies is the need for clinicians to trust the science behind them [94]. 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 deparments across the globe. Miniturisation of mass-spectrosocpy, polymerase chain reaction (PCR) and chromatography technologies offer the potential for more complex nearside testing [95]. 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-sepctrometry 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 monitoringfor 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 maximising treatment benefits and, by minimising overexposure to unneeded antibiotics, will benefit society.

## Author contributions and financial and competing interests disclosure

DL and JL contributed equally to the drafting of the manuscript. JL received honoraria for lectures from MSD and Pfizer, and Institutional support from MSD. DL declares no conflicts of interest. DL and JL declare no financial interest or benefit from this work. This work was not funded.

1. Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. Crit Care Med. 2003;31(9):2332-8.

2. Vincent J-L, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med. 2006;34(2):344-53.

3. Intensive Care National Audit &amp; Research Centre (ICNARC): Case Mix Programme 2009 [cited 2016 1/11]. Available from: <https://www.icnarc.org/Our-Audit/Audits/Cmp/Our-National-Analyses/Sepsis>.

4. Schlapbach LJ, Straney L, Alexander J, MacLaren G, Festa M, Schibler A, et al. Mortality related to invasive infections, sepsis, and septic shock in critically ill children in Australia and New Zealand, 2002-13: a multicentre retrospective cohort study. Lancet Inectious Diseases. 2015;15(1):46-54.

5. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med. 2015;191(10):1147-57.

6. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. J Am Med Assoc. 2009;302(21):2323-9.

7. Cantey JB, Wozniak PS, Sánchez PJ. Prospective surveillance of antibiotic use in the neonatal intensive care unit: results from the SCOUT study. Paediatric Infectious Diseases Journal. 2015;34(3):267-72.

8. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. The Lancet Infectious Diseases.14(8):742-50.

9. Prescription Cost Analysis, England 2016 2017 [cited 7/9/2017]. Available from: <https://www.gov.uk/government/statistics/prescription-cost-analysis-england-2016>.

10. World Health Organisation. Global action plan on amtimicrobial resistance. Geneva,.2015.

11. Gust I. Penicillin: World War II infections and Howard Florey. Microbiol Aust. 2014;35(3):177-8.

12. SWEET LK, DUMOFF-STANLEY E, DOWLING HF, LEPPER MH. THE TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH PENICILLIN. J Am Med Assoc. 1945;127(5):263-7.

13. Täuber MG, Sande MA. The Impact of Penicillin on the Treatment of Meningitis. JAMA. 1984;251(14):1877-80.

14. ROSENBERG DH, ARLING PA. PENICILLIN IN THE TREATMENT OF MENINGITIS. J Am Med Assoc. 1944;125(15):1011-7.

15. Zaffiri L, Gardner J, Toledo-Pereyra LH. History of antibiotics. From salvarsan to cephalosporins. J Invest Surg. 2012;25(2):67-77.

16. Podolsky SH. The changing fate of pneumonia as a public health concern in 20th-century America and beyond. Am J Public Health. 2005;95(12):2144-54.

17. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017;45(3):486-552.

18. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589-96.

19. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017;376(23):2235-44.

20. Nauclér P, Huttner A, van Werkhoven CH, Singer M, Tattevin P, Einav S, et al. Impact of time to antibiotic therapy on clinical outcome in patients with bacterial infections in the emergency department: implications for antimicrobial stewardship. Clin Microbiol Infect.

21. Arulkumaran N, Routledge M, Schlebusch S, Lipman J, Conway Morris A. Antimicrobial-associated harm in critical care: a narrative review. Intensive Care Med. 2020;46(2):225-35.

22. Hamburger M, Jr., Schmidt LH, Sesler CL, Ruegsegger JM, Grupen ES. The Occurrence of Sulfonamide-Resistant Pneumococci in Clinical Practice. The Journal of Infectious Diseases. 1943;73(1):12-30.

23. C. P. Herrington. Chemotherapy in Pneumonia New Orleans Med Surg J. 1943;93 348–53.

24. Barrasa-Villar JI, Aibar-Remón C, Prieto-Andrés P, Mareca-Doñate R, Moliner-Lahoz J. Impact on Morbidity, Mortality, and Length of Stay of Hospital-Acquired Infections by Resistant Microorganisms. Clin Infect Dis. 2017;65(4):644-52.

25. Neidell MJ, Cohen B, Furuya Y, Hill J, Jeon CY, Glied S, et al. Costs of healthcare- and community-associated infections with antimicrobial-resistant versus antimicrobial-susceptible organisms. Clin Infect Dis. 2012;55(6):807-15.

26. Tham J, Odenholt I, Walder M, Andersson L, Melander E. Risk factors for infections with extended-spectrum beta-lactamase-producing Escherichia coli in a county of Southern Sweden. Infect Drug Resist. 2013;6:93-7.

27. Ben-Ami R, Rodríguez-Baño J, Arslan H, Pitout JDD, Quentin C, Calbo ES, et al. A Multinational Survey of Risk Factors for Infection with Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae in Nonhospitalized Patients. Clin Infect Dis. 2009;49(5):682-90.

28. Otter JA, Natale A, Batra R, Tosas Auguet O, Dyakova E, Goldenberg SD, et al. Individual- and community-level risk factors for ESBL Enterobacteriaceae colonization identified by universal admission screening in London. Clin Microbiol Infect. 2019;25(10):1259-65.

29. Oztoprak N, Cevik MA, Akinci E, Korkmaz M, Erbay A, Eren SS, et al. Risk factors for ICU-acquired methicillin-resistant Staphylococcus aureus infections. Am J Infect Control. 2006;34(1):1-5.

30. Santajit S, Indrawattana N. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. BioMed Research International. 2016;2016:2475067.

31. Lewis JM, Lester R, Garner P, Feasey NA. Gut mucosal colonisation with extended-spectrum beta-lactamase producing Enterobacteriaceae in sub-Saharan Africa: a systematic review and meta-analysis. Wellcome Open Res. 2019;4:160-.

32. Pendleton JN, Gorman SP, Gilmore BF. Clinical relevance of the ESKAPE pathogens. Expert Rev Anti Infect Ther. 2013;11(3):297-308.

33. Murray MT, Beauchemin MP, Neu N, Larson EL. Prior antibiotic use and acquisition of multidrug-resistant organisms in hospitalized children: A systematic review. Infect Control Hosp Epidemiol. 2019;40(10):1107-15.

34. Armand-Lefèvre L, Angebault C, Barbier F, Hamelet E, Defrance G, Ruppé E, et al. Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. Antimicrob Agents Chemother. 2013;57(3):1488-95.

35. Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. J Antimicrob Chemother. 2011;66(7):1431-46.

36. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart (British Cardiac Society). 2003;89(11):1363-72.

37. Ball P. Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. J Antimicrob Chemother. 2000;45(5):557-9.

38. Bhattacharyya S, Darby RR, Raibagkar P, Gonzalez Castro LN, Berkowitz AL. Antibiotic-associated encephalopathy. Neurology. 2016;86(10):963.

39. Mackowiak PA. Southwestern internal medicine conference: drug fever: mechanisms, maxims and misconceptions. The American journal of the medical sciences. 1987;294(4):275-86.

40. O'Neill J, Resistance RoA, . RoAR, Grande-Bretagne, Trust W. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations: Review on Antimicrobial Resistance; 2014.

41. O'Neill J, Resistance RoA, Trust W. Tackling Drug-resistant Infections Globally: Final Report and Recommendations: Review on Antimicrobial Resistance; 2016.

42. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proceedings of the National Academy of Sciences. 2018;115(15):E3463.

43. World Health Organisation. Antimicrobial resistance 2020, July 31 [Available from: <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>.

44. Van Boeckel TP, Pires J, Silvester R, Zhao C, Song J, Criscuolo NG, et al. Global trends in antimicrobial resistance in animals in low- and middle-income countries. Science. 2019;365(6459):eaaw1944.

45. Vikesland P, Garner E, Gupta S, Kang S, Maile-Moskowitz A, Zhu N. Differential Drivers of Antimicrobial Resistance across the World. Acc Chem Res. 2019;52(4):916-24.

46. Frost I, Van Boeckel TP, Pires J, Craig J, Laxminarayan R. Global geographic trends in antimicrobial resistance: the role of international travel. J Travel Med. 2019;26(8).

47. Jackson SE, Chester JD. Personalised cancer medicine. Int J Cancer. 2015;137(2):262-6.

48. Chaponda M, Pirmohamed M. Hypersensitivity reactions to HIV therapy. Br J Clin Pharmacol. 2011;71(5):659-71.

49. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369(9):840-51.

50. Taccone FS, Laterre PF, Dugernier T, Spapen H, Delattre I, Wittebole X, et al. Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care. 2010;14(4):R126.

51. Sime FB, Roberts MS, Peake SL, Lipman J, Roberts JA. Does Beta-lactam Pharmacokinetic Variability in Critically Ill Patients Justify Therapeutic Drug Monitoring? A Systematic Review. Ann Intensive Care. 2012;2(1):35.

52. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med. 2009;37(3):840-51; quiz 59.

53. Conil JM, Georges B, Lavit M, Laguerre J, Samii K, Houin G, et al. A population pharmacokinetic approach to ceftazidime use in burn patients: influence of glomerular filtration, gender and mechanical ventilation. Br J Clin Pharmacol. 2007;64(1):27-35.

54. Shekar K, Fraser JF, Taccone FS, Welch S, Wallis SC, Mullany DV, et al. The combined effects of extracorporeal membrane oxygenation and renal replacement therapy on meropenem pharmacokinetics: a matched cohort study. Critical Care. 2014;18(6):565.

55. Felton TW, Hope WW, Roberts JA. How severe is antibiotic pharmacokinetic variability in critically ill patients and what can be done about it? Diagn Microbiol Infect Dis. 2014;79(4):441-7.

56. Baptista JP, Udy AA, Sousa E, Pimentel J, Wang L, Roberts JA, et al. A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance. Crit Care. 2011;15(3):R139.

57. Baptista JP, Sousa E, Martins PJ, Pimentel JM. Augmented renal clearance in septic patients and implications for vancomycin optimisation. Int J Antimicrob Agents. 2012;39(5):420-3.

58. Udy AA, Lipman J, Jarrett P, Klein K, Wallis SC, Patel K, et al. Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? Critical Care. 2015;19:28.

59. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: Defining Antibiotic Levels in Intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis. 2014:ciu027.

60. De Cock PA, Standing JF, Barker CI, de Jaeger A, Dhont E, Carlier M, et al. Augmented renal clearance implies a need for increased amoxicillin-clavulanic acid dosing in critically ill children. Antimicrob Agents Chemother. 2015;59(11):7027-35.

61. Lipman J, Brett SJ, De Waele JJ, Cotta MO, Davis JS, Finfer S, et al. A protocol for a phase 3 multicentre randomised controlled trial of continuous versus intermittent β-lactam antibiotic infusion in critically ill patients with sepsis: BLING III. Crit Care Resusc. 2019;21(1):63-8.

62. Felton TW, Roberts JA, Lodise TP, Van Guilder M, Boselli E, Neely MN, et al. Individualization of piperacillin dosing for critically ill patients: dosing software to optimize antimicrobial therapy. Antimicrob Agents Chemother. 2014;58(7):4094-102.

63. European Committee on Antimicrobial Susceptibility Testing (EUCAST). The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0 2020 [Available from: <http://www.eucast.org>.

64. Carlier M, Noe M, De Waele JJ, Stove V, Verstraete AG, Lipman J, et al. Population pharmacokinetics and dosing simulations of amoxicillin/clavulanic acid in critically ill patients. J Antimicrob Chemother. 2013;68(11):2600-8.

65. Delgado-Valverde M, Valiente-Mendez A, Torres E, Almirante B, Gómez-Zorrilla S, Borrell N, et al. MIC of amoxicillin/clavulanate according to CLSI and EUCAST: discrepancies and clinical impact in patients with bloodstream infections due to Enterobacteriaceae. J Antimicrob Chemother. 2017;72(5):1478-87.

66. Choudhury G, Mandal P, Singanayagam A, Akram AR, Chalmers JD, Hill AT. Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia—a propensity-adjusted analysis. Clin Microbiol Infect. 2011;17(12):1852-8.

67. Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. The Cochrane database of systematic reviews. 2015;2015(8):Cd007577.

68. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection— 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2013;68(10):2183-91.

69. Michael M, Hodson EM, Craig JC, Martin S, Moyer VA. Short compared with standard duration of antibiotic treatment for urinary tract infection: a systematic review of randomised controlled trials. Arch Dis Child. 2002;87(2):118.

70. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, et al. Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection. N Engl J Med. 2015;372(21):1996-2005.

71. Pouwels KB, Hopkins S, Llewelyn MJ, Walker AS, McNulty CA, Robotham JV. Duration of antibiotic treatment for common infections in English primary care: cross sectional analysis and comparison with guidelines. BMJ. 2019;364:l440.

72. Yi SH, Hatfield KM, Baggs J, Hicks LA, Srinivasan A, Reddy S, et al. Duration of Antibiotic Use Among Adults With Uncomplicated Community-Acquired Pneumonia Requiring Hospitalization in the United States. Clin Infect Dis. 2017;66(9):1333-41.

73. Pepper DJ, Sun J, Rhee C, Welsh J, Powers JH, III, Danner RL, et al. Procalcitonin-Guided Antibiotic Discontinuation and Mortality in Critically Ill Adults: A Systematic Review and Meta-analysis. Chest. 2019;155(6):1109-18.

74. Daubin C, Valette X, Thiollière F, Mira J-P, Hazera P, Annane D, et al. Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study. Intensive Care Med. 2018;44(4):428-37.

75. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest. 2009;136(5):1237-48.

76. Tellor B, Skrupky LP, Symons W, High E, Micek ST, Mazuski JE. Inadequate Source Control and Inappropriate Antibiotics are Key Determinants of Mortality in Patients with Intra-Abdominal Sepsis and Associated Bacteremia. Surg Infect (Larchmt). 2015;16(6):785-93.

77. Vazquez-Guillamet C, Scolari M, Zilberberg MD, Shorr AF, Micek ST, Kollef M. Using the number needed to treat to assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock. Crit Care Med. 2014;42(11):2342-9.

78. Goal-Directed Resuscitation for Patients with Early Septic Shock. N Engl J Med. 2014;371(16):1496-506.

79. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of Early, Goal-Directed Resuscitation for Septic Shock. N Engl J Med. 2015;372(14):1301-11.

80. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). J Am Med Assoc. 2016;315(8):801-10.

81. Stevens JP, Kachniarz B, Wright SB, Gillis J, Talmor D, Clardy P, et al. When Policy Gets It Right: Variability in U.S. Hospitals’ Diagnosis of Ventilator-Associated Pneumonia\*. Crit Care Med. 2014;42(3).

82. Mansbach JM, Espinola JA, Macias CG, Ruhlen ME, Sullivan AF, Camargo CA. Variability in the Diagnostic Labeling of Nonbacterial Lower Respiratory Tract Infections: A Multicenter Study of Children Who Presented to the Emergency Department. Pediatrics. 2009;123(4):e573.

83. Palmgren J, Paoli J, Schmidtchen A, Saleh K. Variability in the diagnosis of surgical-site infections after full-thickness skin grafting: an international survey. Br J Dermatol. 2019;180(5):1169-75.

84. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2013;13(5):426-35.

85. Schuetz P, Beishuizen A, Broyles M, Ferrer R, Gavazzi G, Gluck EH, et al. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. Clin Chem Lab Med. 2019;57(9):1308-18.

86. Sutherland A, Thomas M, Brandon RA, Brandon RB, Lipman J, Tang B, et al. Development and validation of a novel molecular biomarker diagnostic test for the early detection of sepsis. Crit Care. 2011;15(3):R149.

87. Sinha M, Jupe J, Mack H, Coleman TP, Lawrence SM, Fraley SI. Emerging Technologies for Molecular Diagnosis of Sepsis. Clin Microbiol Rev. 2018;31(2):e00089-17.

88. Vincent J-L, Brealey D, Libert N, Abidi NE, O'Dwyer M, Zacharowski K, et al. Rapid Diagnosis of Infection in the Critically Ill, a Multicenter Study of Molecular Detection in Bloodstream Infections, Pneumonia, and Sterile Site Infections. Crit Care Med. 2015;43(11):2283-91.

89. Tkadlec J, Bebrova E, Berousek J, Vymazal T, Adamkova J, Martinkova V, et al. Limited diagnostic possibilities for bloodstream infections with broad-range methods: A promising PCR/electrospray ionization-mass spectrometry platform is no longer available. Microbiologyopen. 2020;9(5):e1007-e.

90. Pierrakos C, Velissaris D, Bisdorff M, Marshall JC, Vincent J-L. Biomarkers of sepsis: time for a reappraisal. Critical Care. 2020;24(1):287.

91. Larsen FF, Petersen JA. Novel biomarkers for sepsis: A narrative review. Eur J Intern Med. 2017;45:46-50.

92. Kondo Y, Umemura Y, Hayashida K, Hara Y, Aihara M, Yamakawa K. Diagnostic value of procalcitonin and presepsin for sepsis in critically ill adult patients: a systematic review and meta-analysis. Journal of Intensive Care. 2019;7(1):22.

93. Nemati S, Holder A, Razmi F, Stanley MD, Clifford GD, Buchman TG. An Interpretable Machine Learning Model for Accurate Prediction of Sepsis in the ICU. Crit Care Med. 2018;46(4):547-53.

94. Asan O, Bayrak AE, Choudhury A. Artificial Intelligence and Human Trust in Healthcare: Focus on Clinicians. J Med Internet Res. 2020;22(6):e15154.

95. Chong Y-K, Ho C-C, Leung S-Y, Lau SKP, Woo PCY. Clinical Mass Spectrometry in the Bioinformatics Era: A Hitchhiker's Guide. Comput Struct Biotechnol J. 2018;16:316-34.

96. McKenzie C. Antibiotic dosing in critical illness. J Antimicrob Chemother. 2011;66 Suppl 2:ii25-31.

## Tables

Table 1 Commonly used antimicrobials and their solubility characteristics

|  |  |
| --- | --- |
| Hydrophilic antibiotics | Lipophilic antibiotics |
| Aminoglycosidesβ-lactams Glycopeptides  | FluoroquinolonesMacrolidesRifampicinLicosamides |

Table adapted from McKenzie [96] and Roberts and Lipman [52]