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The case for precision dosing: medical conservatism does not justify inaction

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The need for precision dosing has been challenged on the basis of insufficient evidence. Herein, we argue that adequate evidence exists to conduct therapeutic drug monitoring (TDM) and precisely target antibiotic exposures. While achievement of any antibiotic concentration does not guarantee efficacy sans toxicity for any single patient, stochastic control optimizes the probability of achieving favourable responses across patients. We argue that variability in targets (such as the organism's MIC) can be considered with models. That is, complexity alone does not relegate the decision-making framework to 'clinician intuition'. We acknowledge the exposure–response relationships are modified by patient-specific factors (other drugs, baseline organ functional status etc.) and describe how precision dosing can inform clinical decision making rather than protocolize it. Finally, we call for randomized, controlled trials; however, we suggest that these trials are not necessary to make TDM standard of care for multiple classes of antibiotics.

We read "The case for 'conservative pharmacotherapy'"[1] with interest. While we agree with the authors that scarce healthcare resources should be used in the most judicious manner, we find that many of their statements are inaccurate and misrepresent the goals of precision dosing and its supporting evidence. Although the authors outline several points in their argument against therapeutic drug monitoring (TDM), they largely suggest that there is too much variability in antimicrobial exposure–response relationships across patients for TDM to be clinically useful. They support their argument by stating, in a rather black and white fashion, that "patients are frequently cured of their infection despite 'subtherapeutic' antimicrobial exposures, while others unfortunately succumb despite 'therapeutic' or 'supratherapeutic' exposures". Furthermore, they indicate that there is a lack of 'compelling evidence that implementing TDM to achieve exposure within the therapeutic range leads to improved patient outcomes over sound clinical judgement alone'. Based on their rationale, they argue that TDM has minimal value and that 'focusing on TDM may distract from careful clinical monitoring of the patient for efficacy and drug-related toxicities and shift finite resources from other valuable interventions'.

The basis for their arguments against TDM fails to consider the fundamental principles of causality[2] and account for the critical interplay between the host, drug and pathogen. It is well established that all outcomes are multi-causal and no one exposure or factor is responsible for a given outcome. Furthermore, a constellation of exposures/factors mediates responses across patients. This is precisely why there is variability of outcomes across patients, even within groups of individuals with similar antimicrobial concentration–time profiles. As a case in point, most patients have a functioning immune system. Suboptimal drug exposures may still result in clinical cure in such patients, not because drug exposures are meaningless, but instead because the therapeutic targets are not absolute. Other factors, such as increased morbidity scores[3] or difficult-to-treat infections (e.g. endocarditis), lead to failures even in patients with optimized exposures.

While inter-patient variability is known, and outcomes are not guaranteed at any target concentration, it raises the question as to what we can do, as clinicians, to optimize patient outcomes. Precision dosing is one answer: to administer a dose and schedule of an antimicrobial that confers the highest likelihood of success with the lowest probability of a concentration-driven toxicity. This rationale for performing TDM is the same as for other facets of precision medicine, to maximize outcomes across the highest proportion of patients possible. The authors' conclusion that precision dosing is the 'latest and greatest' fad created solely on hyperbole

requires further examination. Below, we have addressed the sentiments that we believe are oversimplified or are grossly incorrect.

(i) The imperfection of the MIC obviates its utility

The MIC is widely recognized as the gold, yet imperfect, standard for defining drug susceptibility.[4,5] Approval of new antibiotics requires a comprehensive understanding of the MIC ranges for target pathogens,[6] which are highly clinically useful for predicting microbiological and clinical failure when they are high and when inter-occasion variability is unlikely to affect the outcome. Low MICs, in the 'susceptible' range, are not a guarantee of success, but still serve as a surrogate that can be factored into the decision-making process for the complex and ever-changing patient. In fact, inclusion of the MIC in modern TDM targets, e.g. free time above the MIC for β-lactams, is a step towards exactly the kind of personalized target setting that the authors rightly promote. Just as with all tests in medicine, clinicians should not simply ignore MIC results when making dosing decisions because variability in the precision and accuracy of the MIC's measurement may exist. Innovations, such as continuous MICs, which are not based on finite drug dilutions, but infinite gradients,[7] may provide more precise estimates of potency in the future; however, perfect precision is not a reasonable expectation and it is not necessary to improve patient outcomes.

(ii) Pharmacokinetic and pharmacodynamic (PK/PD) relationships are not useful because they cannot represent the dynamic and complex relationship between the drug, host and pathogen

PK/PD and exposure–response relationships for many antibiotics are solidly founded on biological principles[5] with direct application to human outcomes.[4] Because of high biological relevance, regulatory bodies, such as the FDA[6,8,9] and the EMA,[10] have drug development requirements for understanding PK/PD before drugs are approved.[11] In fact, the largest reason that anti-infectives fail to obtain drug approval is because of unfavourable pharmacokinetics.[12,13] Solid data exist for PK/PD relationships for fluoroquinolones (efficacy)[14] and aminoglycosides (efficacy and toxicity),[15] as well as β-lactams (efficacy) and vancomycin (toxicity), as described below. The authors are incorrect when they indicate that pharmacodynamic relationships are always developed *post hoc*. We are aware of at least three publications whose analysis plans were prospectively filed with the FDA or EMA.[14,16,17] These studies identified significant PK/PD relationships and utilized other factors besides drug exposure to explain a substantial portion of the observed variance in outcome.

Nevertheless, it is true that many relationships for antibiotic exposure response (i.e. efficacy and toxicity) have been identified from retrospective analyses.[4] Exposure–effect and exposure–toxicity relationships are quantifiable probability density functions with effect modifiers and they should be should not be confused with interpatient variability in responses. Probability density functions allow for the rational choice of dose and schedule to optimize outcomes. For example, an exposure toxicity profile can be understood to shift with an effect modifier (e.g. a second toxic drug). While models never explain 100% of variability (i.e. outcomes), the understood relationship is often useful to guide clinicians when dealing with any number of challenging patients who do not fall into a neat category with fixed dosing recommendations, for example an obese child in renal failure with drug-resistant Gram-negative sepsis.

(iii) Medical evidence must be in the form of randomized clinical trials

While the randomized, double-blind, placebo controlled clinical trial is generally considered to be the top of the evidence pyramid, most medicine is practiced on the basis of 'lesser' evidence. The randomized, double-blind, placebo controlled clinical trial is simply not always practical or ethical. There is no randomized evidence that parachutes prevent death or major trauma related to gravitational challenge.[18] Furthermore, the analysis of such trials depends on demonstrating that the probability of the observed inter-group difference in effect size is too low to believe if there really was no difference. Effect size is the ratio of mean difference and standard deviation, a grouping of patients that is the very antithesis of individualized therapy. A 'successful' randomized, double-blind, placebo controlled clinical trial with a low *P* value is neither a guarantee of reproducible results[19] nor success for the individual patient who needs therapy. One should not conflate a lack of evidence of benefit with evidence for a lack of benefit. As veterans of prospective TDM studies, we can attest to the varied reasons patients require TDM and the even more varied adjustments to therapy that are difficult to protocolize in a prospective, randomized, placebo-controlled study that is impossible to blind. The absence of clinical trial data should encourage funding bodies to study interventions that have become standard of care (such as with vancomycin[20] or aminoglycoside monitoring).[21,22] Despite the challenges of gold-standard trial design for TDM, we applaud that investigators are rising to the challenge of conducting such trials and establishing high levels of evidence, and more high-level evidence will be available soon.[23] Until that time, the best available evidence from β-lactam pre-clinical studies, retrospective reviews and clinical trials[24–28] suggests that precision dosing and optimizing PK/PD benefits some patients.[29–31] For vancomycin, clear relationships have been found between exposure, toxicity[17,32] and optimal monitoring strategies[33] in prospective studies. The authors cite the latter,[33] among others, as 'quasi-experimental' because of confounding changes in 'disease management, referral patterns and pathogen virulence' over time. We can assure the authors and readers that the management of Gram-positive infections did not change at Children's Hospital Los Angeles in the 3 years we conducted our prospective study and there was no evidence that the types of organisms or infections changed over time. In summary, it is our assessment that the level of evidence available for precision dosing with β-lactams and vancomycin at least meets if not exceeds evidence for other standards of care of widely accepted interventions, such as antibiotic stewardship.

Further, the authors propose reliance on close clinical observation. Where are the randomized, placebo-controlled, non-'quasi-experimental' clinical trial data that support this approach? What observations will drive decisions, especially those focused on dosing? It would seem difficult to make informed dosing decisions based on clinical observations, such as pulse, respiration or

temperature. What are the positive and negative predictive values for these observations for success versus failure and over what time frame? We contend that if the authors wish to hold precision dosing to a certain standard that they adopt the same standard for their 'close clinical observation' recommendations. We also argue that TDM is also extremely useful in situations when there is interest in minimizing the occurrence of exposure-related downstream outcomes like adverse events that cannot be detected by close clinical monitoring alone. A perfect example of the value of TDM is use of vancomycin-guided AUC dosing and monitoring to minimize the vancomycin-associated acute kidney injury. It is well established that serum creatinine is an insensitive and delayed indicator of renal injury and serum creatinine only increases after a substantial amount of damage has occurred to the nephrons. Because of renal reserve, it is estimated that up to 50% of the kidney function is lost before there is any detectable increase in serum creatinine.[34,35] As such, the serum creatinine may take 24–36 h to rise after a definite renal insult, a point too late in the cascade to minimize the short- and long-term consequences of acute kidney injury.[36] Studies indicate that even modest cases of acute kidney injury, regardless of cause, lead to substantial increases in morbidity, mortality and healthcare resource utilization.[37–43]

(iv) A therapeutic range is an absolute that compels the clinician to act when concentrations are below or above the range for any patient

It is a common misconception that antimicrobial therapeutic ranges are absolute goals. Rather, the therapeutic range is a means to an intended goal rather than the goal itself. The authors state that the appeal of TDM is the unambiguous nature of the measurement. We suggest that TDM and precision dosing strategies should inform clinical decision making rather than be blindly applied as an unadjusted therapeutic range. Precision dosing aims for a target and uses drug concentration measurement to understand the necessary trajectory to reach the desired goal. A range can be useful, but we carry on Dr Jelliffe's long-standing argument that measured drug concentrations at the extremes of the range or even beyond the range carry distinct probabilities of either treatment failure or adverse effect, i.e. a concentration anywhere within a range does not carry the same probability of success. This approach yet again amplifies individualized therapy by forcing the clinician to think, 'What does my patient really need?'.[44] Such thoughtful TDM activities do not cause clinicians to be blinded from performing other patient monitoring. Thoughtless care in any domain compromises outcomes. The 'appeal' of carefully applied TDM in our opinion is that it is possible to use antecedent laboratory values to inform decision making specifically tailored to the patient rather than to only rely upon clinician intuition as a means of guiding care.

(v) Variability is either not quantifiable or too complex to be factored into patient decisions

We agree with the authors that simply choosing a target without the understanding of potential variability can lead to poor outcomes. It is well known that other covariates, such as severity of illness, drive patient outcomes.[3] However, precision dosing (e.g. optimizing the antibiotic therapy) is a significant tool within the clinician's control to mediate the highest probability of an optimal outcome for the patient,[45] especially the patient who is unexpectedly different from the majority. TDM allows the clinician to understand where the patient's drug concentrations are in relation to those patients that have good and poor outcomes. As we have stated previously, TDM targets do not guarantee a good or poor outcome. The discerning clinician can use this information to devise patient-specific goals and apply precision dosing strategies to further improve the likelihood of positive outcomes. Just because a patient's condition is complex does not mean that we should ignore information known to affect patient outcomes. Perfect prediction is an unrealistic goal.

Variability and the ability to control systems are part of everyday life. A great example of a highly complex stochastic control is that airplanes arrive at the target destination as a function of incorporating system variability (such as change in wind direction and velocity) into the navigation process (stochastic control). We contend that applying these same principles in medicine gives patients the highest likelihood of successful therapy posterior to other patient factors that are not amenable to rapid change.

We do agree with the authors' sentiments that the discerning clinician should 'remain skeptical of guideline recommendations when they are based on methodologically weak evidence' and that patients display unique diseases and covariates that require individualized therapeutic approaches that cannot simply be distilled into a series of algorithms. We also agree that over-reliance on targets for antibiotics has the potential to result in poorly tailored therapy for the individual. Precision dosing is broadly defined as improving treatment outcomes by achieving the optimal dose for an individual patient.[46] We challenge clinicians to use the best available data, not be fixed by blind decision rules or lab-reported therapeutic ranges and understand the relationships between concentrations and outcomes where they have been demonstrated to exist. We understand that change in medicine is often met with staunch opposition where nostalgic persuasions are made to clinicians based on simpler times and pure clinician intuition. However, medical conservatism should not mean medical nihilism. As pharmacokinetic studies and methods have become more rigorous and widespread, the burden of proving clinical superiority should rest squarely with those who prefer to ignore the tremendous variability in drug exposures between patients with fixed dosing. We believe that TDM will eventually become akin to computer flight programs that aid a pilot during the flight of aircraft. Continuously updated predictions will be offered based on individual and time-specific external factors. This information will augment the clinician's decision process (rather than replace it). Just as in aviation, pilot intuition will be supplemented with decision support from computer models, whether a trial of several hundred flights demonstrates a difference between the strategies or not. It is our opinion that it is not defensible to favour a strategy of inaction until the evidence demonstrates clear harm from such inaction. Precision dosing has been a valuable intervention for far too many patients for us to follow the

advice to return to fixed dosing in the hopes that 'average care' is good enough for everyone.

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References

1 Jorgensen SCJ, Stewart JJ, Dalton BR. The case for 'conservative pharmacotherapy'. *J Antimicrob Chemother* 2021; **76**: 1658–60.

2 Rothman KJ, Greenland S. Causation and causal inference in epidemiology. *Am J Public Health* 2005; **95** Suppl 1: S144–50.

3 Miglis C, Rhodes NJ, Kuti JL *et al.* Defining the impact of severity of illness on time above the MIC threshold for cefepime in Gram-negative bacteraemia: a 'Goldilocks' window. *Int J Antimicrob Agents* 2017; **50**: 487–90.

4 Ambrose PG, Bhavnani SM, Rubino CM *et al.* Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. *Clin Infect Dis* 2007; **44**: 79–86.

5 Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; **26**: 1–10; quiz 11–2.

6 U.S. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER). Microbiology Data for Systemic Antibacterial Drugs — Development, Analysis, and Presentation Guidance for Industry. Revision 2. February 2018. https://www.fda.gov/media/77442/download.

7 van de Kassteele J, van Santen-Verheuvel MG, Koedijk FDH *et al.* New statistical technique for analyzing MIC-based susceptibility data. *Antimicrob Agents Chemother* 2012; **56**: 1557–63.

8 U.S. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications. April 2003. https://www.fda.gov/media/71277/download.

9 U.S. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Population Pharmacokinetics Guidance for Industry. Draft Guidance. July 2019. https://www.fda.gov/media/128793/download.

10 EMA. Guideline on the Use of Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products. March 2016. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-use-pharmacokinetics-pharmacodynamics-development-antibacterial-medicinal-products_en.pdf.

11 FDA. Workshop. Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting. August 2019. https://www.fda.gov/drugs/precision-dosing-defining-need-and-approaches-deliver-individualized-drug-dosing-real-world-setting.

12 Sacks LV, Shamsuddin HH, Yasinskaya YI *et al.* Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs, 2000-2012. *Jama* 2014; **311**: 378–84.

13 Institute for Clinical Pharmacodynamics. White Paper. De-Risking Antibiotic Drug Development with PK-PD. http://icpd.com/downloads/ICPD-White-Paper-De-risking-Drug-Development-with-PK-PD.pdf.

14 Preston SL, Drusano GL, Berman AL *et al.* Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. *JAMA* 1998; **279**: 125–9.

15 Drusano GL, Ambrose PG, Bhavnani SM *et al.* Back to the future: using aminoglycosides again and how to dose them optimally. *Clin Infect Dis* 2007; **45**: 753–60.

16 Drusano GL, Preston SL, Fowler C *et al.* Relationship between fluoroquinolone area under the curve: minimum inhibitory concentration ratio and the probability of eradication of the infecting pathogen, in patients with nosocomial pneumonia. *J Infect Dis* 2004; **189**: 1590–7.

17 Lodise TP, Rosenkranz SL, Finnemeyer M *et al.* The emperor's new clothes: PRospective Observational evaluation of the association between initial VancomycIn exposure and failure rates among aDult hospitalizEd patients with methicillin-resistant *Staphylococcus aureus* bloodstream infections (PROVIDE). *Clin Infect Dis* 2020; **70**: 1536–45.

18 Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003; **327**: 1459–61.

19 Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature* 2019; **567**: 305–7.

20 Rybak MJ, Le J, Lodise TP *et al.* Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2020; **77**: 835–64.

21 Rhodes A, Evans LE, Alhazzani W *et al.* Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017; **45**: 486–552.

22 Kalil AC, Metersky ML, Klompas M *et al.* Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; **63**: e61–111.

23 Beta-Lactam InfusioN Group Study (BLING III). https://clinicaltrials.gov/ct2/show/NCT03213990.

24 Abdul-Aziz MH, Lipman J, Akova M *et al.* Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort. *J Antimicrob Chemother* 2016; **71**: 196–207.

25 Dulhunty JM, Roberts JA, Davis JS *et al.* A multicenter randomized trial of continuous versus intermittent β-lactam infusion in severe sepsis. *Am J Respir Crit Care Med* 2015; **192**: 1298–305.

26 Roberts JA, Paul SK, Akova M *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; **58**: 1072–83.

27 Abdul-Aziz MH, Sulaiman H, Mat-Nor MB *et al*. β-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent β-lactam infusion in critically ill patients with severe sepsis. *Intensive Care Med* 2016; **42**: 1535–45.

28 Scaglione F. Can PK/PD be used in everyday clinical practice. *Int J Antimicrob Agents* 2002; **19**: 349–53.

29 Vardakas KZ, Voulgaris GL, Maliaros A *et al*. Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. *Lancet Infect Dis* 2018; **18**: 108–20.

30 Roberts JA, Webb S, Paterson D *et al*. A systematic review on clinical benefits of continuous administration of β-lactam antibiotics. *Crit Care Med* 2009; **37**: 2071–8.

31 Tamma PD, Putcha N, Suh YD *et al*. Does prolonged β-lactam infusions improve clinical outcomes compared to intermittent infusions? A meta-analysis and systematic review of randomized, controlled trials. *BMC Infect Dis* 2011; **11**: 181.

32 Liu J, Tong SYC, Davis JS *et al*. Vancomycin exposure and acute kidney injury outcome: a snapshot from the CAMERA2 study. *Open Forum Infect Dis* 2020; **7**: ofaa538.

33 Neely MN, Kato L, Youn G *et al*. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. *Antimicrob Agents Chemother* 2018; **62**: e02042–17.

34 Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. *J Am Soc Nephrol* 2009; **20**: 672–9.

35 Ronco C, Rosner MH. Acute kidney injury and residual renal function. *Crit Care* 2012; **16**: 144.

36 Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care* 2016; **20**: 299.

37 Doyle JF, Forni LG. Acute kidney injury: short-term and long-term effects. *Crit Care* 2016; **20**: 188.

38 Jeffres MN, Isakow W, Doherty JA *et al*. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. *Clin Ther* 2007; **29**: 1107–15.

39 van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother* 2013; **57**: 734–44.

40 Cano EL, Haque NZ, Welch VL *et al*. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP Database. *Clin Ther* 2012; **34**: 149–57.

41 Kullar R, Davis SL, Levine DP *et al*. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clin Infect Dis* 2011; **52**: 975–81.

42 Minejima E, Choi J, Beringer P *et al*. Applying new diagnostic criteria for acute kidney injury to facilitate early identification of nephrotoxicity in vancomycin-treated patients. *Antimicrob Agents Chemother* 2011; **55**: 3278–83.

43 Patel N, Huang D, Lodise T. Potential for cost saving with iclaprim owing to avoidance of vancomycin-associated acute kidney injury in hospitalized patients with acute bacterial skin and skin structure infections. *Clin Drug Investig* 2018; **38**: 935–43.

44 Jelliffe R. Goal-oriented, model-based drug regimens: setting individualized goals for each patient. *Ther Drug Monit* 2000; **22**: 325–9.

45 Miglis C, Rhodes NJ, Liu J *et al*. Quantifying the importance of active antimicrobial therapy among patients with Gram-negative bloodstream infections: cefepime as a representative agent. *Int J Antimicrob Agents* 2019; **53**: 95–7.

46 Darwich AS, Ogungbenro K, Vinks AA *et al*. Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future. *Clin Pharmacol Ther* 2017; **101**: 646–56.