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ARTICLE

Genetic Algorithms as a Tool for Dosing Guideline Optimization: Application to Intermittent Infusion Dosing for Vancomycin in Adults

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This paper demonstrates the use of a genetic algorithm (GA) for the optimization of a dosing guideline. GAs are well-suited to derive combinations of doses and dosing intervals that go into a dosing guideline when the number of possible combinations rule out the calculation of all possible outcomes. GAs also allow for different constraints to be imposed on the optimization process to safeguard the clinical feasibility of the dosing guideline. In this work, we demonstrate the use of a GA for the optimization of intermittent vancomycin administration in adult patients. Constraints were placed on the dose strengths, the length of the dosing intervals, and the maximum infusion rate. In addition, flexibility with respect to the timing of the first maintenance dose was included in the optimization process. The GA-based optimal solution is compared with the Scottish Antimicrobial Prescribing Group vancomycin guideline.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Genetic algorithms (GAs) have been explored in the context of pharmacokinetic/pharmacodynamic (PK/PD) model selection, the optimization of sampling schemes, and as alternative structural PK models in a machine learning approach to PK/PD.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Are GAs informed by clinical trial simulations useful for deriving dosing guidelines? If so, how does the GA-based solution compare with current expert knowledge-based derived guidelines?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ GAs can be successfully applied to derive dosing guidelines. An advantage is that GAs require formalization of the different steps in the process, which increases transparency in decision making, and that practical constraints can be imposed, which facilitate the implementation of the guideline in clinical practice.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ GAs could help to move away from modeling and simulation (M&S)-based trial-and-error type optimizations of dosing guidelines and could be seen as a natural extension of the M&S centered approach to drug development.

Genetic algorithms (GAs) were invented by John Holland in the 1960s to study biological evolution and the phenomenon of adaptation as it occurs in nature.[1] Currently, GAs are considered "general-purpose" search methods that find the optimal solution to a problem by examining only a small fraction of the possible candidate solutions. This is particularly interesting for complex optimization and search problems when the number of possible solutions prevent the evaluation of all possible solutions. GAs are omnipresent in science and are used in machine learning, the development of artificially intelligent systems, economics, social sciences, etc.

In clinical pharmacology, GAs have been explored in the context of pharmacokinetic/pharmacodynamic (PK/PD) model selection,[2,3] the optimization of sampling times for PK studies,[4] and as alternative structural models to the multicompartment mammillary models in a machine learning approach to PK/PD.[5]

To the best of our knowledge, GAs have not been used previously to develop a drug dosing guideline. Nevertheless, GAs are a more efficient approach to the (modeling and simulation (M&S) supported) trial-and-error type evaluations that usually go into the development of a dosing guideline. Furthermore, algorithm-based optimization of dosing regimens is a natural extension to the already widely embraced M&S centered approach to drug development (i.e., model-informed drug development). Finally, the approach of using a GA to develop a dosing guideline aligns with the use of optimal control techniques to mathematically optimize drug dosing regimens, as recently advocated by Moore.[6]

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In this work, we demonstrate the use of a GA for the optimization of a dosing guideline for intermittent infusions of vancomycin in adult patients. As a starting point for the optimization, we used a modified version of the Scottish Antimicrobial Prescribing Group (SAPG) vancomycin guidelines.[7] The SAPG guidelines contain loading and maintenance dosage regimens based on body weight and kidney function. These guidelines are currently being revised and the modified version, based on expert opinion, aimed to address feedback from users that patients who are obese or with estimated creatinine clearance (eCL_{CR}) > 120 mL/min tend to be underdosed. During the GA optimization, constraints were placed on the dose strengths, the length of the dosing intervals, and the maximum infusion duration to facilitate implementation of the final guideline in clinical practice. In addition, flexibility with respect to the timing of the first maintenance dose was included in the optimization process. The final GA-based optimal dosing guideline was compared with the modified and the original versions of the SAPG guideline.

METHODS

A steady-state GA was used to identify the optimal combination of doses and dosing intervals for the different weight-function and kidney-function classes specified in the modified SAPG dosing guideline (**Table 1**). For this, we simultaneously optimized a combination of six loading doses and nine maintenance doses and dosing intervals. In the remainder of the paper, one such combination of doses and dosing intervals is called a "solution." There were $1.51 \cdot 10^{12}$ theoretical solutions taking into account the practical constraints as detailed in the section "Evaluation of the fitness of the solutions." The individual components of the solutions are referred to as control variables. The general workflow for the GA-based optimization is described in the following sections. The "tidyverse" package (version 1.1.1.; Wickham H. 2017) in R (R Foundation for Statistical Computing, Vienna, Austria) was used for data management, calculations, and graphical analyses.

Selection of the initial population of solutions

An initial population of 200 solutions was randomly generated. This was achieved by randomly sampling a value for each control variable from the discrete distribution of possible values, taking into account the following practical constraints provided by clinicians:

1. Loading doses were multiples of 250 mg and ranged between 500 mg and 4,000 mg.
2. Maintenance doses were multiples of 250 mg and ranged between 500 mg and 2,000 mg.
3. Dosing intervals were q48h, q24h, q12h, or q8h.

Next, the fitness of the solutions was tested. Solutions not meeting the practical constraints, as outlined in the next section, were not included in the initial population.

Evaluation of the fitness of the solutions

A two-stage approach was used to evaluate the fitness of the solutions. First, to ensure that the optimal dosing guideline was practical for implementation in routine clinical practice, we evaluated the following practical constraints:

1. Loading doses do not decrease with increasing patient weight.
2. The dosing interval does not increase with increasing patient eCL_{CR}.
3. Daily doses (product of maintenance dose and dosing interval) do not decrease with increasing patient eCL_{CR}.

Candidate solutions not fulfilling these criteria were penalized (i.e., their fitness criterion was fixed to –10). For all other candidate solutions, the fitness criterion was derived from the simulated concentration time profiles. To simulate concentration time profiles, we used a virtual adult patient population based on the adult data from the vancomycin PK model developed by our group[8] (n = 1,635 patients from 10 studies). From this dataset, 10,000 sets of patient characteristics were randomly sampled. In the virtual population the median [min, max] age, weight, serum creatinine, body mass index, and eCL_{CR} was 66 years [19; 100], 71 kg [29; 282], 0.94 mg/dL [0.17; 9.7], 25 kg/m^2 [10; 80], and 80 mL/min [5.4; 427], respectively.

PK parameters were then simulated according to the model by Colin *et al.*,[8] taking into account interindividual variability. Vancomycin administration was simulated as a short infusion. The infusion duration was calculated by dividing the dose by the maximum infusion rate of 500 mg/h and rounding up to the nearest half hour (i.e., infusion durations were multiples of 30 minutes). To reflect clinical practice,[9] some flexibility was allowed in the timing of the first maintenance dose relative to the loading dose. The first maintenance dose on the q12h, q24h, and q48h regimen was allowed to be given in an interval between 6 and 12, 12 and 24, and 24 and 48 hours after the loading dose, respectively. We added this flexibility to 50% of all simulated dosing regimens, with the exact moment of administration determined by a random draw from a uniform distribution. For simulations without flexibility, the first maintenance dose was given as defined by the dosing interval (i.e., 12, 24, or 48 hours after the loading dose).

Next, concentration time profiles from 0 to 72 hours were calculated using the deSolve package[10] in R. Areas under the curve (AUCs) were calculated from the differential equations. Calculations were parallelized on an HP Z640 workstation with an Intel E5-2670 version 3 (2.30 GHz) 12-core processor using the future package (version 1.13.0; Bengtsson H. 2019) in R. The fitness criterion was calculated according to Eq. 1.

$$\begin{aligned} \text{fitness} = {} & 1 - f\text{AUC}_{0-24\text{hours}} < 400 - f\text{AUC}_{0-24\text{hour}} > 600 \\ & + 1 - f\text{AUC}_{24-48\text{h}} < 400 - f\text{AUC}_{24-48\text{h}} > 600 \\ & + 1 - f\text{AUC}_{48-72\text{h}} < 400 - f\text{AUC}_{48-72\text{h}} > 600 \end{aligned} \quad (1)$$

In this equation, fAUC denotes the fraction of calculated patients where the AUC is below 400 (mg.h)/L or above 600 (mg.h)/L. The fraction of patients with AUC_{24} between 400 and 600 (mg.h)/L is calculated for each day as 1 minus the fraction of patients where the AUC_{24} is below 400 (mg.h)/L minus the fraction of patients where the

Table 1 Comparison among the original SAPG dosing guideline, the expert knowledge-based modified version of the SAPG guideline, and the GA-based optimal dosing guideline

	Original SAPG dosing guideline	Modified SAPG dosing guideline	GA-based optimal solution
Patient weight, kg		Loading dose, mg	
< 40	750	750	1,000
40–59	1,000	1,000	1,500
60–89	1,500	1,500	2,000
> 90	2,000	-	-
90–119	-	2,000	2,500
120–160	-	2,500	3,250
> 160	-	3,000	3,750
Patient eCL_{CR}, mL/min		Maintenance dose (mg)/tau (h)	
< 20	500/48	500/48	750/48
20–25	-	500/24	500/24
20–30	500/24	-	-
26–34	-	750/24	1,000/24
30–40	750/24	-	-
35–49	-	500/12	1,250/24
40–55	500/12	-	-
50–69	-	750/12	750/12
55–75	750/12	-	-
70–89	-	1,000/12	500/8
75–89	1,000/12	-	-
90–119	-	750/8	750/8
90–110	1,250/12	-	-
> 110	1,500/12	-	-
120–180	-	1,000/8	1,000/8
> 180	-	1,250/8	1,250/8
Performance			
C_{max} after LD, mg/L	26.5 [26.3; 26.7]*	26.6 [26.4; 26.8]**	33.7 [33.4; 33.9]*,**
C_{min} after LD, mg/L	9.01 [8.90; 9.11]*	11.0 [10.9; 11.1]**	15.7 [15.5; 15.8]*,**
AUC_{0-24h}, (mg.h)/L	376 [373; 379]*	404 [401; 407]**	485 [481; 489]*,**
*f*AUC $[400–600]_{0–24h}$	0.336 [0.324; 0.348]*	0.398 [0.385; 0.411]**	0.492 [0.479; 0.505]*,**
*f*AUC $[400–600]_{24–48h}$	0.400 [0.387; 0.413]*	0.430 [0.417; 0.443]	0.445 [0.432; 0.458]*
*f*AUC $[400–600]_{48–72h}$	0.411 [0.398; 0.424]	0.429 [0.416; 0.442]	0.432 [0.419; 0.445]
$C_{min,SS}$, mg/L	17.9 [16.8; 19.0]*	20.1 [19.0; 21.2]	21.0 [19.4; 22.7]*
*f*AUC < 10 mg/L	0.242 [0.231; 0.253]*	0.146 [0.137; 0.155]	0.156 [0.147; 0.165]*
*f*AUC [10–15 mg/L]	0.278 [0.266; 0.290]	0.262 [0.251; 0.273]	0.260 [0.249; 0.271]
*f*AUC [15–20 mg/L]	0.211 [0.200; 0.222]*	0.240 [0.229; 0.251]	0.234 [0.223; 0.245]*
*f*AUC > 20 mg/L	0.268 [0.257; 0.279]*	0.352 [0.340; 0.364]	0.350 [0.338; 0.362]*
C_{ss}, mg/L	26.3 [25.2; 27.4]	27.3 [26.2; 28.4]	28.8 [27.1; 30.4]
$AUC_{24,SS}$, (mg.h)/L	632 [606; 659]	656 [629; 682]	690 [651; 730]
*f*AUC < 400 (mg.h)/L	0.214 [0.203; 0.225]*	0.171 [0.161; 0.181]	0.170 [0.160; 0.180]*
*f*AUC [400–600 (mg.h)/L]	0.376 [0.364; 0.388]	0.375 [0.363; 0.387]	0.361 [0.349; 0.373]
*f*AUC > 600 (mg.h)/L	0.410 [0.397; 0.423]*	0.455 [0.442; 0.468]	0.469 [0.456; 0.482]*

Green and red shading depicts loading doses and daily maintenance doses (mg q24h), which are higher or lower for the GA-based solution compared with the expert knowledge-based solution. Performance metrics are reported as means or proportions and corresponding 99% confidence intervals (CIs). Significant differences, judged by nonoverlapping CIs, between the GA-based solution and the original and modified SAPG guideline are shown with asterisks.
C_{max}, maximum concentration; C_{min}, minimum concentration; C_{SS}, steady-state concentration; eCL_{CR}, estimated creatinine clearance; fAUC, fraction of area under the curve; GA, genetic algorithm; LD, loading dose; SAPG, Scottish Antimicrobial Prescribing Group.

AUC_{24} is above 600 (mg.h)/L. This target exposure window is a frequently reported target in the literature for the optimization of vancomycin therapy assuming a minimum inhibitory concentration ≤ 1 mg/L.[11,12] To avoid the optimization being driven by the most populated subgroup in the virtual patient population, we split up the calculation of the fitness criterion according to body mass index (< 18.5, < 30, or > 30 kg/m^2), age (< 50, < 75, or > 75 years), and eCL_{CR} according to Cockcroft-Gault[13] (< 50, < 120, or > 120 mL/min). Subgroups with less than 100 individuals (i.e., < 1% of the virtual population) were combined. The fitness criterion used for the optimization was the mean

across the subgroups. By design, the fitness criterion ranged between 0 and 3, with 3 indicating the best possible performance.

Elitism, crossover, and mutation

After evaluating the fitness of all candidate solutions in the population, a new generation of 200 solutions was generated according to the following rules:

1. The two best performing solutions were carried over to the next generation (this is also known as "elitism").
2. The other candidate solutions were created as follows:
   a Two parent solutions (also referred to as chromosomes) were selected via tournament selection (i.e., for each parent, first two candidate solutions are randomly selected and the solution with the higher fitness criterion is retained as the parent solution).
   b Fivefold crossover was performed with a crossover rate of 0.8.
   c Pointwise mutation was performed with a mutation rate of 0.05.
   d Steps a-c were repeated until a new population of size 200 was reached.

There were 14 locations on the solution where crossover was allowed. Positions between adjacent loading doses ($n = 6$) and daily doses ($n = 9$; i.e., combinations of maintenance doses and dosing intervals) on the chromosome were eligible for crossover. The crossover locations were determined by a random draw from the 14 possible crossover locations.

Pointwise mutations were considered for loading doses and maintenance doses. Mutation consisted of randomly sampling from the discrete distribution of possible values for each variable as described under "Selection of the initial population of solutions."

Additional calculations to benchmark the optimal solution

The AUC and maximum concentration (C_{max}) and minimum concentration (C_{min}) at steady-state were calculated from Eqs. 2–4.

$$AUC_{SS} = \frac{MD \cdot 24}{CL \cdot \tau} \tag{2}$$

$$Cmax_{SS} = \frac{MD}{CL \cdot DUR} \cdot \frac{1 - e^{\left(-\frac{CL}{V1} \cdot DUR\right)}}{1 - e^{\left(-\frac{CL}{V1} \cdot \tau\right)}} \tag{3}$$

$$Cmin_{SS} = Cmax_{SS} \cdot e^{\left(-\frac{CL}{V1} \cdot (\tau - DUR)\right)} \tag{4}$$

In Eqs. 2–4, MD denotes the maintenance dose, τ is the dosing interval, and DUR is the duration of the drug infusion.

RESULTS

The evolution of the fitness of the solutions for the first 100 generations is shown in **Figure 1**. The median fitness in the population increased over the first 50 generations from 0.991 to 1.293 and leveled off over the next 50 generations at a mean value of 1.320 (SD = 0.029). The original SAPG guideline had a fitness of 1.126 and the modified guideline (i.e., the expert-knowledge-based dosing guideline had a fitness of 1.244). The fraction of solutions performing better than the modified SAPG guideline increased during the optimization from 4.5% in the first generation to 61% in the 100th generation.

The solution with the highest average fitness was selected as the final solution. This approach was taken because the fitness for a particular solution varied slightly across evaluations (mean SD = 0.004). This was due to the stochastic nature of the simulations to accommodate the flexibility in the timing of the first maintenance dose. The overall highest average fitness was 1.352. There was only one solution associated with this maximum fitness. Nevertheless, several solutions with similar fitness were identified. **Figure 2** shows the distribution of loading doses, maintenance doses, and dosing intervals for 33 solutions that had a fitness < 2 SDs below the fitness of the final solution (i.e., fitness > 1.344). **Figure 2** shows that there was some variability in the individual components of the solutions. Except for the loading dose for patients with body weights between 120 and 160 kg (LD5) and the maintenance dose for patients with eCL_{CR} below 20 mL/min (MD1), the distribution of solutions centered around the final solution.

A comparison between the dosing guideline according to the GA-based optimal solution and the original and expert knowledge-based modified SAPG guideline is shown in **Table 1**. Loading doses for the optimal GA-based solution were higher, irrespective of patient body weight. Daily maintenance doses (mg q24h) were only higher for patients with eCL_{CR} below 50 mL/min. The fraction of patients who attained an AUC between 400 and 600 (mg.h)/L was higher for the GA-based solution. The increase in AUC target attainment was most pronounced on day 1 (0.492 vs. 0.398 and 0.336) and day 2 (0.445 vs. 0.430 and 0.400). Interestingly, as shown in **Figure 3**, the increase in target attainment was consistent in the virtual population leading to less variable target attainment across subgroups. For example, on day 2, the 10th and 90th percentiles for target attainment across subgroups were 0.413 and 0.481, 0.365 and 0.482, and 0.308 and 0.456 for the GA-based solution compared with the original and modified SAPG guideline. $AUC_{24,SS}$ was highest for the GA-based solution (690 vs. 656 vs. 632 (mg.h)/L) and the fraction of patients who attained an AUC_{ss} between 400 and 600 (mg.h)/L was lowest (0.361 vs. 0.375 vs. 0.376).

The high dimensionality of the problem presented here, with 24 individual components to optimize, resulted in 62 hours of computation time for the GA optimization. The practical constraints on the optimization added to the complexity of the calculations and likely slowed down convergence of the GA. For example, the fraction of solutions not fulfilling the practical constraints increased over the first 20 generations to 92% and then gradually decreased to around ± 50% of the population (data not shown). Overall, 16,833 unique solutions were identified and 5,197 of these

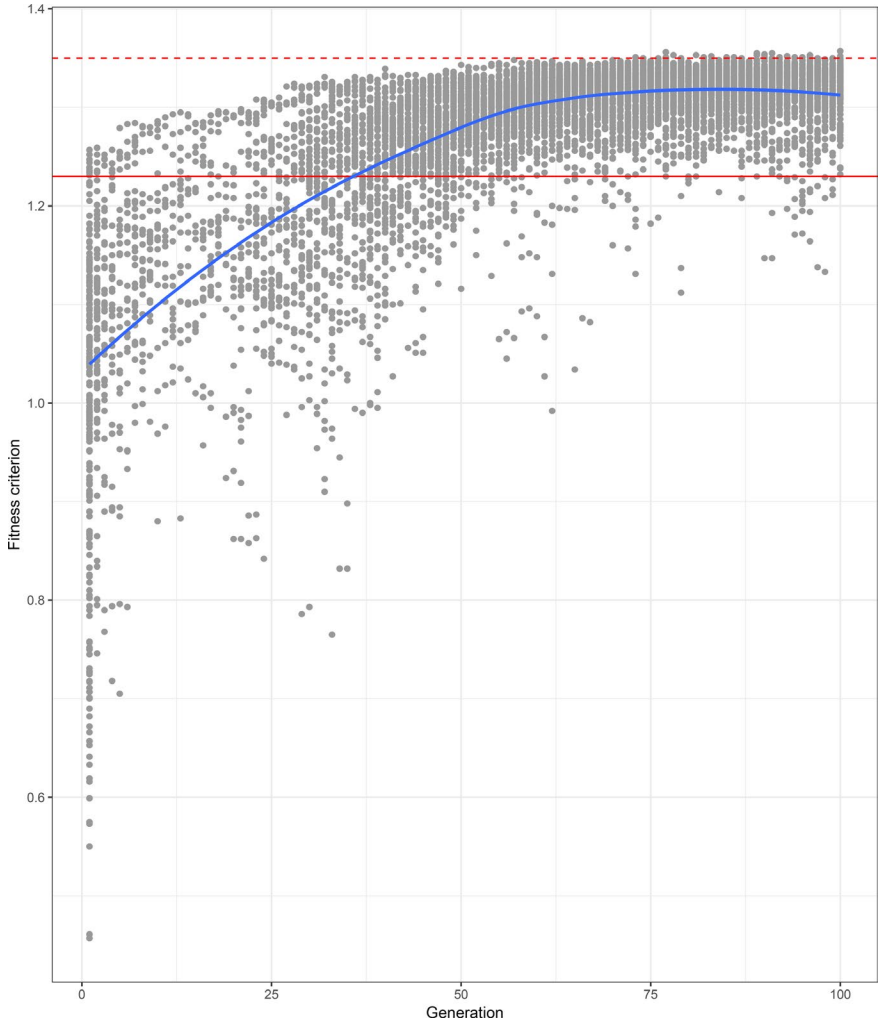

Figure 1 Maximization of the fitness criterion over 100 generations of solutions. Solutions not satisfying the constraints had a fitness of –10 and were excluded from this figure. The fitness for the starting point for the optimization (i.e., the expert knowledge-based modified Scottish Antimicrobial Prescribing Group guideline), is shown with a solid red line. Shown with a dashed red line is the theoretical maximum fitness of 1.353 as explained in the Discussion section of the paper.

satisfied the constraints and performed better than the initial solution.

DISCUSSION

In this study, we have shown that a genetic algorithm is a useful tool to aid the development of a dosing guideline. In this example, GA-based optimization was applied to an adult dosing guideline for intermittent infusion of vancomycin. We found that in order to further optimize the modified SAPG dosing guideline, loading doses should be increased for all patients and daily maintenance doses (mg q24h) should be increased for patients with eCL_{CR} below 50 mL/min. The GA approach allowed us to formalize practical constraints, which will facilitate implementation of the guideline in clinical practice. Moreover, the approach suggested here used a weighted version of the fitness criterion, which resulted in an optimal solution with a balanced performance across subgroups of patients in the population.

Guidelines for dose individualization in routine clinical practice are often based on local experience or expert opinion and it is unclear to what extent such guidelines actually achieve target concentrations or exposure. A recent study[8] found that consensus guidelines produced by the US Food and Drug Administration (FDA) and also the Summary of Product Characteristics for vancomycin performed poorly when tested using a large population of patients. Furthermore, even when guidelines are available, they may not be in a form that can be implemented effectively. For example, although Colin *et al*.[8] found that modified versions of the FDA and Summary of Product Characteristics guidelines were more likely to achieve target exposure, the resulting dose amounts were impractical for routine clinical application. Within Scotland, the SAPG guidelines for vancomycin,[7] originally introduced in 2009, were based on a population study of vancomycin PK.[14] Although effective implementation of these guidelines led to an improvement in the achievement of target concentrations,[15] it became clear that some doses were too low, especially in

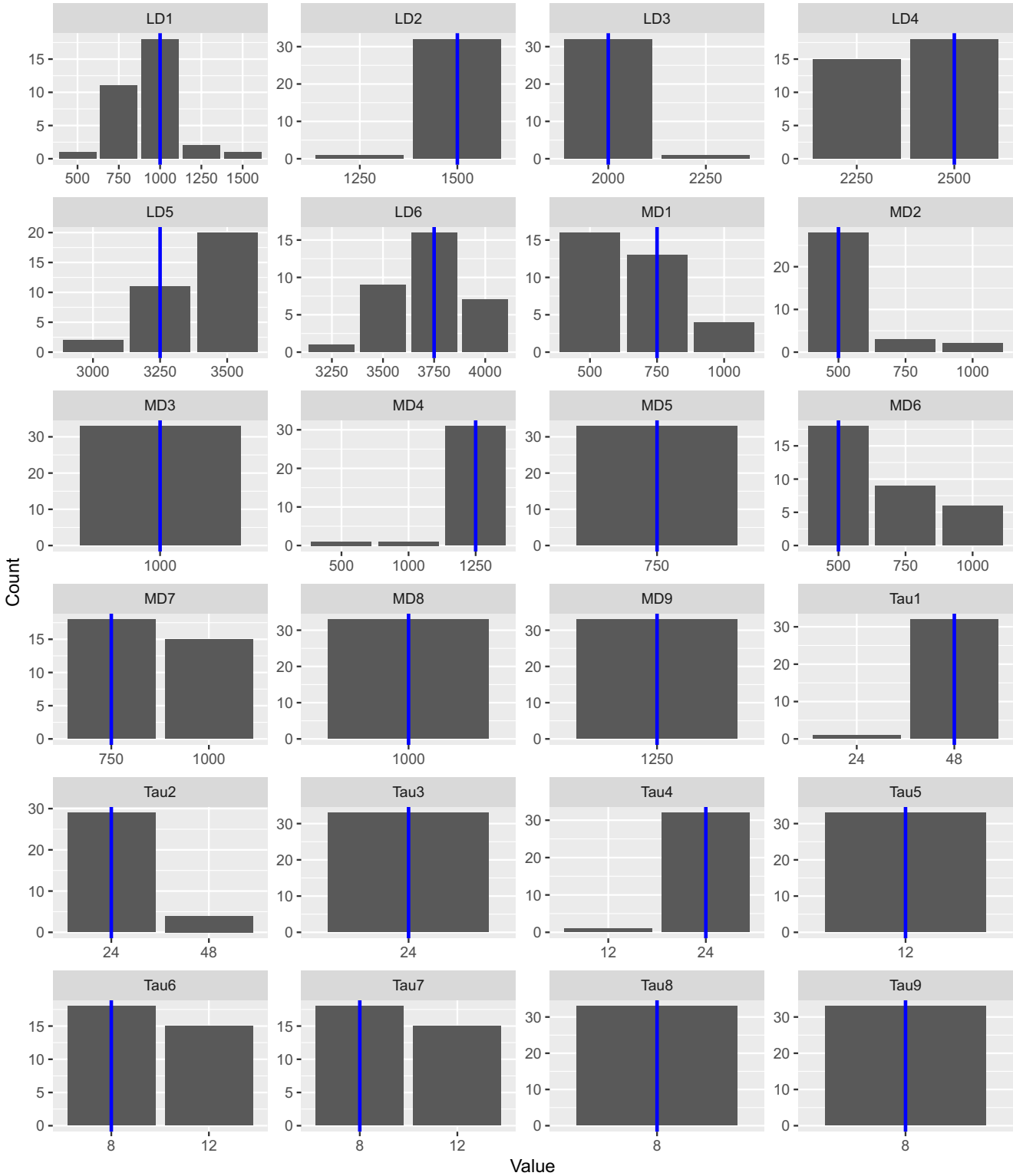

Figure 2 The distribution of the individual components of the solutions with fitness < 2 SDs below the fitness for the final solution (n = 33). The final solution is shown with a vertical blue line. LD denotes loading doses (mg) for the six body weight classes defined in **Table 1**. MD and Tau denote the maintenance dose (mg) and dosing interval (hours) for the nine kidney function classes defined in **Table 1**.

patients who were obese or had higher estimates of eCL_{CR}. Consequently, a set of modified guidelines, based on expert opinion and clinical experience, was developed for discussion.

The present study compares the performance of original and modified guidelines with a GA-based guideline that targets AUC_{24} on days 1–3 of therapy.

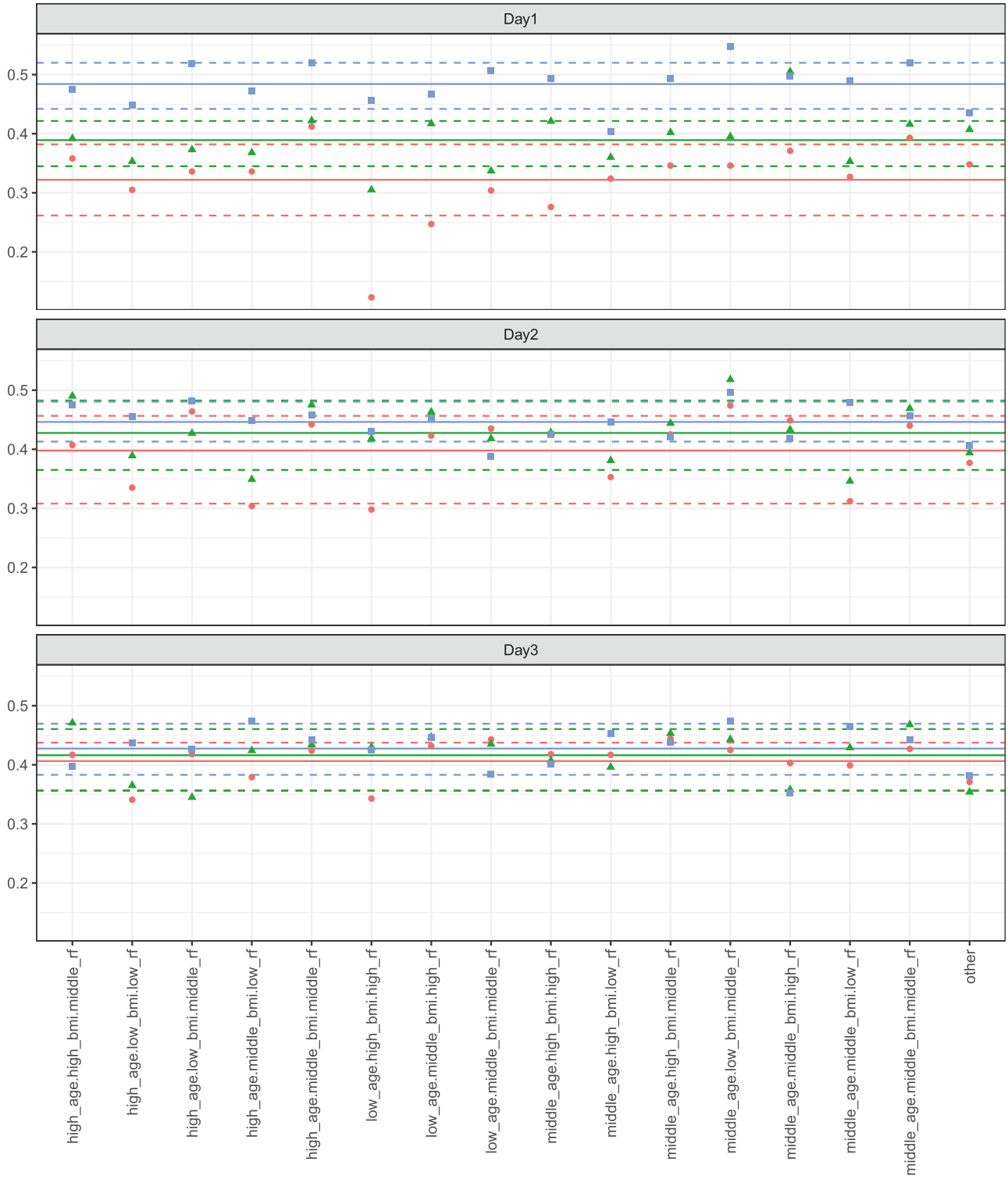

Figure 3 The fraction of the area under the curve (*f*AUC) target attainment for days 1–3 for the original and revised Scottish Antimicrobial Prescribing Group dosing guideline (respectively shown in orange and green) and the genetic algorithm (GA)-based optimal solution (shown in blue). AUC target attainment was defined as the proportion of patients achieving an AUC between 400 and 600 (mg.h)/L in a 24-hour time period. The solid and dashed lines denote the median and 10th and 90th percentiles across the subgroups.

National consensus guidelines that recommended troughs of 15–20 mg/L for patients with serious infections[16–18] has resulted in many new guidelines and nomograms to support vancomycin dosing.[19–24] The methodologies used to create these guidelines ranged from local experience, [21,24–26] regression analysis,[19,23,27,28] simulations based on traditional

or population PK models[20,22] to more sophisticated approaches using Monte Carlo simulation.[29,30] In most cases, the numbers of patients used to develop and validate these guidelines was relatively small and the methodology used to choose the dose amounts and intervals unclear. Furthermore, although these guidelines typically improved target achievement when compared with previous approaches, they often focused on specific patient groups or excluded patients outside restricted ranges of weight or renal function.[19]

The present study uses a novel approach to define a dosing guideline and, due to the extensive patient database used for the original population PK study,[8] covers a wide range of patient characteristics with no specific exclusions except renal replacement therapy. This study aimed to optimize dosing during the first 3 days of therapy, with the assumption that early target attainment potential avoids therapy failure,[31] and that therapeutic drug monitoring samples will be measured within this timescale that can be used to further individualize therapy. The lower target attainment in steady-state for the GA-based solution should be interpreted in this context and represents the unlikely scenario when no therapeutic drug monitoring is used for treatment individualization.

A practical limitation of the GA-based approach is that there are no established rules for assessing convergence of the algorithm, nor are there methods available to ascertain that the global maximum has been found. We handled this by calculating the theoretical maximum target attainment rate that could be achieved when dosing is informed by all covariates in the population PK model. In the absence of any bias in the model, the highest performance would then be achieved by aiming for an AUC_{24} target at the midpoint (on the log scale) of the target AUC_{24} window (i.e., 490 (mg.h)/L). Due to the between-subject variability on clearance, which in the model by Colin *et al*.[8] is 33.9% for a 35-year-old, 70-kg patient with a serum creatinine level of 0.83 mg/dL, only 45.1% of AUCs are expected to fall within the 400–600 (mg.h)/L target window, leading to a maximum fitness of 1.353 (target attainment over 3 days). In situations where no such theoretical value or global maximum can be calculated, convergence of the GA might have to be assumed from empirical testing (running the GA for longer).

Drug labeling is a process of "discrete parameter optimization." Currently, labeling is often supported by M&S to derive optimal dose strengths and/or identify subgroups of patients that require dose modifications. From an economic point-of-view, one of the concerns for drug companies is to keep the label as simple as possible, requiring, for example, as few dose strengths as possible. Regulators and clinicians, however, might favor a more granular approach. In that respect, algorithm-based optimization could be useful because it forces the different stakeholders to agree on a target (i.e., fitness) and practical constraints (number of doses, dose strengths, patient stratification, etc.) up front. At the same time, this approach might facilitate acceptance of the drug label once the drug company has shown that the proposed dosing regimen is optimal, given the constraints, without the need to share data with regulators or having to provide simulations for alternative labeling options.

The use of the GA-based optimization is not restricted to drug development programs. The components that are pivotal for applying the approach are (i) the availability of a PK (PD) simulation model that is fit-for-purpose, and (ii) a good understanding of an appropriate PK(PD) target for the optimization. In addition to the application presented in this study, we envisage an added value for this approach in situations where the development of a dosing regimen is complicated by, for example, a narrow therapeutic toxic margin, nonlinear PKs, acute or chronic tolerance development, etc. The amount of clinical evidence that will be required to confirm the results, much like any other M&S-supported dose finding, will depend on the level of extrapolation and the (clinical) data package supporting the components of the GA-based optimization.

In conclusion, we have shown that a genetic algorithm informed by clinical trial simulations is a useful tool to develop dosing guidelines and could help to move away from (M&S-based) trial-and-error type optimizations of dosing guidelines. For drug development companies, algorithm-based optimization is a natural extension of the M&S centered approach to drug development. Moreover, the prerequisite to algorithm-based optimization (i.e., that the different steps in the process have to be formalized; e.g., choice of patient subgroups, number of dose strengths, PKPD target, …), will increase transparency in the development of dosing guidelines and could facilitate acceptance by clinicians and regulatory authorities.

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1. Mitchell, M. An Introduction to Genetic Algorithms (MIT Press, Cambridge, MA, 1998).
2. Sale, M. & Eric, A.S. A genetic algorithm based global search strategy for population pharmacokinetic/pharmacodynamic model selection. *Br. J. Clin. Pharmacol.* **79**, 28–39 (2015).
3. Bies, R.R., Muldoon, M.F., Pollock, B.G., Manuck, S., Smith, G. & Sale, M.E. A genetic algorithm-based, hybrid machine learning approach to model selection. *J. Pharm. Pharmacodynam.* **33**, 195 (2006).
4. Hughes, J.H., Upton, R.N., Reuter, S.E., Phelps, M.A. & Foster, D.J.R. Optimising time samples for determining area under the curve of pharmacokinetic data using non-compartmental analysis. *J. Pharm. Pharmacol.* **71**, 1635–1644 (2019).
5. Li, Q. *et al.* Warfarin maintenance dose prediction for patients undergoing heart valve replacement—a hybrid model with genetic algorithm and Back-Propagation neural network. *Sci. Rep.* **8**, 9712 (2018).
6. Moore, H. How to mathematically optimize drug regimens using optimal control. *J. Pharmacokinet. Pharmacodyn.* **45**, 127–137 (2018).
7. Scottish Antimicrobial Prescribing Group. Scottish Medicines Consortium. Gentamicin and vancomycin. <https://www.sapg.scot/quality-improvement/hospital-prescribing/gentamicin-and-vancomycin/>.
8. Colin, P.J. *et al.* Vancomycin pharmacokinetics throughout life: results from a pooled population analysis and evaluation of current dosing recommendations. *Clin. Pharm.* **58**, 767–780 (2019).
9. Carruthers, A. *et al.* Timing of the first vancomycin maintenance dose in an acute adult hospital setting - room for improvement? *J. Med. Optimis.* **2**, 51–5 (2016).
10. Soetaert, K.E., Petzoldt, T. & Setzer, R.W. Solving differential equations in R: package deSolve. *J. Statist. Softw.* **33**, 2–25 (2010).
11. Zasowski, E.J. & Lodise, T.P. The importance of individualised vancomycin dosing to ensure optimal exposure early in therapy. *J. Clin. Pharmacol.* **58**, 1131–1133 (2018).

12. Heil, E.L. *et al*. Making the change to area under the curve-based vancomycin dosing. *Am. J. Health-Syst Pharm.* **35**, e828–e837 (2018).
13. Cockcroft, D.W. & Gault, M.H. Prediction of creatinine clearance from serum creatinine. *Nephron* **16**, 31–41 (1976).
14. Thomson, A.H., Staatz, C.E., Tobin, C., Gall, M. & Lovering, A.M. Development and evaluation of vancomycin dosage guidelines designed to achieve new target concentrations. *J. Antimicrob. Chemother.* **63**, 1050–1057 (2009).
15. Semple, Y., Bennie, M., Sneddon, J., Cockburn, A., Seaton, R.A. & Thomson, A.H.Development and evaluation of a national gentamicin and vancomycin quality improvement programme. J. Antimicrob. Chemother. https://doi.org/10.1093/jac/dkaa096. [e-pub ahead of print].
16. Rybak, M. *et al*. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am. J. Health Syst. Pharm.* **66**, 82–98 (2009).
17. Matsumoto, K. *et al*. Practice guidelines for therapeutic drug monitoring of vancomycin: a consensus review of the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. *J. Infect. Chemother.* **19**, 365–380 (2013).
18. Ye, Z.-K. *et al*. Therapeutic drug monitoring of vancomycin: a guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. *J. Antimicrob. Chemother.* **71**, 3020–3025 (2016).
19. Yoon, S. *et al*. Assessment of appropriateness of an initial dosing regimen of vancomycin and development of a new dosing nomogram. *Basic Clin. Pharmacol. Toxicol.* **122**, 233–238 (2018).
20. Kullar, R. *et al*. Validation of the effectiveness of a vancomycin nomogram in achieving target trough concentrations of 15–20 mg/L suggested by the vancomycin consensus guidelines. *Pharmacotherapy* **31**, 441–448 (2011).
21. Golenia, B.S., Levine, A.R., Moawad, I.M., Yeh, D.D. & Arpino, P.A. Evaluation of a vancomycin dosing nomogram based on the modification of diet in renal disease equation in intensive care unit patients. *J. Crit. Care* **28**, 710–716 (2013).
22. Leu, W.J., Liu, Y.C., Wang, H.W., Chien, H.Y., Liu, H.P. & Lin, Y.M. Evaluation of a vancomycin dosing nomogram in achieving high target trough concentrations in Taiwanese patients. *Int. J. Infect. Dis.* **16**, e804–e810 (2012).
23. Thalakada, R., Legal, M., Lau, T.T., Luey, T., Batterink, J. & Ensom, M.H. Development and validation of a novel vancomycin dosing nomogram for achieving high-target trough levels at 2 Canadian teaching hospitals. *Can. J. Hosp. Pharm.* **65**, 180–187 (2012).
24. Wesner, A.R., Brackbill, M.L., Coyle, L.L. & Kidd, R.S. Prospective trial of a novel nomogram to achieve updated vancomycin trough concentrations. *Interdiscip. Perspect. Infect. Dis.* **2013**, 839456 (2013).
25. Michalets, E.L., Pounders, S.J., Hollis, S.J. & Sutherland, S. Outcomes associated with AUC24/MIC nomogram dosing of vancomycin. *Ann. Pharmacother.* **45**, 687–689 (2011).
26. Devabhakthumi, S. *et al*. Evaluation of vancomycin dosing and monitoring in adult medicine patients. *Hosp. Pharm.* **47**, 451–459 (2012).
27. Baptista, J.P., Roberts, J.A., Sousa, E., Freitas, R., Deveza, N. & Pimentel, J. Decreasing the time to achieve therapeutic vancomycin concentrations in critically ill patients: developing and testing of a dosing nomogram. *Crit. Care* **18**, 654 (2014).
28. Pea, F. *et al*. Prospectively validated dosing nomograms for maximizing the pharmacodynamics of vancomycin administered by continuous infusion in critically ill patients. *Antimicrob. Agents Chemother.* **53**, 1863–1867 (2009).
29. Crass, R.L., Dunn, R., Hong, J., Krop, L.C. & Pai, M.P. Dosing vancomycin in the super obese: Less is more. *J. Antimicrob. Chemother.* **73**, 3081–3086 (2018).
30. Medellın-Garibay, S.E., Ortiz-Martın, B., Rueda-Naharro, A., Garcıa, B., Romano-Moreno, S. & Barcia, E. Pharmacokinetics of vancomycin and dosing recommendations for trauma patients. *J. Antimicrob. Chemother.* **71**, 471–479 (2016).
31. Honore, P.M. *et al*. Attainment of therapeutic vancomycin level within the first 24 h. *Crit. Care* **23**, 228 (2019).