Immunocompromised, malnourished and pregnant patients are at most risk.

Given the typical infectious period for measles noted above, it is likely that Patient 1 transmitted the infection to Patient 2, though a common source for both patients is also possible. Although the index sister (Patient 1) was not of the so-called 'Wakefield' generation of children (where parents avoided MMR vaccination due to concerns about its possible link with autism, during 1998–2000), it is likely that she was infected by an individual from this generation, given the social contact history provided. She and her sister had not received the MMR vaccine as children mainly due to parental concerns about possible vaccine-related seizure risks.

Although measles is targeted for elimination from Europe,[6] despite an efficacious vaccine, vaccine refusal or simply missing doses for various other reasons, is an ongoing barrier to this goal.[7,8] This report clearly demonstrates that in some individuals, one MMR vaccine dose is not enough.

Declarations

None of the authors have any conflicts of interest to declare. All authors have seen and approved the final version of the manuscript, and are happy for it to be submitted. This manuscript has not been submitted elsewhere for publication.

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Vancomycin therapy in secondary care; investigating factors that impact therapeutic target attainment

KEYWORDS
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Pharmacokinetic–pharmacodynamic;
Population modelling

Dear editor,

We read with interest the article by Valencia-Rey and colleagues who investigated the role of vancomycin for empirical therapy in coagulase negative staphylococcal blood stream infections.[1] For vancomycin therapy outside of critical care there are limited data describing vancomycin pharmacokinetics. We undertook a retrospective investigation of dosing of vancomycin in the non-critically ill patients managed across three University hospitals in London. Using patient TDM data, the aim was to build a population pharmacokinetic model to estimate population

parameters and identify key factors associated with target attainment.

Routinely collected data from two prospective hospital wide audits of vancomycin therapy in the non-critical care setting were included. Data on patient demographics, infection parameters, biochemical results, antimicrobial treatment, and TDM data was extracted for analysis. Patients on renal replacement therapy were excluded. Age, gender, ethnicity, total body weight (TBW), ideal body weight (IBW), lean body weight (LBW), body mass index (BMI), glomerular filtration rate (GFR; Modification of Diet in Renal Disease [MDRD] formula), and creatinine clearance (CrCL; estimated using the Cockcroft–Gault equation using TBW and IBW) were all collected or calculated for investigation as model covariates. An NPAG population pharmacokinetic algorithm embedded in the program; Pmetrics within R (LAPKB, CA, USA),[2] was used to estimate the population pharmacokinetics of vancomycin.

Comparison between one- and two-compartment models were performed and covariates were tested within the model. Statistical significance was assessed by comparison of twice the log-likelihood values against a chi-squared distribution with the appropriate number of degrees of freedom, depending on the number of parameter values within each model. Population parameters were estimated and assessed. Individual patient 24-h steady state AUC was calculated. Given a paucity of minimum inhibitory concentration (MIC) data, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used to estimate the mean MIC for staphylococcal infections.[3] For estimates of individual AUC:MIC ratio, an MIC of 1 mg/L was selected as the breakpoint. A target AUC:MIC ratio $\geq$400 was defined as appropriate.[4–6] Monte-Carlo simulation was performed (1000 patients) and probability of target attainment (PTA) estimated for eight dosing regimens commonly used in clinical practice at different MIC values (0.25–8). Following this, simulations were performed for different weight ranges (45–75 kg & 75–150 kg) to investigate the effect of weight on AUC:MIC ratios across dosing regimens (n = 2000). Statistical analysis was performed in SPSS 22.0 (IBM, NY, USA). Ethical approval was not required for this study as only routinely collected data were included.

Seventy nine patients were identified on vancomycin therapy. Thirty individuals receiving vancomycin therapy for known or suspected staphylococcal infections were selected for inclusion. Of the 49 patients excluded, 42 had covariate data missing and 7 were on renal replacement therapy. Median age (range) of the included subjects was 60 (21–87) years, with the majority being male (18/30, 60%). Table 1 summarises the key population parameters and indications for therapy. Median (IQR) GFR was 75.85 (38.8–107.8)ml/min/1.73 m^2. Patients received a median (range) of 1500 mg (500–3000 mg) vancomycin 24-hourly and had a median (range) of 3.5 (1–6) TDM samples taken during the observation period. Local target TDM plasma concentration (10–15 mg/L or 15–20 mg/L in severe or deep seated infections) was reached in 26/30 (87%) of cases. Three of the four individuals not reaching these targets were obese (BMI >30 kg/m^2), with the fourth classified as overweight (BMI = 26 kg/m^2).

Table 1 Summary of population parameters and target comparisons between obese and non-obese individuals receiving vancomycin in a non-critical care setting.

Population parameters		Value
Clearance (CL, L/hr)	Mean (SD)	2.40 (1.4)
Volume (central, L)	Mean (SD)	31.85 (15.9)
Kcp (hr^{-1})	Mean (SD)	0.93 (1.6)
Kpc (hr^{-1})	Mean (SD)	3.88 (4.6)
Height (cm)	Mean (SD)	168 (11)
Total body weight (kg)	Mean (SD)	74 (15)
Body mass index (kg/m^2)		
	18–25	16 (53)
	25–30	8 (27)
	>30	6 (20)
Indication for therapy	n = (%)	
	Skin & soft tissue infection	8 (27)
	Blood stream infection	6 (20)
	Hospital acquired pneumonia	4 (13)
	Joint infection	3 (10)
	Other	7 (23)
	Unknown	2 (7)
Obese AUC:MIC ratio	Mean (SD)	320 (74)
Obese meeting AUC:MIC target	n = (%)	1 (17)
Overweight AUC:MIC ratio	Mean (SD)	479 (108)
Overweight meeting target	n = (%)	6 (75)
Normal AUC:MIC ratio	Mean (SD)	524 (174)
Normal weight meeting target	n = (%)	12 (75)[a]

L = litres; hr = hour; cm = centimetres; kg = kilogram; m^2 = meters squared; AUC = steady state 24-h area under the curve; MIC = minimum inhibitory concentration; SD = standard deviation; n = number.

[a] Three patients had AUC > 700, which has been associated with increased risk of nephrotoxicity.

A two-compartment model produced optimal observed-versus-predicted fit for the individual data extracted giving an r^2 of 0.9. TBW and GFR were included as covariates to the model using an allometric scaling and linear association, respectively. These significantly improved the model (−2log likelihood = 602.4 to 590.2 and AIC = 612.9 to 600.8). Population parameter estimates and individual steady state 24-h area under the curve (AUC) estimations are described in Table 1. Overall, mean (SD) AUC:MIC ratio was 471 (163). 19/30 (63%) patients had AUC:MIC ratio $\geq$400. Of these, 3/19 (16%) had AUC values >700, which has been associated with greater risk of toxicity.[7] Of the 11/30 (37%) not meeting the target AUC:MIC ratio, 5/11 (45%) were obese. On comparison of obese versus non-obese subjects, the AUC:MIC ratio were statistically significant (mean (SD) = 320 (74) versus 509 (157); $p < 0.01$). The GFR of those failing to attain a AUC:MIC ratio $\geq$400 were similar to those attaining the target (mean (SD) = 72 (36) vs. 79 (47); $p = 0.70$).