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1

2 **The Clinical Utility and Safety of a Model-Based Patient-Tailored**
3 **Dose of Vancomycin in Neonates**

4

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8

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32 Keywords: personalized dose, neonates, vancomycin, pharmacokinetics, modeling,

33

34 **Abstract**

35 **Background and objective:** Pharmacokinetic modeling was often applied to
36 evaluate vancomycin pharmacokinetics in neonates. However, clinical application of
37 the model-based personalized vancomycin therapy is still limited. The objective of the
38 present study is to evaluate the clinical utility and safety of a model-based patient-
39 tailored dose of vancomycin in neonates.

40 **Methods:** A model-based vancomycin dosing calculator, developed from a
41 population pharmacokinetic study, has been integrated into the routine clinical care in
42 3 NICUs (Robert Debré, Cochin Port Royal, Clocheville Hospitals) between 2012 and
43 2014. The target attainment rate, defined as the percentage of patients with a first
44 therapeutic drug monitoring vancomycin serum concentration achieving the target
45 window of 15-25 mg/L, was selected as endpoint for evaluating the clinical utility. The
46 safety evaluation was focused on nephrotoxicity.

47 **Results:** The clinical application of the model-based patient-tailored dose of
48 vancomycin has been demonstrated in 190 neonates. Mean (SD) gestational and
49 postnatal ages of the study population were 31.1 (4.9) weeks and 16.7 (21.7) days,
50 respectively. The target attainment rate increased from 41% to 72% without any case
51 of vancomycin-related nephrotoxicity.

52 **Conclusion:** This proof-of-concept study provides evidence for integrating model-
53 based antimicrobial therapy in neonatal routine care.

54 **Introduction**

55 Neonatal bacterial sepsis, exacerbated by neonatal immunodeficiency (1), remains a
56 major cause of mortality and morbidity in newborns (2). Vancomycin is widely used for
57 the treatment of late onset sepsis caused by methicillin resistant *staphylococcus*
58 *aureus* and coagulase-negative *staphylococci* in neonatal intensive care units (NICUs)
59 (3), however the clinical use of vancomycin is still hampered by its narrow therapeutic
60 index and high pharmacokinetic variability (4). Indeed, de Hoog et al. reported that
61 vancomycin clearance and half-life varied between 0.63 and 1.4 mL/kg/min, and
62 between 3.5 and 10 hours in neonates, respectively (4). The common adverse effects
63 of vancomycin are nephrotoxicity and ototoxicity, however it has shown that neonates
64 were better tolerated with vancomycin compared with adults. The safety data of high
65 dosing regimen and long-term follow-up are still lacking.”

66 Pharmacokinetic modeling approach is often applied to evaluate and optimize
67 antimicrobial therapy in neonates (5). To date, vancomycin is one of the most studied
68 antimicrobials and numerous studies have been published to characterize its
69 pharmacokinetic parameters and to identify individual factors influencing variability (6).
70 However, the clinical application of the model-based personalized vancomycin therapy
71 is still limited. The objective of the present study was to evaluate the clinical utility and
72 safety of the patient-tailored dose of vancomycin in neonates.

73

74 **Methods**

75 Neonates receiving vancomycin as a continuous infusion in one of three NICUs
76 (Cochin Port Royal, Robert Debré and Clocheville Hospitals) were enrolled between
77 June 2012 and November 2014. This study was designed in accordance with legal
78 requirements and the Declaration of Helsinki, registered at the Commission Nationale

79 Informatique et Liberté (CNIL), and approved by the local research ethics committee
80 (Comité d' Evaluation de l'Ethique des Projets de Recherche Biomédicale [CEERB]).

81 ***Model-based patient-tailored dose of vancomycin***

82 A special training was organised in each NICU: we firstly informed the clinical
83 pharmacology of vancomycin, its pharmacokinetic variability and a large variation of
84 dosage schedules currently used. We then explained the principles of individual
85 dosage adaptation and how we developed the excel dosing calculator using the results
86 from our published population pharmacokinetic model (6):

87 In order to calculate the patient-tailored dosing of vancomycin for each neonate,
88 neonatologists had to enter four patient's covariates in the calculator, including birth
89 weight (g), current weight (g), postnatal age (PNA, day) and serum creatinine
90 concentration ($\mu\text{mol/L}$) measured within 48 hours of starting vancomycin treatment.
91 The developed calculator was locked and no other information was required. Patient-
92 tailored dose is calculated automatically by using the following pharmacokinetic
93 equations:

94 Loading dose (mg) = Target concentration (mg/L) x V (L)

95 Maintenance dose (mg/24 h) = Target concentration (mg/L) x CL (L/h) x 24h

96 where V (L) and CL (L/h) are calculated based on our model [7]:

97 $V = 0.791 \times (\text{current weight}/1416)^{0.898}$

98 $CL = 0.0571 \times (\text{current weight}/1416)^{0.513} \times (\text{birth weight}/1010)^{0.599} \times (1 +$
99 $0.282 \times (\text{PNA}/17)) \times (1/(\text{serum creatinine}/42)^{0.525})$

100 where current weight and birth weight are in g, PNA in days, serum creatinine in
101 $\mu\text{mol/L}$ and target concentration in mg/L.

102 The loading dose is infused over 60 minutes and followed by the maintenance dose
103 administered as continuous infusion over 24 hours. Only patients with complete
104 information were included into the final analysis.

105 ***Clinical utility and safety***

106 The target attainment rate was selected as the endpoint for evaluating the clinical
107 utility of the patient-tailored dose. It was defined as the percentage of patients with a
108 vancomycin serum concentration within the target window of 15-25 mg/L, calculated
109 using the first therapeutic drug monitoring (TDM) sample taken 6-24 hours after
110 starting vancomycin treatment. This TDM practice has become a part of the routine
111 clinical care in the 3 NICUs. One TDM sample per patient (0.5 mL) was required. The
112 relative error to the concentration of 20 mg/L [calculated using the equation: (observed
113 concentration (mg/L) – 20) / 20] was also used to evaluate the impact of covariates on
114 the performance of patient tailored-dose.

115 The safety evaluation was focused on nephrotoxicity, which was evaluated based on
116 changes in serum creatinine concentrations from baseline obtained within 48hours of
117 starting vancomycin administration. Nephrotoxicity was defined as either a two-fold
118 increase or increase by at least 0.6 mg/dL from the start and any time until the end of
119 vancomycin therapy (7). The causality of nephrotoxicity was analyzed individually to
120 discuss potential relation with vancomycin.

121 ***Analytical method of vancomycin***

122 The serum vancomycin trough concentrations were determined by fluorescence
123 polarisation immunoassay using a Cobas Integra system (Roche Diagnostics, Meylan,
124 France). The lower limit of quantification and coefficients of variation were 0.74 mg/L
125 and <3.3% respectively. The TDM samples were analyzed locally in the pharmacology
126 lab of each hospital according to clinical practice. All these three laboratories used the

127 same analytical method, and followed the same external quality control programme
128 and good clinical practice.

129

130 ***Statistical analysis***

131 Results are presented as mean, standard deviation and range. The simple linear
132 regression was used to evaluate the potential impact of patient characteristics (birth
133 weight, current weight, postnatal age and baseline serum concentration) on the
134 relative error to target concentration. The permutational two-sample t-test was used to
135 compare the characteristics of patients who had vancomycin concentration within
136 versus out of the targeted range. Statistical analyses were conducted using R software
137 (V.3.0). A value of $p < 0.05$ was considered statistically significant.

138

139 **Results**

140 ***Study population***

141 The pharmacokinetic and safety data from 190 neonates were available. The mean
142 (SD) current weight and postnatal age were 1755.0 (872.5) grams (range, 540-4750)
143 and 16.7 (21.7) days (range 0-196) days, respectively. Summary of the population
144 characteristics are presented in Table 1.

145 Eight patients were excluded because of incomplete information (creatinine
146 concentration was not measured). Patients were treated for suspected or proven late
147 onset sepsis mainly caused by coagulase-negative staphylococci. Duration of
148 treatment was 7 to 10 days for proven infections and 2 to 5 days for suspected
149 infections.

150 ***Clinical utility of patient-tailored dose***

151 The mean loading dose and maintenance dose were 11.1 mg/kg and 28.3 mg/kg/day,
152 respectively. After receiving these patient-tailored doses, the mean of the first
153 vancomycin TDM concentrations was 20.0 mg/L (10th-90th percentiles: 13.1-27.6). The
154 target attainment rate was 72% (n=136) within the range of 15-25 mg/L (91% within
155 the range of 10-30 mg/L). Only 6 patients (3.1%) had concentrations < 10 mg/L and 12
156 (6.3%) had concentrations > 30 mg/L. TDM results are illustrated in Figure 1.

157 The relative error between observed and target TDM concentrations was not
158 significantly linked to birth weight (p=0.35), current weight (p=0.26), postnatal age
159 (p=0.54) and baseline serum creatinine concentration (p=0.90). Moreover, no
160 significant differences were found between patients who had vancomycin
161 concentration within versus out of the target range, in terms of birth weight (p=0.67),
162 current weight (p=0.65), postnatal age (p=0.69) and serum creatinine concentration
163 (p=0.80).

164 ***Safety of patient-tailored dose***

165 Among the 190 neonates receiving the patient-tailored dose of vancomycin, only 2 (1.1
166 %) patients developed nephrotoxicity. The two neonates were 22 days old (birth
167 weight 760g) and 10 days old (birth weight 990g), respectively. Both of them were
168 treated on the basis of proven coagulase negative staphylococcus infections and the
169 increases of serum creatinine levels (the first one from 0.35 to 1.62 mg/dl, the other
170 one from 0.52 to 1.22 mg/dl) were concomitant with the onset of hemodynamic
171 instability requiring vasoactive drugs (noradrenaline, dopamine). The altered renal
172 function was resolved after restitution of the hemodynamic state, without any cessation
173 of vancomycin therapy or reduction of dose. Therefore, the rise in serum creatinine
174 level was not considered related to vancomycin for these patients.

175

176 **Discussion**

177 The present work provides the evidence-based data to demonstrate the clinical utility
178 and renal safety of a model-based patient-tailored dose of vancomycin in neonates.

179 The findings from population pharmacokinetic study were successfully integrated into
180 neonatal clinical practice to individualise vancomycin therapy, showing that the
181 percentage of patients achieving the target concentrations rose from 41% (using the
182 standard dosing regimen) in our previous study (6) to 72% in the present study. The
183 patient characteristics are similar between the two studies (mean postmenstrual age of
184 33.8 weeks and weight of 1700 grams in our previous study). Most of the patients
185 were preterm neonates and had low birth weight.

186 Due to the wide inter-individual pharmacokinetic variability of many drugs evidenced in
187 neonates (8), dosage individualization is a key issue faced by neonatologists and
188 pediatric pharmacologists to optimize neonatal drug treatment (9). Traditionally, the
189 antimicrobial pharmacokinetic study in neonates was focused on average drug
190 exposure to achieve adult levels and the neonatal recommended dose is usually
191 administered on a mg/kg basis (10). This approach obviously simplifies the analysis of
192 developmental changes in drug disposition and clinical conditions on pharmacokinetic
193 parameters. It assumes an "average newborn" with an "average weight" and therefore
194 a simple linear maturation relationship between weight and drug clearance. This
195 simplification of the complex developmental pharmacokinetics resulted in only 41% of
196 patients achieving the vancomycin target concentrations of 15 to 25 mg/L using the
197 standard mg/kg based vancomycin dose (6).

198 According to regulatory guidelines, antibacterial agents are a good example of drugs
199 for which the exposure-response relationship can be assumed to be similar in adults
200 and neonates. An AUC_{0-24}/MIC ratio (area under the concentration-time curve over

201 24h at steady-state divided by the minimum inhibitory concentration) over 400h has
202 been shown to best predict the clinical and bacteriological response for invasive
203 methicillin-resistant *Staphylococcus aureus* infections in adults (11). Therefore, the
204 target AUC_{0-24} of 400 mg*h/L (assumed a standard MIC of 1 mg/L) was often used as
205 a surrogate of efficacy to optimize dose in neonates. A positive correlation between
206 vancomycin trough concentration and risk of nephrotoxicity was demonstrated in
207 adults (12). Vancomycin (continuous infusion) target concentration of 15 to 25 mg/L
208 allowed achieving this target AUC and demonstrated a good safety profile in the
209 present study.

210 Appropriate neonatal dosage regimen needs to integrate the rapid developmental
211 changes during the neonatal period, as reflected by covariates influencing drug
212 disposition (13). As vancomycin is almost entirely eliminated by the kidneys,
213 covariates reflecting both renal maturation and renal function should be taken into
214 account to personalize vancomycin dosage. Pharmacokinetic modeling approach has
215 been used for many years to evaluate pharmacokinetics of vancomycin (14,15) and
216 identify the major covariates in neonates, including weight, age and creatinine
217 concentration. The next step is now to implement such mathematic tool into clinical
218 practice. Using our developed population pharmacokinetic model, the patient-tailored
219 dose regimen was established and tested prospectively using the identified covariates.
220 In the present study, we have shown a great improvement in the target attainment rate
221 using the patient-tailored dose. The clinical benefits of such personalized therapy are
222 clear: the target attainment rate is reached early and will increase efficacy while
223 reducing the risks of bacterial resistance and toxicity. In addition, the earlier target
224 achievement will reduce the numbers of TDM samples and dosage adjustments.
225 Obviously, the reduced blood loss in newborns has a considerable clinical benefit. Of

226 note, there is still a considerable number of neonates (28%) had first TDM
227 concentration out of target range, making TDM still recommended for vancomycin
228 therapy in neonates.

229 Only 2/190 (1.1%) neonates showed nephrotoxicity as quantified by serum creatinine
230 concentration during vancomycin treatment and this was most probably related to
231 patients' clinical condition and hemodynamic instability. In a previous study, Bhatt-
232 Metha et al. reported 8.7% (n=6/69) newborn infants with nephrotoxicity (using the
233 same definition that in our study) while receiving standard vancomycin dose
234 administered as an intermittent infusion (7). Although it is not possible to directly
235 compare these safety results because of different method of administration, our study
236 did not evidence any deleterious effect on renal function with the patient-tailored dose
237 of vancomycin administrated as a continuous infusion.

238 A limitation of our study is that all the patients were followed until the end of
239 hospitalization and the long-term follow-up data was not available. Obviously, the
240 developmental toxicity, e.g. ototoxicity, cannot be evaluated in our study and a long-
241 term safety study of vancomycin is required in neonates (16). Despite the limitation of
242 the use of creatinine concentration as a surrogate of nephrotoxicity in neonates, it
243 allows us to compare the incidences of nephrotoxicity with previously published
244 studies (4, 7). Numerous novel biomarkers of nephrotoxicity (i.e. N-acetyl-
245 glucosaminidase, neutrophil gelatinase-associated lipocalin, cystatin C etc.) are being
246 studied, however, the clinical value of these biomarkers needs to be validated in
247 neonates (17). The training of the correct use of dosing calculator is extremely
248 important. The impact of entering imprecise covariates information into the calculator
249 may introduce medication error. As highlighted by the excluded patients, the serum
250 creatinine concentration changes rapidly at the beginning of the life. The individual

251 dose, calculated using creatinine measured far always from day of starting treatment,
252 may have 2-fold difference. Obviously, the error of dose calculation will increase the
253 risks of toxicity or treatment failure.

254 In summary, a model-based patient-tailored dose of vancomycin administered as a
255 continuous infusion has been successfully implemented in routine care in 3 NICUs and
256 demonstrated positive results in terms of pharmacokinetics and safety. This study
257 really provides a proof-of-concept for the clinical utility and safety of model-based
258 patient-tailored dosing regimen of vancomycin in neonates. The next step will be to
259 confirm our results with a prospective controlled trial. This innovative personalized
260 dosing approach, certainly applicable to other antimicrobial therapy, is a promising
261 way to optimize drug therapy in neonates.

262

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269 **Conflict of Interest**

270 The authors declare no conflict of interest related to this work.

271 **VANCO IVC** (Continuous intravenous administration of vancomycin) **study group**

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338

339 **Table and Figure**

340 Table 1- Baseline characteristics of the 190 neonates

341

342 Figure 1- Vancomycin first TDM concentrations after receiving the model-based
343 patient-tailored dose regimen in 190 neonates

344

345 Figure Legend:

346 The first Therapeutic Drug Monitoring samples are taken 6 to 24 hours after starting
347 vancomycin treatment (one sample per patient)

348 The bold lines represent the boundaries of the target concentrations

349 The points represent observed concentrations (mg/L)

350

1

Table 1- Baseline characteristics of the 190 neonates

2

	Number	Mean (sd)	Median (range)
Patients	190		
Gestational age (weeks)		31.1 (4.9)	30 (24-42)
Birth weight (g)		1563.0 (844.0)	1290 (512-4180)
Current weight (at time of dosing) (g)		1755.0 (872.5)	1525 (540-4750)
Postnatal age (days)		16.7 (21.7)	10 (0-196)
Baseline serum creatinine concentration* ($\mu\text{mol/L}$)		48.6 (21.8)	46 (14.0-125.0)
Vancomycin loading dose (mg/kg/day)		11.1 (0.6)	11.1 (9.9-12.6)
Vancomycin maintenance dose (mg/kg/day)		28.3 (9.9)	25.4 (13.0-61.0)

3

4 *within 48 hours before inclusion

