

# Design of modified vancomycin dosage guidelines

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# Concerns with current guidelines

- Troughs are mainly 10 – 15 mg/L but targets for serious infection are 15 - 20 mg/L
- Trough concentrations too low in the first 24-48 hours
- Underdosing observed in young patients with high creatinine clearance
- Difficult to identify optimal doses for obese patients

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

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## IDSA guidelines 19 March 2020

- “Trough-only monitoring, with a target of 15 to 20 mg/L, is no longer recommended based on efficacy and nephrotoxicity data...”
- “... an individualized target AUC of **400 to 600 mg.h/L** ( $MIC_{BMD}$  of 1 mg/L) should... achieve clinical efficacy while improving patient safety”

Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections:  
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## IDSA adult dosage guidelines 19 March 2020

- **Loading dose**                      20 – 35 mg/kg actual body weight (max **3000 mg**)
- **Maintenance dose**              15 – 20 mg/kg actual body weight every 8 – 12 hours (max **4500 mg** daily)


# Proposed revisions to current guidelines - based on collaborative work with group in the Netherlands

Clinical Pharmacokinetics (2019) 58:767–780  
<https://doi.org/10.1007/s40262-018-0727-5>

ORIGINAL RESEARCH ARTICLE



## Vancomycin Pharmacokinetics Throughout Life: Results from a Pooled Population Analysis and Evaluation of Current Dosing Recommendations

Pieter J. Colin<sup>1,2</sup>  · Karel Allegaert<sup>3,4,5</sup> · Alison H. Thomson<sup>6</sup> · Daan J. Touw<sup>7,8</sup> · Michael Dolton<sup>9</sup> · Matthijs de Hoog<sup>10</sup> · Jason A. Roberts<sup>11</sup> · Eyob D. Adane<sup>12</sup> · Masato Yamamoto<sup>13</sup> · Dolores Santos-Buelga<sup>14</sup> · Ana Martín-Suarez<sup>14</sup> · Nicolas Simon<sup>15</sup> · Fabio S. Taccone<sup>16</sup> · Yoke-Lin Lo<sup>17,18</sup> · Emilia Barcia<sup>19</sup> · Michel M. R. F. Struys<sup>1,20</sup> · Douglas J. Eleveld<sup>1</sup>

- Pooled population pk analysis of 14 studies, 2554 patients, 8300 concentrations
- 720 adults, 512 elderly, 158 underweight, 274 obese, 559 newborns, 118 children and adolescents
- Vancomycin clearance related to postmenstrual age, weight, creatinine concentration, volume of distribution related to weight

ARTICLE

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

Pieter J. Colin<sup>1,\*</sup>, Douglas J. Eleveld<sup>1</sup> and Alison H. Thomson<sup>2</sup>

- Simulation study based on 1,625 adults from 2019 study; virtual population of 10,000 patients
- Algorithm aimed to optimise doses to achieve  $AUC_{24}$  in the range 400 to 600 mg.h/L  
Doses rounded to 250 mg, intervals constrained to 6, 8, 12, 24, 48 h
- Fraction of  $AUC_{24}$  for 24, 48, 72 hours within 400 – 600 mg.h/L range compared for current, modified and “optimised” dosage guidelines

# Loading doses (*Colin et al, 2020*)

	Original SAPG dosing guideline	Modified SAPG dosing guideline	GA –based optimal solution
Patient weight (kg)		Loading dose (mg)	
< 40	750	750	1000
40 – 59	1000	1000	1500
60 – 89	1500	1500	2000
> 90	2000	-	-
90 – 119	-	2000	2500
120 -160	-	2500	3250
> 160	-	3000	3750

- Some “optimised” doses above 35 mg/kg and 3000 mg recommended by IDSA

# Recommended loading doses

Current guidelines		Modified guidelines		
Patient weight (kg)	Loading dose (mg)	Patient weight (kg)	Loading dose (mg)	Dose range (mg/kg)
		<35	25 mg/kg	25
<40	750	35 - 44	1000	23 - 28
40 - 59	1000	45 - 59	1500	25 - 33
60 - 89	1500	60 - 89	2000	22 - 33
>90	2000	90 - 119	2500	21 - 28
		>120	3000	≤25



# Maintenance doses (*Colin et al, 2020*)

	Original SAPG dosing guideline	Modified SAPG dosing guideline	GA –based optimal solution
<b>Patient eCL<sub>CR</sub> (mL/min)</b>		<b>Maintenance dose (mg) / tau (h)</b>	
< 20	500 / 48	500 / 48	750 / 48
20 – 25	-	500 / 24	500 / 24
20 – 30	500 / 24	-	-
26 – 34	-	750 / 24	1000 / 24
30 – 40	750 / 24	-	-
35 – 49	-	500 / 12	1250 / 24
40 – 55	500 / 12	-	-
50 – 69	-	750 / 12	750 / 12
55 – 75	750 / 12	-	-
70 – 89	-	1000 / 12	500 / 8
75 – 89	1000 / 12	-	-
90 – 119	-	750 / 8	750 / 8
90 – 110	1250 / 12	-	-
> 110	1500 / 12	-	-
120 – 180	-	1000 / 8	1000 / 8
> 180	-	1250 / 8	1250 / 8

ARTICLE

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Pieter J. Colin<sup>1\*</sup>, Douglas J. Eleveld<sup>1</sup> and Alison H. Thomson<sup>2</sup>

Range	Current	Modified	Optimal
Median AUC <sub>24ss</sub>	548	574	582
Median C <sub>ss</sub> average	22.8	23.9	24.5
Median C <sub>ss</sub> trough	14.6	16.8	16.7

# Maintenance dose options

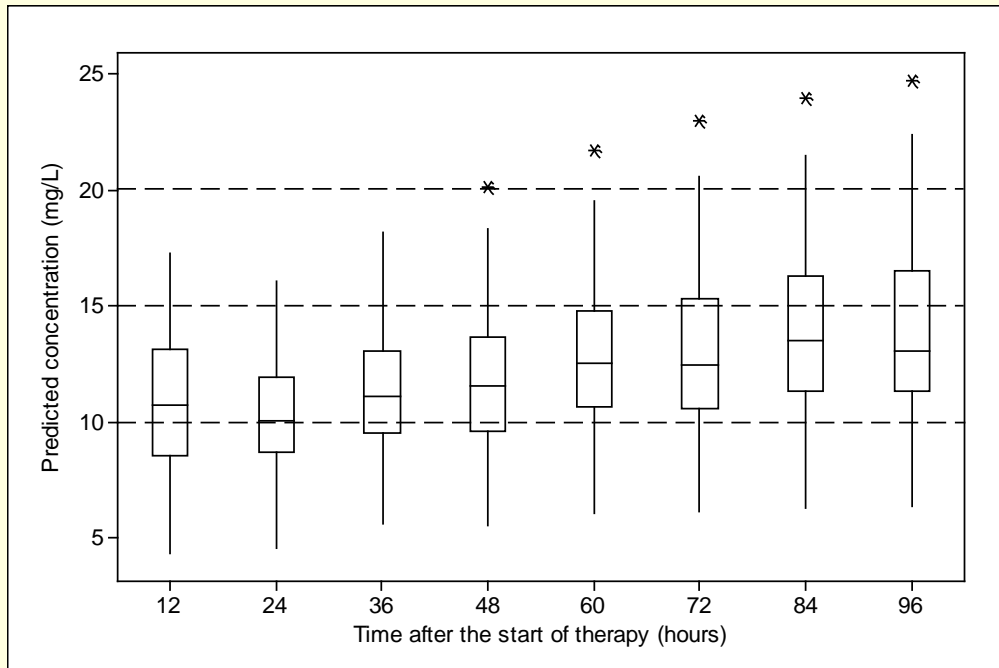
Current guidelines		Modified guidelines	
Creatinine CL (ml/min)	Maintenance dose (mg/h)	Creatinine CL (ml/min)	Maintenance dose (mg/h)
<20	500/48	<20	500/48
20-30	500/24	20-25	500/24
30-40	750/24	26-34	750/24
40-55	500/12	35-49	500/12
55-75	750/12	50-69	750/12
75-89	1000/12	70-89	1000/12
90-110	1250/12	90-119	1250/12
>110	1500/12	120-180	1500/12
		>180	1250/8

# Obesity

- Simulations used **total body weight** but population model has a **non-linear relationship** between weight and clearance
- **Current guidelines**
  - creatinine clearance estimate uses actual weight to a maximum of ideal body weight (IBW)+20%
- **Modified guidelines**
  - use “adjusted body weight” to estimate renal function
  - **AJBW = IBW + 0.4 (TBW-IBW)**
  - more evidence-based than “maximum body weight”

# Predicted vancomycin troughs with current and modified guidelines (validation data from 2009, n = 100)

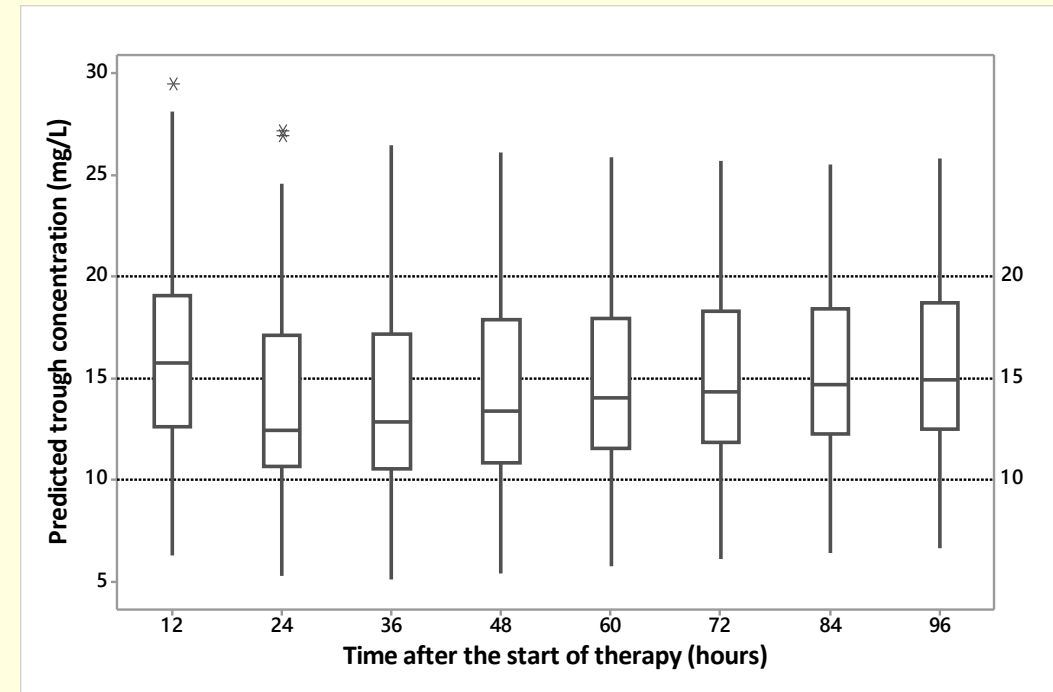
## Current guidelines



Predicted  $AUC_{24}$  520 (124) **mg.h/L**

Predicted  $C_{av}^{SS}$  21.7 (5.2) **mg/L**

## Modified guidelines



Predicted  $AUC_{24}$  550 (90) **mg.h/L**

Predicted  $C_{av}^{SS}$  22.9 (3.8) **mg/L**

# Summary

## Loading doses

- Modified loading doses should achieve target  $AUC_{24}$  and trough concentrations earlier
  - *Concentrations will remain high for prolonged periods in patients with poor renal function*

## Maintenance doses

- Modified guidelines will achieve higher concentrations in some patients, lower in others
- Similar  $AUC_{24}^{ss}$  and  $C_{av}^{ss}$
- Higher doses if creatinine clearance  $> 180$  ml/min