

Final Study Report

Study Title: *Impact of model-informed precision dosing in adults receiving vancomycin via continuous infusion: a randomized, controlled clinical trial*

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Sponsor: *Ghent University Hospital*

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Funder: *not applicable*

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Date of report: *12/05/2026*

By signing this final study report, I acknowledge that the information is accurate and complete.

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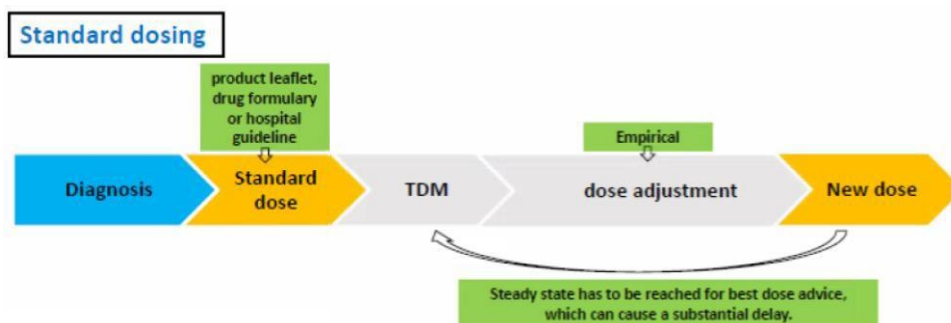
1. Introduction

Vancomycin is a commonly prescribed antibiotic to treat serious gram-positive infections, predominantly in the empirical and directed treatment of septicemia, endocarditis, bone infections and skin and soft-tissue infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of these community or healthcare associated infections, with vancomycin as the cornerstone therapy.^{1,2} According to the last prevalence report from the European Antimicrobial Resistance Network, in 2018, 9,1% of invasive staphylococcal infections are due to methicillin-resistant *Staphylococcus aureus* in Belgium, with proportions of up to 43 % in some regions in the European Economic Area (EEA).³

Efficacy of vancomycin is known to be directly related to the pharmacokinetic/pharmacodynamic (PK/PD) index of area under the concentration-time curve (AUC) divided by the minimal inhibitory concentration (MIC) of the pathogen (AUC/MIC). To date, the advocated steady-state 24 hour AUC/MIC for favorable clinical outcome in humans with methicillin-resistant *Staphylococcus aureus* and enterococci infections is at least 400.⁴ Since MIC measurements are not standard-of-care in most institutions and MIC measurements are prone to twofold errors, a MIC of 1 mg/L was chosen. Moreover, for pathogen isolates with an MIC of 2 mg/L or higher (measured using the reference technique of broth macrodilution), it is presumed that the optimal AUC/MIC cannot be achieved safely, and an alternative agent is strongly encouraged.⁴ On the other hand, a 24 hour AUC of 600 µg/L*h or higher is known to be independently associated with increased risk of acute kidney injury (AKI), indicating its narrow therapeutic index.⁵

There is a high heterogeneity in reported AKI incidences in patients treated with vancomycin. For continuous infusion dosing regimens, incidences from 3,6% to 27,7% are reported in critically ill patients.⁶ Continuous infusion of vancomycin is also used in outpatient parenteral antibiotic therapy (OPAT) with reported nephrotoxicity incidence of 15,7% and described risk factors been the concomitant use of other nephrotoxic agents, hypertension, renal disease or increased serum creatinine at baseline.⁷ It is further known that (even mild) AKI is linked to significantly increased morbidity, mortality, hospital length of stay and costs.⁸

To date, vancomycin is commonly initiated on a mg per kg basis according to institutional guidelines. After reaching steady-state conditions (24 hours after start of a continuous infusion), therapeutic drug monitoring (TDM) is performed to ensure attainment of target concentrations.⁴ Since traditional AUC/MIC calculations cause much patient burden and are labour- and cost-intensive, in routine practice, steady-state plasma concentrations (C_{ss}) are measured as a 'surrogate' single-point parameter for target AUCs during continuous infusion dosing regimens.⁴ If necessary, empiric dose adjustments are performed, aiming at a steady-state plasma concentration target ranges for continuous infusions (see figure below).⁹



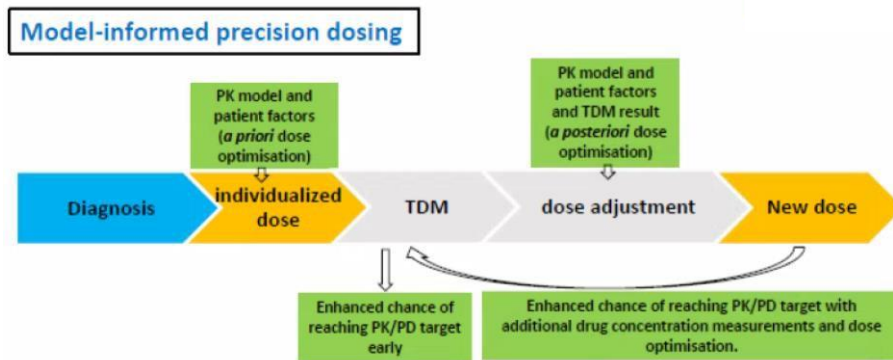


Figure: Standard versus model-informed precision dosing (adapted from Tängden et al. Intensive Care Med. 2017;43(7):1021-1032)

Pharmacokinetic (PK) modelling involves the development of mathematical models to describe a drug PK behavior. Once available, these models can be used to predict the drug PK in the individual patient. In the Bayesian approach, estimates of an individual patient's PK parameters (e.g. clearance and volume of distribution), are provided using the PK model and patient characteristics (e.g. weight, age, serum creatinine) known as prior information. Then when a TDM concentration becomes available, PK parameters can be re-estimated using this new source of information. These PK estimates, referred to as the Bayesian conditional posteriors, can be used to estimate a patient-specific AUC.

In recent decades, a priori Bayesian (without TDM) and a posteriori (in combination with TDM measurement(s)) model-informed precision dosing (MIPD) has extensively been used to ensure efficacious antibiotic treatment with significant success (**Figure 1**).^{9,10} For vancomycin, Bayesian AUC guided MIPD has been shown to lead to significantly decreased nephrotoxicity, lower total vancomycin doses, reduced per-patient blood sampling, and shorter length of therapy in adults receiving intermittent dosing, without compromising efficacy, when compared to trough-only monitoring.^{4,5,11}

Besides improved clinical outcome, most modern Bayesian MIPD is more “patient- and caregiver-friendly” by allowing AUC estimation using one blood sample taken at a most convenient time point. Moreover, this approach implies that vancomycin concentrations can be measured on left-over samples obtained from daily clinical care (i.e. opportunistic or scavenged sampling).^{4,12}

Bayesian model-informed precision dosing is widely applied now, and is being considered the gold standard for vancomycin dosing in some countries like the Netherlands and Australia.^{13,14} However, to date, it remains a complex task requiring intervention from “happy few” specialists in those countries with solid knowledge of clinical pharmacology, PK modelling, and clinical guidelines.¹⁵

This low uptake is due to the lack of high-level clinical evidence on its clinical impact and the absence of validated, easy-to-use, “clinician proved” software tools.⁴

2. Objectives of the study

The overall objective of this study was to investigate the utility of model-informed precision dosing of vancomycin in adults.

2.1 Primary objectives

This study tested the primary hypothesis that AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator, increases the proportion of patients reaching the therapeutic target AUC_{24h}/MIC (400-600) between [48-72] h after start of treatment, when compared to the use of standard-of-care dosing regimens with therapeutic drug monitoring.

2.2 Secondary objectives

This study also aimed to test the following secondary hypotheses:

- AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator, reduces the proportion of patients with (worsening) acute kidney injury during and until 48 hours after stop of treatment with vancomycin, when compared to the use of standard-of-care dosing regimens with therapeutic drug monitoring;
- AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator, increases the proportion of patients reaching the therapeutic target AUC_{24u}/MIC (400-600) between [72-96] h after start of treatment, when compared to the use of standard-of-care dosing regimens with therapeutic drug monitoring;
- AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator, increases the proportion of time within therapeutic target range AUC_{24u}/MIC (400-600) during vancomycin treatment, when compared to the use of standard-of-care dosing regimens with therapeutic drug monitoring;

2.3 Tertiary objectives

This study also aimed to test the following tertiary hypotheses:

- AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator reduces the number of (additional) blood samples during treatment, when compared to the use of standard-of-care dosing regimens with therapeutic drug monitoring;
- AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator reduces the cumulative number of (additional) blood samples during treatment, when compared to the use of standard-of-care dosing regimens with therapeutic drug monitoring;
- AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator reduces the number of dose adjustments during treatment, when compared to the use of standard-of-care dosing regimens with therapeutic drug monitoring;
- AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator reduces the cumulative vancomycin dose and corresponding AUC during vancomycin treatment, when compared to the use of standard-of-care dosing regimens with therapeutic drug monitoring.

3. Investigational Medicinal Product

3.1 MIPD dosing calculator

MIPD dosing calculator: InsightRX software (<https://insight-rx.com/>) is a web application for pharmacokinetic and pharmacodynamic (PK/PD) analysis. It is intended for use in a hospital setting with a desktop or personal computer enabled with internet access. It allows integration in hospital information systems eg. Electronic Health Record (EHR) to enable automated data transfer of user identifying information, and patient identifying information and required clinical data.

The software allows end-users to leverage population PK/PD models and Bayesian estimation/fitting methods to forecast, calculate, analyze individual patient PK/PD characteristics in real-time (e.g. 24h AUC and cumulative AUC for vancomycin).

The Colin et al. PK vancomycin model was implemented in the MIPD dosing calculator.¹⁶ It is a meta-analysis PK model, pooling PK data from premature neonates to elderly, ICU and obese patients (n=2554 patients). In this model, current weight, age and serum creatinine are input variables for dose forecasting, eventually in combination with individual vancomycin measurements.¹⁶ This model was chosen since it was one of the best performing models in retrospective data-analysis within of the patient population of UZ Ghent and AZ Sint Jan Bruges receiving vancomycin treatment.¹⁷

AUC-based dose estimation

In the interventional arm, vancomycin starting doses were prescribed by the attending physician according to the institutional dosing regimen guidelines. After initially dosing, dose adjustments were based on a posteriori (Bayesian) MIPD software dose calculations carried out by clinical pharmacists.

Dose adjustments suggested by the MIPD software end-user were directly communicated to the attending physician and subsequently implemented/prescribed.

Starting (1st) dose regimen:

Loading dose and starting continuous infusion rate dosing were initiated by the attending physician according to the institutional dosing regimen guidelines.

Dose calculations:

AUC_{24h} was estimated within an 8h interval after the TDM concentration became available in the lab report using following input variables in the Colin et al model, targeting a AUC_{24h} of 400 to 600 between 48 and 72h after start treatment: weight, age, measured serum creatinine, dosing history and TDM concentration.

3.2 Vancomycin

Vancomycin is a commonly prescribed glycopeptide antibiotic drug with activity against most Gram positive pathogens including Staphylococci e.g. methicillin resistant *Staphylococcus aureus* or *Staphylococcus epidermidis*.

Vials for intravenous administration are available on the Belgian market in 500 mg and 1 G quantities. Two generic brands were commercially available on the Belgian market at the time the study was conducted (Vancomycin Mylan® and Vancomycin Sandoz®).

Vancomycin exerts a large interpatient variability in drug exposure. To avoid therapy failure and toxicity, therefore, therapeutic drug monitoring, eventually in combination with model-based precision dosing tools for a priori and/or a posteriori dosing is performed and within the marketing authorization.¹⁴

4. Study Protocol Summary

4.1 Study design

This study was a prospective individual randomized clinical trial in hospitalized non-ICU adult patients. Patients were randomized to the standard-of-care comparator or intervention arm.

4.2 Inclusion criteria

- age: ≥18 years
- admitted to the participating ward units (non-critically ill patients)
- suspected or confirmed Gram positive infection
- planned to start or started on intravenous continuous infusion (CI) vancomycin treatment.
 - if the patient was previously treated with vancomycin, the minimum interval to a previous vancomycin treatment episode is 48 hours
- informed consent signed by the patient or legal representatives (details section 8.2)
- not previously enrolled in this trial

Note: a patient restarted on vancomycin within the 20 day study period is considered not a new enrollment if previous vancomycin treatment did not exceed 48 hours and should receive the treatment assigned for the first episode of vancomycin dosing.

4.3 Exclusion criteria

- extracorporeal treatment at inclusion (extracorporeal membrane oxygenation, dialysis, body cooling)
- serum creatinine level above 2.5 mg/dL at inclusion

- patient death is deemed imminent and inevitable

4.4 Primary endpoint

Proportion of patients reaching target AUC_{24h}/MIC (400-600) between 48h and 72h after start of vancomycin treatment

4.5 Secondary endpoints

- Proportion of patients with (worsening) AKI during and until 48h after stop of vancomycin treatment

AKI classes were defined using the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury.¹⁸

- Proportion of patients reaching target 24hAUC (400-600) between [72 to 96] h after start of vancomycin treatment
- Proportion of time within target 24hAUC (400-600)

4.6 Tertiary endpoints

- Number of (additional) blood samples during vancomycin treatment
- Cumulative number of (additional) blood samples during vancomycin treatment
- Number of dose adjustments during vancomycin treatment
- Cumulative vancomycin dose and AUC during vancomycin treatment

4.7 Procedures

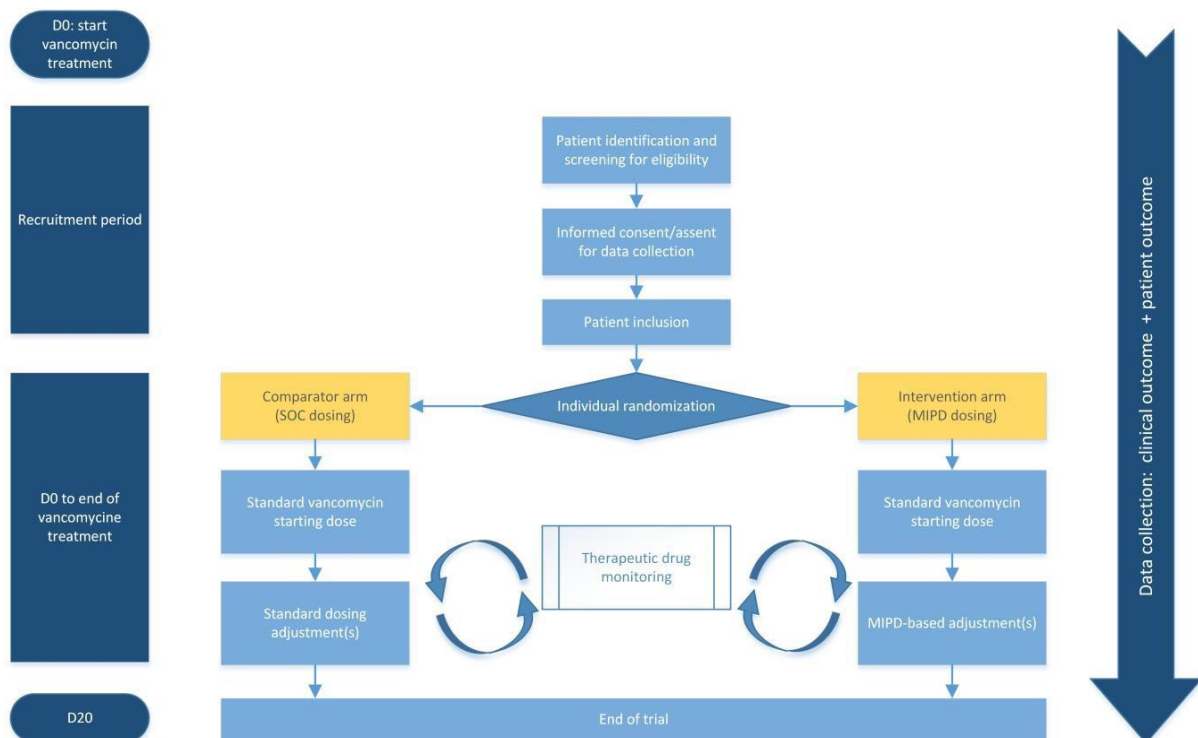


Figure: Study flowchart

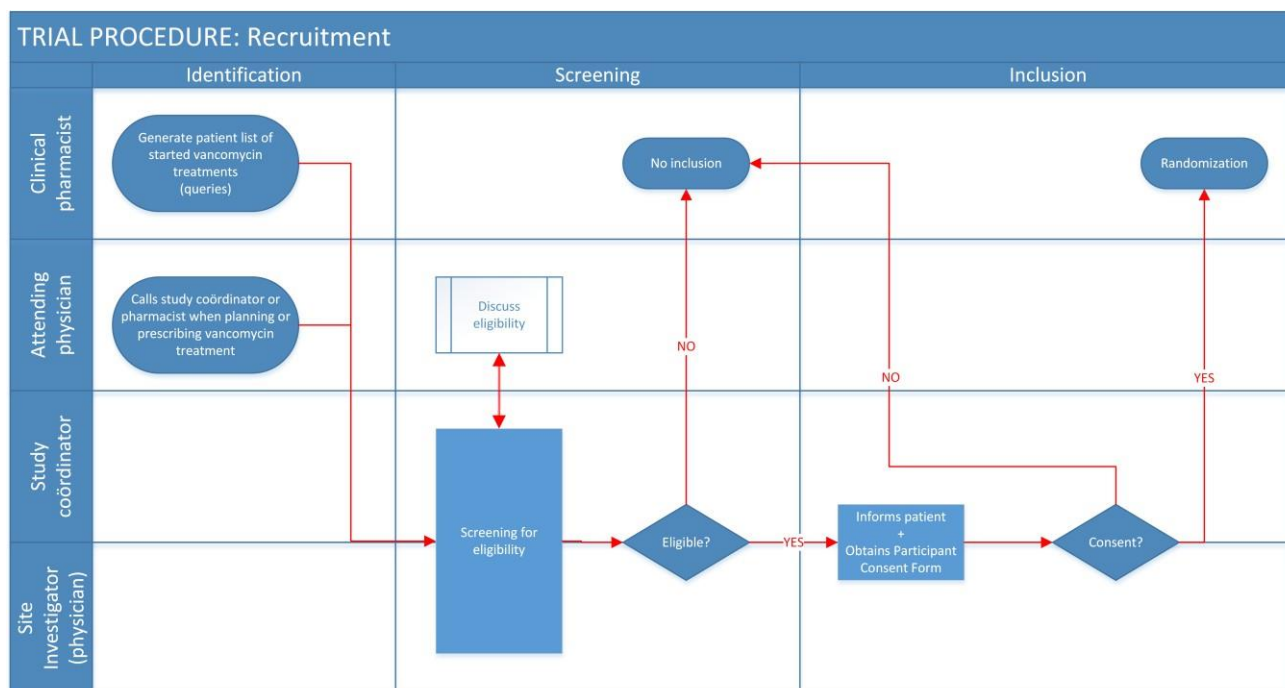


Figure: Flowchart recruitment

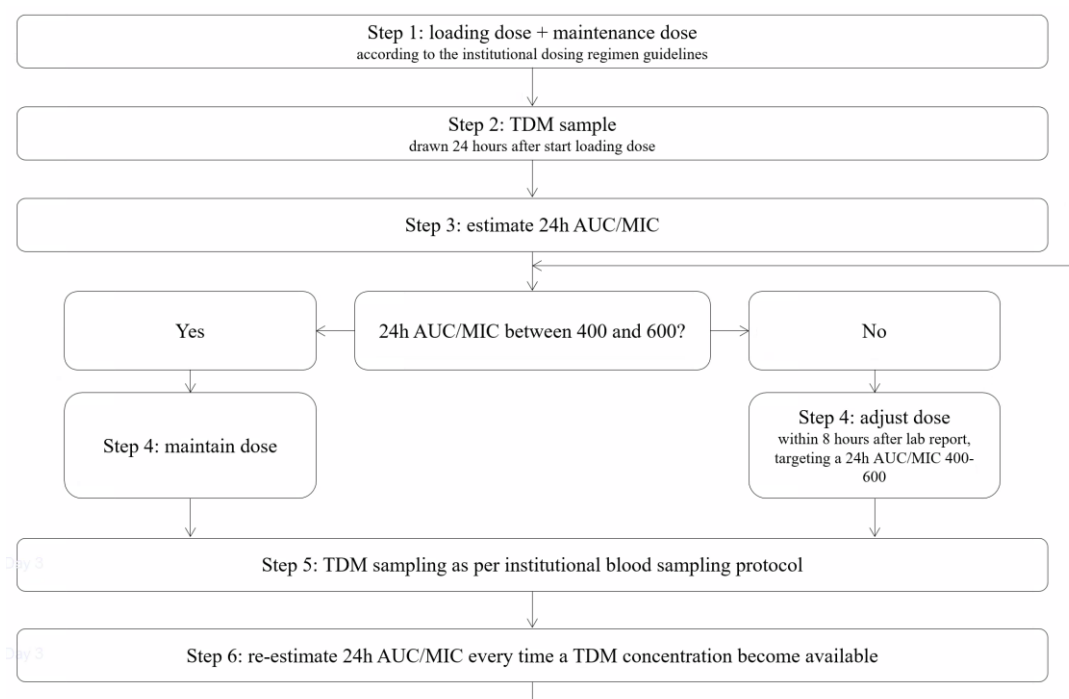


Figure: Workflow for AUC/MIC-based dose calculation and dose adjustment in the intervention arm

4.8 Randomization and blinding

Trial randomization

Patients were randomly allocated to the interventional arm or standard-of-care arm at inclusion. The study was a parallel-group RCT with a 1:1 allocation ratio. Randomization was stratified by medical discipline. Random permuted blocks was created with a computer random number generator with variable size (sizes 2, 4, 6 and 8) permuted blocks to avoid that the treatment allocation can be predicted.

The stratified randomization was performed using the randomization module of REDCap (Research Electronic Data Capture). REDCap is a secure, web-based application designed to support data capture

for research studies. The REDCap software randomized patients based on an allocation table that is provided by the statistician.

Before a patient was randomized, the baseline characteristics (at least the stratification factor medical discipline) of the patient needed to be entered in REDCap.

Following randomization and during the 20 day study period, every effort was made to ensure patients continued to receive the assigned dosing method:

- If vancomycin was stopped and treatment was recommenced prior to D20 on a ward unit participating in the study, the study assigned dosing method needed to be followed.
- If a patient was still prescribed vancomycin following discharge from the participating ward unit to a ward unit not participating in the study or home, the standard dosing method was used.
- If a patient was readmitted from home or a ward unit not participating in the study to one of the participating ward units, the study assigned dosing method needed to be followed.

Blinding

The research team, physicians and clinical pharmacists were unblinded to the allocation of individual patients, except for the statistician who was kept blinded until after the data analysis. Participants or legal representatives were blinded for the allocation to the intervention or standard-of-care arm until the end of the study.

4.9 Monitoring and quality measures

Regular on-site and remote monitoring was performed by the sponsor's CTU HIRUZ according to ICH GCP E6(R2) and all applicable regulatory requirements.

Prior to commencing recruitment, the monitor met the study team by a trial initiation visit to review trial specific procedures such as the protocol, safety reporting procedures, ICF procedures, ISF content, PI's responsibilities, eCRF completion guidelines and study timelines. Following written standard operating procedures (SOP), the monitors verified on-site whether the clinical trial was conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Data recorded in the eCRF was evaluated for accuracy in relation to source documents. The monitor provided a monitoring report after each visit for the sponsor and the investigator. The frequency, extent and nature of monitoring was defined in more detail in a monitoring plan.

5. Study analysis

5.1 Sample size calculation

Sample size calculation for the primary analysis was performed in SAS version 9.4 using the power procedure. The outcome on which this sample size calculation was based upon, was the proportion of patients reaching target AUC_{24h}/MIC between 48 and 72h after start vancomycin treatment.

The sample size calculation was based on the assumption that the proportion of patients reaching the therapeutic target 24h AUC/MIC (400-600 mg*h/L) between [48 to 72] h after start of treatment is 50% in the standard-of-care dosing group and 75% in the AUC/MIC based vancomycin dosing group. Since patients are randomized individually, patients of both groups (standard-of-care and AUC/MIC based vancomycin dosing) will be treated in the same ward.

Sample size calculation based on actual sample size of the interim analysis:

An interim analysis was applied after inclusion of 26 patients.

O'Brien-Fleming approach was applied to ensure that these additional analyses do not increase the chance for a type I error (a false positive conclusion). Alpha levels defined based on the O'Brien-Fleming approach were 0.02% for the interim analysis and 4.99 % for the final analysis.

In total 116 participants (for which the primary endpoint is available) were required to achieve power ($1-\beta$) of 80% at a significance level (α) of 4.99 %, to detect an OR of 3 ($b= 1.099$) when the proportion in the control group is 50% (odds=1, intercept= 0) using logistic regression. An assignment ratio of 1 was applied.

The actual power with a total sample of 118 patients for which the primary endpoint (between 48h and 72h after start of vancomycin treatment) could be calculated, was 80.9%.

5.2 Framework

This was a superiority trial to compare the intervention arm (MIPD) with the standard-of-care arm.

5.3 Statistical methods for primary outcome analysis

A logistic regression model was applied, with “reaching the target 24h AUC/MIC between 48h and 72h after start vancomycin” as binary outcome variable and with randomization group (interventional versus the standard-of-care arm) as categorical predictor of interest. The stratification factor “medical discipline” was added as a covariate in the model.

The primary analysis is the intention-to-treat analysis, preferably performed because it avoids bias associated with non-random loss of participants. All randomized patients were included in the analysis in the groups to which they were originally assigned, regardless of what subsequently occurred. Imputation techniques were used for outcome data that are missing. The intervention effect was expressed by using the OR, together with the estimated proportion per group.

Intercurrent events

The ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials was taken into account when defining the strategy for handling intercurrent events [European Medicines Agency (2021)]. The intercurrent events for the primary outcome and corresponding strategy for data analysis are summarized below.

Intercurrent events (if occurring within 72h after start vancomycin)	Strategy for accounting intercurrent events
Death	Composite strategy – Subjects who die will be considered to have an unfavourable outcome
Discontinuation of vancomycin treatment because of	
clinical cure	Composite strategy – Subjects will be considered to have a favourable outcome
adverse event	Composite strategy – Subjects will be considered to have an unfavourable outcome
clinical failure	Composite strategy – Subjects will be considered to have an unfavourable outcome
no Gram-positive microbiological culture or only contamination in microbiological culture	Composite strategy – Subjects will be considered to have a favourable outcome
Treatment withdrawal in the context of palliative care	While on treatment strategy – Estimated AUC/MIC prior to the discontinuation of vancomycin treatment The “while on treatment strategy” is not expected to cause bias because the occurrence of the intercurrent event is not expected to differ between the treatments being compared (the occurrence of this ICE will be reported by treatment arm)
Discontinuation of vancomycin treatment because of change in antimicrobial therapy within 72h after start vancomycin	While on treatment strategy – Estimated AUC/MIC prior to the discontinuation of vancomycin treatment The “while on treatment strategy” is not expected to cause bias because the occurrence of the intercurrent event is not expected to differ between the treatments being compared (the occurrence of this ICE will be reported by treatment arm)

Treatment switch (intervention and standard-of-care or vice versa)	Treatment policy strategy – Observed outcomes are used regardless of whether or not this IE occurred
Early discontinuation of calculator	Treatment policy strategy – Observed outcomes are used regardless of whether or not this IE occurred
Major protocol deviation with possible impact on primary endpoint	Treatment policy strategy – Observed outcomes are used regardless of whether or not this IE occurred

Table: The intercurrent events for the primary outcome and corresponding strategy for data analysis

Statistical methods to handle missing data

The primary analysis was based on the multiple imputed data. All participants were included in the analysis in the groups to which they were originally assigned, regardless of what subsequently occurred. Multivariate imputation by fully conditional specification was used to apply multiple imputation of missing data. The imputation model will be applied separately by randomization group. The predictors used for the imputation model included:

- Medical discipline
- Nephrotoxic medication (at randomization or start date nephrotoxic medication smaller or equal to start date vancomycin + 3 days)
- Duration of treatment
- Vancomycin start dose
- Age, serum creatinine (mg/dL) and weight at baseline

Once the missing AUCs were imputed, the obtained values were converted to the binary outcome variable “reaching the target 24h AUC/MIC between 48h and 72h after start vancomycin”.

Results of the logistic regression model with categorical predictors randomization group (predictor of interest) and “Medical discipline” (stratification factor) were pooled using the pool() function of the mice R-package.

Additional estimand for the primary endpoint

The unconditional Absolute Risk Difference and the proportion of patients reaching primary endpoint were estimated in line with the 2023 Food and Drug Administration guidance “Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products”. The unconditional treatment effect for the primary outcome was calculated using the plug-in estimator as described by Freedman et al. By averaging predicted probabilities based on the logistic regression model.¹⁹ In order to reduce the variability of the estimation of the treatment effect and thus obtain narrower CIs and more power, the model was correct for the following potentially prognostic baseline covariates (these covariates are a selection of the baseline covariates included in the imputation model):

- Medical discipline
- Baseline serum creatinine (mg/dL)
- Weight
- Age
- Indication for vancomycin treatment

Ninety-five percent CIs around the proportions and the unconditional Absolute Risk Difference were computed using the Boot MI method as described in Schomaker et al.: 2000 bootstrap samples (including missing data) D^* were drawn, and each of them was imputed 5 times using the same imputation model as described for the “Primary analysis/estimator for the main estimand for the primary objective”. Thus, there were 10 imputed data sets for each bootstrap sample D^* . Point estimates for the Absolute Risk Differences are obtained for each of these 2000 bootstrap samples. The set of ordered point estimates was used to construct the 95% CI for the unconditional Absolute Risk Difference.

Subgroup analyses

Prespecified subgroup analyses for the primary outcome were carried out according to medical discipline and the presence of a documented bacterial infection. A documented infection was defined

as an infection with a pathogen grown in blood or sterile site or an abscess or volume of infected tissue e.g. pneumonia, soft tissue.

A first post-hoc non-predefined subgroup analysis was performed for the factor study site (Ghent University Hospital versus General Hospital Sint-Jan Bruges AV). The statistical methods were analogous as used for the 'Primary analysis'. The subgroup variable study site was incorporated into the model as a categorical predictor. The interaction term between study site and randomization group (intervention arm versus standard-of-care arm) was included in the model.

A second post-hoc non-predefined subgroup analysis was performed for the factor target range according to the standard-of-care (20-25 mg/L versus 25-30 mg/L). For the intervention arm, these target ranges were hypothetical. The statistical methods were analogous as used for the 'Primary analysis'. The subgroup variable target range was incorporated into the model as a categorical predictor. The interaction term between target range and randomization group (intervention arm versus standard-of-care arm) was included in the model.

Sensitivity analysis

For the primary analysis, low model prior weight (0.3) was used to estimate the AUC. To assess the sensitivity of the results to the choice of model prior weight, an MIPD sensitivity analysis with a model prior weight of 0.5 was performed. The statistical analyses were the same as the analysis for the estimator for the main estimand for the primary objective, and the additional estimand for the primary objective.

5.4 Statistical methods for secondary endpoints

The secondary outcomes (worsening) AKI and "Proportion of patients reaching target 24h AUC between [72 to 96] h AUC/MIC after start treatment" were analysed using the same methods as for the primary outcome. For (worsening) AKI a different set of predictors was used in the imputation model: medical discipline, duration of vancomycin treatment (log-transformed) and number of nephrotoxic medications at baseline. The proportion of time within target range was analysed using linear regression.

The intercurrent events and corresponding strategy for the secondary endpoints are summarized below.

Estimand	Strategy for accounting intercurrent events	Endpoints
While on treatment	While on treatment strategy: Discontinuation of vancomycin treatment Composite strategy: Death (unfavourable outcome) Treatment policy strategy: Treatment switch (MIPD and standard-of-care or vice versa) Early discontinuation of calculator	Proportion of patients with (worsening) AKI during vancomycin treatment
While on treatment	While on treatment strategy: Discontinuation of vancomycin treatment Death Treatment policy strategy: Treatment switch (MIPD and standard-of-care or vice versa) Early discontinuation of calculator	Proportion of time within therapeutic target range

Table: The intercurrent events and corresponding strategy for the secondary endpoints

5.5 Statistical methods for tertiary endpoints

For the tertiary outcomes, the number of (additional) blood samples and the number of dose adjustments during vancomycin treatment were analysed using negative binomial regression, with randomization group and medical discipline included as predictors. The cumulative vancomycin dose and cumulative AUC were analysed using linear regression.

5.6 Evaluation criteria for Acute Kidney Injury

AKI is defined as any of the following (not graded):

- Increase in SCr by ≥ 0.3 mg/dl within 48 hours
- Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days

Baseline serum creatinine is defined as the most recent documented serum creatinine value within 7 days before the start of the vancomycin therapy. If no value is available, baseline serum creatinine is estimated using the Modification of Diet in Renal Disease (MDRD) study equation assuming that the baseline estimated glomerular filtration rate (eGFR) is 75 ml/min/1.73 m², in patients with no evidence of chronic kidney disease. (Worsening)

AKI during vancomycin treatment was defined as increase in AKI category during vancomycin treatment.

Table: Definition of AKI

Stage	Serum creatinine
1	1.5 -1.9 times baseline OR ≥ 0.3 mg/dl increase
2	2.0 - 2.9 times baseline
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl OR Initiation of renal replacement therapy

AKI classes are defined using the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury

Table: Staging of AKI

6. Ethics Committee and Competent Authority

OVERVIEW APPROVED DOCUMENTS		
Initial submission : - Protocol, v1.0 dd. 2021-06-10 - ICF, v1 dd. 2021-06-14 (NL, FR, ENG) - SmPC Vancomycin Mylan® 03/2021 - Declaration of Conformity dosiscalculator	Approval EC: Not approved	Approval FAMHP: 2021-08-20
Submission after comments CEC: - Protocol, v1.0 dd. 2021-09-07 - ICF, v1 dd.2021-09-02 (NL, FR, ENG)	Approval EC: 2021-09-22	Approval FAMHP: N.A.
Substantial Amendment #1: - Protocol, v2.0 dd. 2021-12--30 - ICF, v2 dd. 2021-12-30 (NL, FR, ENG) - Addition AZ Sint-Jan Brugge	Approval EC: 2022-02-09	Approval FAMHP: 2022-01-24
Substantial Amendment #2: - Protocol, v3.0 dd. 2023-04-21 - ICF, v3 dd. 2023-04-21 (NL, FR, ENG)	Approval EC: 2023-05-16	Approval FAMHP: 2023-05-09

7. Results

7.1 Subject enrollment and demographics

Between 12th of November 2021 and 19th of October 2023, 155 patients were randomized: 78 to standard-of-care and 77 to the intervention.

Site	Not yet active	Active	Closed	Number of subjects included	Data of first inclusion	Date of site closure (LSLV)
Ghent University Hospital	☐	☐	☒	121	12/11/2021	07/11/2023
AZ Sint-Jan Bruges	☐	☐	☒	34	15/06/2022	24/04/2023

Table 1: Participation per site during the study period

Site	Medical discipline	Standard-of-care arm (n = 78)	Intervention arm (n = 77)
Ghent University Hospital	Orthopaedics	28	25
	Haematology	21	20
	General internal medicine	8	8
	Hepatobiliary/gastrointestinal surgery	6	5
General Hospital Sint-Jan Bruges AV	Haematology	7	9
	Orthopaedics	4	5
	General internal medicine	4	5

Table 2: Enrolment by site

Baseline characteristics of the patients are shown below. Vancomycin was most commonly prescribed for bone or joint infections (65 patients, 41.9%). At baseline, 103 patients (66.5%) had a documented infection, and Gram-positive pathogens were identified in 87 patients (56.1%).

Characteristics	Standard-of-care arm (n = 78)	Intervention arm (n = 77)
Age (years)	64.5 (55-71.8; 20-84)	66 (56-71; 21-84)
Female, n (%)	25 (32.1%)	33 (42.9%)
Weight (kg)	80.5 (70.1-94; 45-141)	74.1 (61.4-85; 41-131.5)
Serum creatinine (mg/L)	0.8 (0.7-1.1; 0.4-2.1)	0.8 (0.7-1.1; 0.4-1.5)
Centre		
Ghent University Hospital	63 (80.8%)	58 (75.3%)
General Hospital Sint-Jan Bruges AV	15 (19.2%)	19 (24.7%)
Medical discipline		
Haematology	28 (35.9%)	29 (37.7%)
Orthopaedics	32 (41%)	30 (39%)
Internal medicine	12 (15.4%)	13 (16.9%)
Hepatobiliary/gastrointestinal surgery	6 (7.7%)	5 (6.5%)
Number of concomitant nephrotoxic drugs		
0	4 (5.1%)	3 (3.9%)
1	13 (16.7%)	13 (16.9%)
2	29 (37.2%)	17 (22.1%)
3	16 (20.5%)	16 (20.8%)
>4	16 (20.5%)	28 (36.4%)
Indication for vancomycin treatment		
Bone or joint infection	34 (44.2%)	31 (39.7%)
Bloodstream infection	14 (18.2%)	16 (20.5%)
Febrile neutropenia or other form of manifestation of infection in immunocompromised host with no clear anatomical site	8 (10.4%)	8 (10.3%)
Gastro-intestinal infection	6 (7.8%)	7 (9.0%)
Skin and soft tissue infection	5 (6.5%)	3 (3.8%)
Clinical sepsis, excluding febrile neutropenia	3 (3.9%)	3 (3.8%)
Urinary tract infection	3 (3.9%)	3 (3.8%)
Cardiovascular infection	2 (2.6%)	-

Other	1 (1.3%)	3 (3.8%)
Systemic inflammatory response with no clear anatomical site	1 (1.3%)	1 (1.3%)
Infection of ear, nose, throat, larynx and mouth	-	2 (2.6%)
Pneumonia	-	1 (1.3%)
Documented infection ^a	52 (66.7%)	51 (66.2%)
Documented infection with Gram-positive pathogen	41 (52.6%)	46 (59.7%)
Concomitant antibiotics	62 (79.5%)	65 (84.4%)

Data are presented as median (Q1-Q3; range); missing or *n*.

^a Documented infection was defined as an infection with a pathogen grown in blood or sterile site or an abscess or volume of infected tissue e.g. pneumonia, soft tissue.

Table 3: Baseline characteristics of the intention-to-treat population

Pathogen	Standard-of-care arm (<i>n</i> = 78)	Intervention arm (<i>n</i> = 77)
Coagulase-negative staphylococci	19	19
<i>Enterococcus</i> spp.	9	19
Viridans group streptococci	7	5
Methicillin-sensitive <i>Staphylococcus aureus</i> (MSSA)	4	2
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	1	2
<i>Corynebacterium</i> spp.	3	0
<i>Cutibacterium</i> spp.	1	2
<i>Lysinibacillus</i> spp.	1	0
<i>Bacillus</i> spp.	1	0
<i>Rothia mucilaginosa</i>	1	0

Data are presented as *n* patients. Some patients had more than one Gram-positive pathogen at baseline.

Table 4: Identified Gram-positive pathogens at baseline

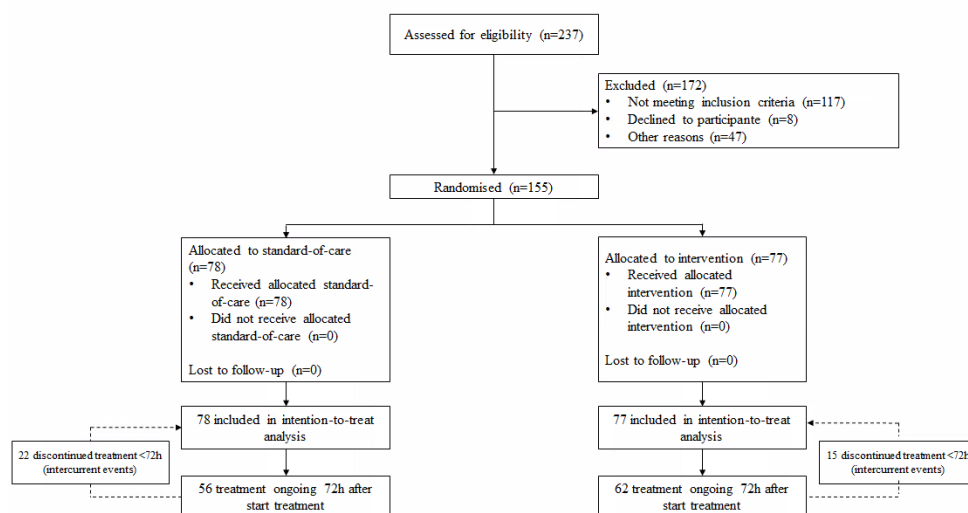


Figure 1: Trial profile for the primary endpoint

7.2 Study specific results

As previously describes, 155 patients were randomized: 78 to standard-of-care and 77 to the intervention. All randomized patients were included in the ITT population. Intercurrent events for the primary and secondary outcomes are described in Tables 5-7.

	Standard-of-care arm (n = 78)	Intervention arm (n = 77)
Discontinuation of vancomycin treatment because of change in antimicrobial therapy within 72h after start vancomycin treatment	14 (17.9%)	9 (11.7%)
Discontinuation of vancomycin treatment because of clinical cure	2 (2.6%)	2 (2.6%)
Discontinuation of vancomycin treatment because of adverse event	-	1 (1.3%)
Treatment withdrawal in the context of palliative care	-	-
Other	6 (7.7%)	3 (3.9%)

Data are presented as n (%).

Table 5: Reporting of intercurrent events for the primary endpoint

	Standard-of-care arm (n = 78)	Intervention arm (n = 77)
Proportion of patients with (worsening) AKI	-	2 (2.6%) (*)

Data are presented as n (%).

(*) One patient received palliative care and died during the study period.

Table 6: Reporting of intercurrent events for the secondary endpoint for safety

	Standard-of-care arm (n = 78)	Intervention arm (n = 77)
Discontinuation of vancomycin treatment because of change in antimicrobial therapy within the 72-96h interval after start vancomycin treatment	7 (9%)	4 (5.2%)
Discontinuation of vancomycin treatment because of clinical cure	2 (2.6%)	1 (1.3%)
Discontinuation of vancomycin treatment because of adverse event	-	-
Treatment withdrawal in the context of palliative care	-	1 (1.3%)
Other	1 (1.3%)	1 (1.3%)

Data are presented as n (%). Intercurrent events are reported for the 72-96h interval.

Table 7: Reporting of intercurrent events for the secondary endpoint 72-96h 24h AUC/MIC

In the ITT population, 35 (47.3%) of 74 patients with available data in the standard-of-care group and 55 (72.4%) of 76 patients with available data in the intervention group achieved the target 24h AUC/MIC within 48–72h of treatment initiation, an absolute difference of 25.2% (95% CI: 3.6-47.1; p=0.002) (Table 8). Figure 2A shows the distribution of individual AUC/MIC values in both groups. Corresponding proportions of target attainment are shown in Figure 3. Tables 9, 10 and Figure 4 present the results for each target group in the standard-of-care arm. The sensitivity analysis supported higher target attainment in the intervention group (Table 11). In predefined subgroups, target attainment at 48–72h was significantly higher with the intervention compared to standard-of-care among patients in haematology and orthopaedics, and among those with a documented infection (Table 8; Fig. 5).

The post-hoc site-specific subgroup analysis showed higher target attainment with the intervention at Ghent University Hospital but not at General Hospital Sint-Jan Bruges AV; the interaction was not significant (Table 12; Fig. 6). In the post-hoc subgroup analysis stratified by standard-of-care target range, target attainment was significantly higher in the intervention arm than in the standard-of-care arm within the 25–30 mg/L subgroup. In contrast, no significant difference between treatment arms was observed in the 20–25 mg/L subgroup. The interaction term was borderline significant, meaning that the effect of the intervention differed across target-range subgroups (Table 13; Fig. 7).

AKI incidence was comparable in both groups (7/77 [9.1%] versus 7/77 [9.1%]; difference -0.4%; 95% CI -9.0 to 8.4]) (Table 8). Between 72–96h, target 24h AUC/MIC was achieved by 33/74 (44.6%) standard-of-care patients and 58/76 (76.3%) intervention patients, an absolute difference of 34.3% (95% CI: 14.1-54) (Table 8, Fig. 2B, Fig. 3). The mean proportion of time within the therapeutic range was 43% (SD 34%) with standard care versus 70% (SD 33%) with the intervention (difference 27%; 95% CI: 16-38) (Table 8).

The mean number of dose adjustments was 2.1 (SD 2.1) in the standard-of-care group and 1.36 (SD 1.46) in the intervention group (difference -0.74; 95% CI -1.3 to -0.23). The mean number of blood samples was 4.9 (SD 3.91) and 5.0 (SD 3.26) respectively (difference 0.07; 95% CI -1.17 to 1.15). The mean cumulative vancomycin dose was similar between groups (277 mg/kg [SD 209] versus 279 mg/kg [SD 213]; difference 2.4 mg/kg, 95% CI -64.8 to 72). The mean cumulative AUC was lower in the intervention group (5019 mg×h/L [SD 2898] versus 5494 mg×h/L [SD 3565]; difference -437 mg×h/L, 95% CI -1505 to 650), although not statistically significant (Table 8).

Outcome	Standard-of-care arm (n = 78)	Intervention arm (n = 77)	Absolute difference in mean or proportion, % (95% CI)	OR/HR or mean ratio (95% CI)	p (for OR)
Primary endpoint					
Proportion of patients reaching the target ^a between 48-72h after initiation	35 (47.3%); 4	55 (72.4%); 1	25.2% (3.6% to 47.1%)	3.01 (1.50 to 6.05)	0.002
Primary endpoint by subgroups					
Medical discipline					
Internal medicine (n = 25)	6/12 (50%)	6/12 (50%); 1	-3.8% (-40.4% to 33.8%) §	1.01 (0.2 to 5.18)	0.988
Hepatobiliary/gastro-intestinal surgery (n = 11)	4/6 (66.7%)	3/5 (60%)	-6.7% (-57.5% to 46.6%) §	0.75 (0.06 to 9.29)	0.819
Haematology (n = 57)	12/27 (44.4%); 1	22/29 (75.9%)	33.0% (7.4% to 54.7%) §	3.91 (1.22 to 12.51)	0.02
Orthopaedics (n = 62)	13/29 (44.8%); 3	24/30 (80%)	39.4% (15.2% to 59.2%) §	5.17 (1.60 to 16.70)	0.006
Documented infection (n = 103)	25/49 (51.0%); 3	37/51 (72.5%)	20% (-5.9% to 46.4%)	2.62 (1.12 to 6.13)	0.026
Secondary endpoint					
Proportion of patients with (worsening) AKI ^b	7 (9.1%); 1	7 (9.1%)	-0.4% (-9% to 8.4%)	0.99 (0.31 to 3.17)	0.981
Proportion of patients reaching the target ^a between 72-96h after initiation	33 (44.6); 4	58 (76.3%); 1	34.3% (14.1% to 54%)	4.48 (2.12 to 9.44)	0.000
Proportion of time within target	43% (34%); 36.9% (15.1%-66.7%); 6	70% (33%); 76.9% (57.9%-100%); 4	27% (16% to 38%)	NA	NA
Tertiary endpoint					
Number of dose adjustments during vancomycin treatment	2.1 (2.1); 2 (1-3)	1.36 (1.46); 1 (0-2)	-0.74 (-1.3 to -0.23) §§	0.65 (0.48 to 0.89)	NA
Number of blood samples during vancomycin treatment	4.9 (3.91); 4 (1-8)	5.0 (3.26); 4 (3-7)	0.07 (-1.17 to 1.15) §§	1.01 (0.79 to 1.27)	NA
Number of additional blood samples during vancomycin treatment	2.92 (2.59); 3 (1-4)	2.70 (1.77); 2 (1-4)	-0.22 (-0.93 to 0.41) §§	0.92 (0.73 to 1.17)	NA
Cumulative dose during vancomycin treatment (mg/kg)	277.4 (209.1); 225.3 (110.6-392.3)	279.0 (212.5); 242.8 (133.6-342.3)	2.4 (-64.8 to 72.0)	NA	NA
Cumulative AUC during vancomycin treatment (mg×h/L)	5494 (3565); 4792 (2543-7827); 6	5019 (2898); 4542 (2493-6922); 3	-437 (-1505 to 650)	NA	NA

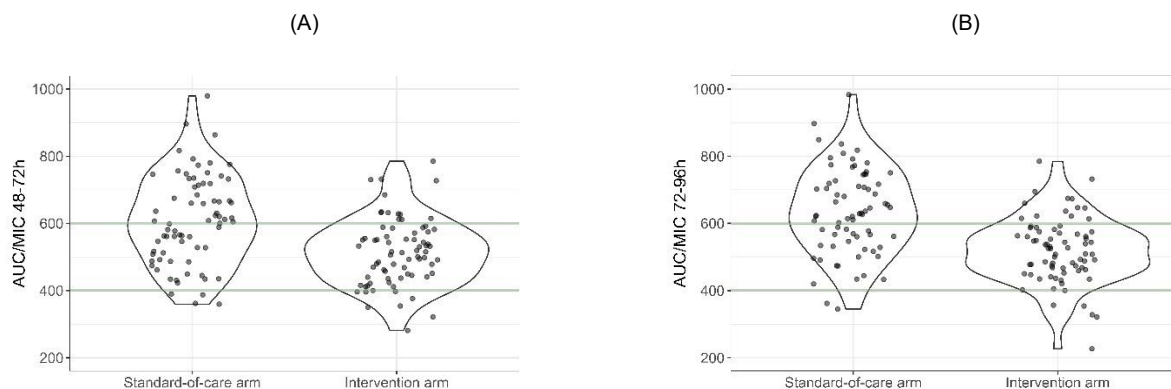
Data are presented as mean (SD), median (Q1-Q3); missing or n (%). The descriptive statistics in the standard-of-care group and intervention group columns are based on participants who had available data for that particular outcome. For the data in the subsequent columns, multiple imputation was used to account for these missing data, so these results apply to all randomly assigned participants (i.e. the ITT population), except for the Wilson score confidence intervals (§). § 95% Wilson score confidence interval for difference in proportion. §§ Mean ratio.

AKI, acute kidney injury; NA, not applicable; OR Odds Ratio; HR Hazard Ratio

^a The target AUC/MIC is 400-600, assuming a pathogen MIC ≤ 1 mg/L. AUC, Area-Under-the-Concentration Time Curve (AUC); MIC, Minimal Inhibitory concentration

^b According to Kidney Diseases Improving Global Outcomes (KDIGO) assessment criteria

Table 8: Primary, secondary and tertiary endpoints in the intention-to-treat population



The solid horizontal green line represents the target range of AUC/MIC 400-600.

Figure 2: Violin plot for standard-of-care and intervention arm showing distribution of AUC/MICs (assuming a pathogen MIC ≤ 1 mg/L) in the interval (A) 48-72h after start of vancomycin treatment, (B) 72-96h after start of vancomycin treatment

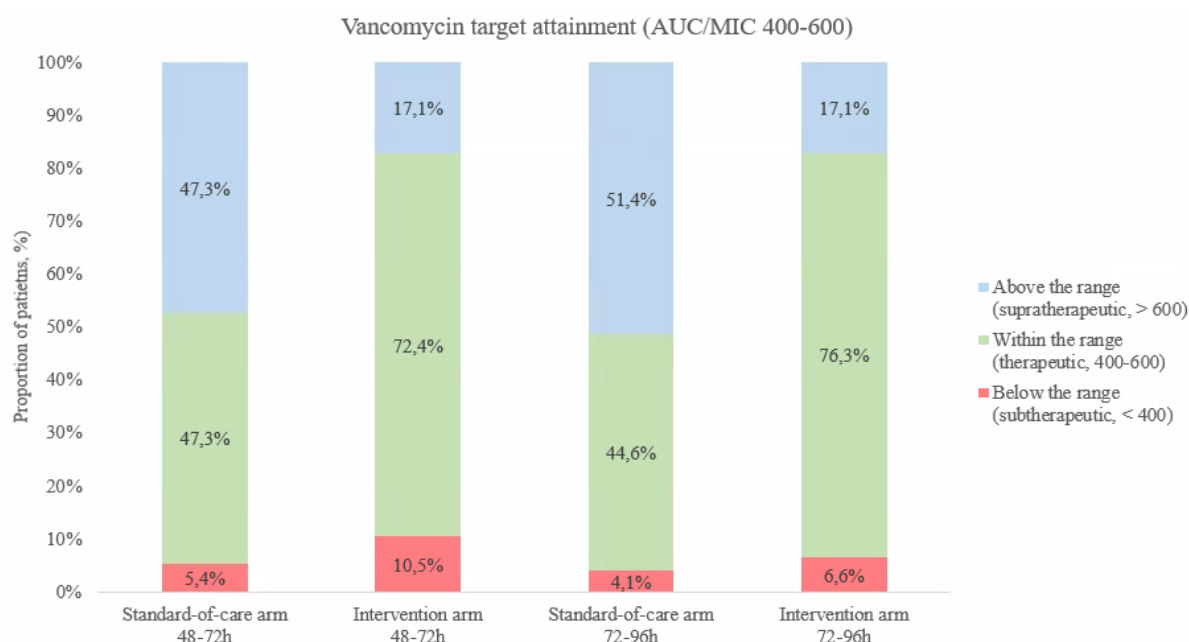


Figure 3: Proportion of patients achieving vancomycin target attainment in the intervals 48–72h (left) and 72–96h (right) after treatment initiation. Target attainment is shown as within the therapeutic range (AUC/MIC 400–600; green), below the range (subtherapeutic; red), or above the range (supratherapeutic; blue).

		Standard-of-care arm (n = 78)	
		20-25 mg/L (n = 31; 39.7%)	25-30 mg/L (n = 47; 60.3%)
Distribution per site	Ghent University Hospital	16	47
	General Hospital Sint-Jan Bruges AV	15	0
Distribution per medical discipline	Haematology	15	13
	Orthopaedics	4	28
	General internal medicine	6	6
	Hepatobiliary/gastrointestinal surgery	6	0

Data are presented as n (%).

Table 9: Target range for TDM (only for standard-of-care arm)

Outcome: primary endpoint	Standard-of-care arm, target 20-25 mg/L (n = 31)	Standard-of-care arm, target 25-30 mg/L (n = 47)	Intervention arm (n = 77)
Proportion of patients reaching the target ^a between 48-72h after initiation	19 (61.3%)	16 (37.2%); 4	55 (72.4%); 1

Data are presented as n (%). ^a The target AUC/MIC is 400-600, assuming a pathogen MIC ≤ 1 mg/L. AUC, Area-Under-the-Concentration Time Curve (AUC); MIC, Minimal Inhibitory concentration

Table 10: Primary endpoint in the intention-to-treat population, standard-of-care stratified by target range (20-25 mg/L versus 25-30 mg/L), post-hoc non-predefined analysis



The solid horizontal green line represents the target range of 24h AUC/MIC 400-600.

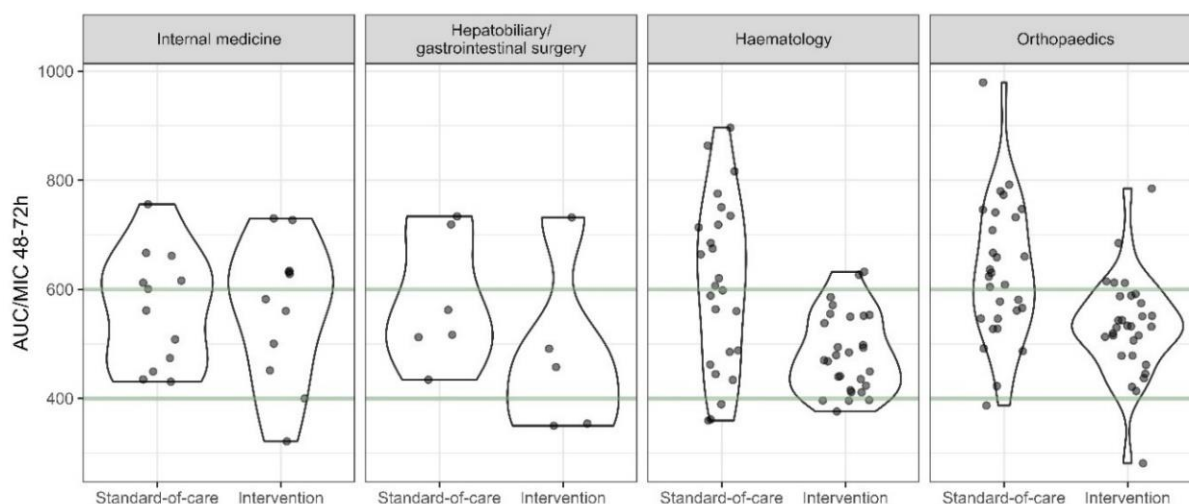
Figure 4: Violin plot for standard-of-care (stratified by target group) and intervention arm showing distribution of AUC/MIC (assuming a MIC ≤ 1 mg/L) in the interval 48–72h after start of treatment, post-hoc non-predefined analysis

Outcome	Standard-of-care arm (n = 78)	Intervention arm (n = 77)	Odds ratio (95% CI)	p (for OR)
Sensitivity analysis	35 (47.3%); 4	56 (73.7%); 1	3.21 (1.58 to 6.49)	0.001

Data are presented as n (%); number of missing values. Sensitivity analysis: 50% weight is given to the PK model for 24h AUC/MIC estimation.

AUC, Area-Under-the-Concentration Time curve; MIC, Minimal Inhibitory Concentration

Table 11: Reporting of sensitivity analysis of primary outcome



The solid horizontal green line represents the target range of 24h AUC/MIC 400-600.

Figure 5: Violin plot for standard-of-care and intervention arm per medical discipline showing distribution of AUC/MICs (assuming a MIC ≤ 1 mg/L) in the interval 48-72h after start of treatment

Primary endpoint: Proportion of patients reaching the target ^a between 48-72h after initiation	Standard-of- care arm (n = 78)	Intervention arm (n = 77)	OR (95% CI)	p (for OR)
General Hospital Sint-Jan Bruges AV (n = 34)	11/15 (73.3%)	14/19 (73.7%)	1.017 (0.209 to 4.942)	0.983
Ghent University Hospital (n = 121)	24/59 (40.7%); 4	41/57 (71.9%); 1	3.847 (1.731 to 8.550)	0.001

Data are presented as n (%); number of missing values.

^a The target AUC/MIC is 400-600, assuming a pathogen MIC ≤ 1 mg/L. AUC, Area-Under-the-Concentration Time Curve (AUC); MIC, Minimal Inhibitory concentration

p-value for the interaction term is not significant: Ratio of odds ratios 3.78, 95% CI [0.64-22.23], p-value 0.135

Table 12: Primary endpoint in the intention-to-treat population, post-hoc non-predefined subgroup analysis by site



The solid horizontal green line represents the target range of 24h AUC/MIC 400-600.

Figure 6: Violin plot for standard-of-care and intervention arm per site showing distribution of AUC/MICs (assuming a MIC ≤ 1 mg/L) in the interval 48-72h after start of treatment, post-hoc non-predefined analysis

Primary endpoint: Proportion of patients reaching the target ^a between 48-72h after initiation	Standard-of-care arm	Intervention arm	OR (95% CI)	p (for OR)
Target range 20-25 mg/L ^b (n = 69)	19/31 (61.3%)	26/38 (68.4%)	1.347 (0.483 to 3.756)	0.5628
Target range 25-30 mg/L ^b (n = 86)	16/43 (37.2%); 4	29/38 (76.3%); 1	5.559 (2.055 to 15.042)	0.0007

Data are presented as n (%); number of missing values.

^a The target AUC/MIC is 400-600, assuming a pathogen MIC ≤ 1 mg/L. AUC, Area-Under-the-Concentration Time Curve (AUC); MIC, Minimal Inhibitory concentration

^b Hypothetical range for the intervention arm

p-value for the interaction term is borderline significant: Ratio of odds ratios 4.13, 95% CI [0.99-17.25], p-value 0.049

Table 13: Primary endpoint in the intention-to-treat population, post-hoc subgroup analysis by target range according to standard-of-care (20-25 mg/L versus 25-30 mg/L)

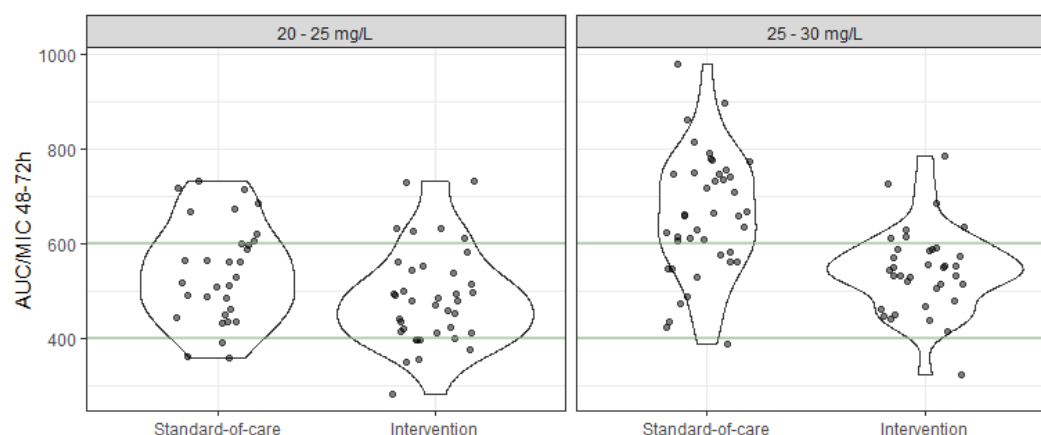


Figure 7: Violin plot for standard-of-care and intervention arm per target range according to standard-of-care (20-25 mg/L versus 25-30 mg/L), showing distribution of AUC/MICs (assuming a MIC ≤ 1 mg/L) in the interval 48–72h after start of treatment, post-hoc non-predefined analysis

Additional tables

Details on vancomycin therapy, TDM sampling and reasons for treatment cessation are shown below.

	Standard-of-care arm (n = 78)	Intervention arm (n = 77)
Duration of first episode of vancomycin treatment (h)	130.2 (65-264)	172.3 (89.7-258.2)
Patients with >1 episode of treatment	6 (7.7%)	7 (9.1%)
Vancomycin dosing details		
Loading dose (mg/kg)	24.0 (17.3 – 31.5)	21.5 (17.8 – 27.6)
First continuous infusion dose (mg/kg/24h)	32.9 (30.0 - 35.0)	32.6 (29.6 – 35.0)
Time until dose adjustment, after sampling (h)	4.7 (2.1 – 10.8)	4.6 (2.5 – 7.4)
Vancomycin blood concentration measurements		
Time between loading dose and sampling (h)	24.5 (23.7 – 25.6)	24.2 (22.0 – 25.6)
Time between dose adjustment and sampling (h)	23.3 (18.9 – 24.4)	22.8 (19.2 – 24.2)

Data are presented as median (Q1-Q3) or n (%). TDM, Therapeutic Drug Monitoring

Table 14: Vancomycin treatment, dosing and sampling details for TDM

	Standard-of-care arm (n = 78)	Intervention arm (n = 77)
Reasons for stopping vancomycin		
Change in antimicrobial therapy	42 (53.8 %)	36 (46.8%)
Clinical cure	22 (28.2%)	27 (35.1%)
No Gram-positive microbiological culture or only contamination in microbiological culture	10 (12.8%)	8 (10.4%)
Treatment withdrawal in the context of palliative care	-	2 (2.6%)
Vancomycin flushing syndrome	-	1 (1.3%)
Viral infection	-	1 (1.3%)
Patients still receiving vancomycin treatment on day 20	4 (5.1%)	2 (2.6%)

Data are presented as n (%).

Table 15: Reasons for stopping vancomycin treatment

8. Safety

Serious adverse events were reported in 1/78 (1.3%) in the standard-of-care group and 3/77 (3.9%) in the intervention group.

All severe adverse events (SAE) were resolved. No Serious Unexpected Serious Adverse Reactions (SUSAR) were reported.

Three patients in the intervention arm experienced the vancomycin flushing syndrome. One patient in the standard-of-care arm experienced another significant safety issue.

No patients developed a severe acute kidney injury (KDIGO stage 3 of AKI) during vancomycin treatment.

All serious adverse events are summarized in the table below:

SAE Overview				
Subject ID	Study Arm (if applicable)	SUSAR (Y/N)	SAE Description	Outcome (ongoing, resolved, death, ...)
554-6	Intervention arm	N	Onset of vancomycin infusion syndrome (also known as red man syndrome) with itching and erythema during loading dose. Reoccurrence in continuous infusion phase.	Resolved
554-25	Standard-of-care arm	N	Other significant safety issue (including death) at the discretion of the investigator thought to be at least possibly related to the vancomycin dosing method: High vancomycin concentration (80.6 mg/L) 24 hours after starting dose. Sample was considered correctly drawn.	Resolved
554-71	Intervention arm	N	Onset of vancomycin infusion syndrome (also known as red man syndrome) with itching and erythema on third day.	Resolved (treated with H1-antihistamines and restart)

554-108	Intervention arm	N	Itching on day 4	Resolved (treated with H1-antihistamines).
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Except the SAE of 554-25, none of the other SAEs were reported within the timelines as mentioned in the latest approved protocol to the sponsors.

9. Device deficiencies

Not applicable

10. Protocol deviations

An overview of the protocol deviations and corrective actions is added below.

Deviation by category	Standard-of-care arm (n = 31)	Intervention arm (n = 47)
Trial assessments	16 (51.6%)	24 (51.1%)
Major	5	-
Minor	11	24
Informed consent	8 (25.8%)	4 (8.5%)
Minor	8	4
Noncompliance with randomized arm	-	2 (4.3%)
Minor	-	2
Safety reporting	-	3 (6.4%)
Major	-	2
Minor	-	1
Other	7 (22.6%)	14 (29.8%)
Major	2	-
Minor	5	14

Data are presented as n protocol deviations (%).

Subject ID	Site	Date of protocol deviation	Protocol deviation concerning	Description of deviation	Classification of protocol deviation	Action taken
554-1	UZ Gent	13/11/2021	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-2	UZ Gent	27/11/2021	Trial assessments	Multiple consecutive necessary blood samples for vancomycin concentration measurement were not taken in time, despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-3	UZ Gent	24/11/2021	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-4	UZ Gent	27/11/2021	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-6	UZ Gent	4/05/2022	Safety reporting	On 10/12/2022, vancomycin infusion reaction (Redman syndrome) has occurred during the vancomycin loading dose in subject 554-6. This safety issue has not been noticed until data collection in the context of the interim analysis. So timely reporting (within 24h) was not done.	Minor	The SAE was belatedly reported to sponsor and medical PI using the SAE reporting form and documented in the eCRF and ISF.
554-7	UZ Gent	21/12/2021	Other	No 6 h infusion stop after supratherapeutic concentration >30mg/L. The >30 mg/L supratherapeutic level occurred outside the 48–72 h window and thus did not affect the primary endpoint.	Minor	A meeting will be planned to discuss this with the staff members, if necessary retraining will be organised.
554-10	UZ Gent	29/12/2021	Trial assessments	Not all baseline information was entered correctly in the dosing calculator.	Minor	Retraining during MV
554-11	UZ Gent	1/01/2022	Trial assessments	Multiple consecutive necessary blood samples for vancomycin concentration measurement were not taken in time, despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-12	UZ Gent	7/01/2022	Other	No 6 h infusion stop after supratherapeutic concentration >30mg/L. The >30 mg/L supratherapeutic level occurred outside the 48–72 h window and thus did not affect the primary endpoint.	Minor	A meeting will be planned to discuss this with the staff members, if necessary retraining will be organised.
554-14	UZ Gent	2/02/2022	Trial assessments	Multiple consecutive necessary blood samples for vancomycin concentration measurement were not taken in time, despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported

554-14	UZ Gent	14/02/2022	Other	Incorrect dose of the first continuous infusion (35 mg/kg instead of 30 mg/kg)	Minor	A meeting will be planned to discuss this with the staff members, if necessary retraining will be organised.
554-15	UZ Gent	2/02/2022	Informed consent	Subject randomized before written ICF has been obtained	Minor	Retraining during MV#1
554-15	UZ Gent	8/02/2022	Other	Outdated body weight was used (80kg vs. 97kg on 8/2)	Minor	A meeting will be planned to discuss this with the staff members, if necessary retraining will be organised.
554-17	UZ Gent	18/02/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-18	UZ Gent	7/03/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-18	UZ Gent	7/03/2022	Other	Incorrect loading dose (25 mg/kg instead of 20 mg/kg)	Minor	A meeting will be planned to discuss this with the staff members, if necessary retraining will be organised.
554-18	UZ Gent	28/02/2022	Trial assessments	No dose calculation performed after correctly sampled vancomycin concentration being available;	Minor	Retraining during MV
554-20	UZ Gent	5/03/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-21	UZ Gent	5/03/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-22	UZ Gent	10/03/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-23	UZ Gent	16/03/2022	Trial assessments	Multiple consecutive necessary blood samples for vancomycin concentration measurement were not taken in time, despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-23	UZ Gent	14/03/2023	Trial assessments	TDM sample of 13/3 at 17h16 was taken off along vancomycin side.	Minor	New TDM sample was drawn at 14/3 1h31 and was used for dose adjustment.

554-24	UZ Gent	25/03/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-25	UZ Gent	25/03/2021	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-26	UZ Gent	1/04/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-27	UZ Gent	12/04/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-27	UZ Gent	7/04/2021	Informed consent	Wrong version of the ICF has been obtained.	Minor	Retraining during MV#1
554-28	UZ Gent	16/04/2022	Other	Incorrect dose reduction (2000mg/d to 1000mg/d)	Minor	A meeting will be planned to discuss this with the staff members, if necessary retraining will be organised.
554-28	UZ Gent	12/04/2022	Informed consent	Subject randomized before written ICF has been obtained	Minor	Retraining during MV#1
554-28	UZ Gent	15/04/2022	Trial assessments	Multiple consecutive necessary blood samples for vancomycin concentration measurement were not taken in time, despite defined as necessary in the institutional guidelines or research protocol for the study sample(s)	Minor	Reported
554-34	UZ Gent	18/05/2022	Other	No baseline serum creatinine at start of vancomycin.	Minor	eScr calculated using the MDRD formula
554-36	UZ Gent	28/05/2022	Other	The patient received a wrong infusion rate for one of the continuous infusions and it occurred outside the 48-72 h window and thus did not affect the primary endpoint.	Minor	TDM sample and restart based on vancomycin. measurement.
554-36	UZ Gent	28/05/2022	Noncompliance with randomized arm	Patient in the intervention arm who received vancomycin from 19/5/22 to 1/6/22. Patient was discharged to neurology ward on the evening of 27/5 (ward not participating in the study). Therefore, patient should have been switched to standard of care from 28/5 (no longer calculated by dosing software). On 28/5 the dose was calculated using the dosing software. The second sample taken after discharge was therapeutic according to the dose calculator (idem according to SOC, target 25-30). Classified as a minor deviation because it occurred on day 9 and had no effect on endpoints.	Minor	/

554-62	UZ Gent	20/10/2022	Trial assessments	Based on the measured vancomycin concentration, both the loading and maintenance doses were insufficiently increased during dose adjustment.	Major	New sample 24h after dose adjustment --> too low (21,4) as expected. Dose was increased, based on protocol.
554-71	UZ Gent	14/11/2023	Safety reporting	SAE is not reported within the timelines as per protocol i.e. 24h after site staff awareness.	Major	Email sent to the study team to pay special attention to report SAE's as per protocol
554-75	UZ Gent	20/01/2023	Informed consent	SI signed after randomisation	Minor	Reported
554-80	UZ Gent	11/02/2023	Trial assessments	TDM sample taken 24 hours earlier. Same dose after calculation	Minor	Reported
554-82	UZ Gent	5/03/2023	Noncompliance with randomized arm	Noncompliance with randomized arm: patient was restarted on vancomycin on 4/3/2023 (= D19, on Saturday) within the 20 day study period (three days after first stop). Patient did not receive the same study assigned method as assigned for the first period (intervention arm). There was no dose calculation based on sample of 5/3/2023 17:09 (= D20, on Sunday). Dose was increased with 500mg by physician (as in SOC). Minor because no impact on endpoints or safety.	Minor	No action as vancomycin would be stopped on Monday (= D21)
554-87	UZ Gent	16/03/2023	Informed consent	SI signed after randomisation	Minor	Reported
554-92	UZ Gent	28/03/2023	Informed consent	SI signed after randomisation	Minor	Reported
554-93	UZ Gent	31/03/2023	Trial assessments	On 31/03 (65h after start): Low measured vancomycin concentration (11.8 mg/L). Checking MIPD software: gap between 2 doses which made it look like patient did not receive vancomycin for several hours. Hence software advised on 29/03 (24h after start vancomycin) to keep dose on despite low concentration. Simulated in InsightRx: same dosing advice. Not clear what went wrong in Insight Rx. Classified as minor, because no impact on primary endpoint.	Minor	Now advice for increasing dose (to 2500mg/d). => dose adjustment and new sample after 24h.
554-93	UZ Gent	28/03/2023	Informed consent	SI signed after randomisation	Minor	Reported
554-97	UZ Gent	14/06/2023	Trial assessments	Used Scr from after starting vancomycin. However minor deviation given SCr according to MDRD formula in protocol would differ minimally Scr = 0.84 vs 0.82 used.	Minor	None
554-97	UZ Gent	14/06/2023	Trial assessments	Doctor himself adjusted dose to 1900 mg/24h.	Minor	Use software to determine dose and inform doctor that dose needs to be adjusted to 1500mg/24h with TDM on 15/6 at 12h.
554-98	UZ Gent	19/06/2023	Informed consent	SI signed after randomisation	Minor	Reported
554-100	UZ Gent	21/06/2023	Informed consent	SI signed after randomisation	Minor	Reported

554-102	UZ Gent	1/07/2023	Trial assessments	Dosing advice on 30/6 in the evening was not implemented immediately, not until 1/7 at 10 pm.	Minor	Sample on 2/7 at 8h was used for extra dose calculation.
554-103	UZ Gent	29/06/2023	Informed consent	SI signed after randomisation	Minor	Reported
554-107	UZ Gent	4/08/2023	Informed consent	SI signed after randomisation	Minor	Reported
554-108	UZ Gent	17/11/2023	Safety reporting	SAE is not reported within the timelines a per protocol i.e. 24h after site staff awareness.	Major	Email sent to the study team to report SAE's as per protocol
554-112	UZ Gent	29/08/2023	Informed consent	SI signed after randomisation	Minor	Reported
554-115	UZ Gent	23/09/2023	Other	The patient received a wrong infusion rate for one of the continuous infusions and it occurred outside the 48-72 h window and thus did not affect the primary endpoint.	Minor	Wait for 12h, then TDM sample was taken. Input concentration in software. Vancomycin was restarted.
554-115	UZ Gent	27/09/2023	Trial assessments	30/9: During calculation in software, it was noticed that in the previous calculation of 27/9, the concentration of 19.3 mg/L was not entered.	Minor	Concentration of 19.3 mg/L was entered (after three days). No impact on endpoints (because on D9).
554-120	UZ Gent	9/10/2023	Trial assessments	On 9/10, first vancomycin concentration (17.2) was not taken into account.	Minor	Simulated what the advice would be if first sample was taken into account: identical dose recommendation.
554-122	UZ Gent	13/10/2023	Other	The patient received a wrong infusion rate for one of the continuous infusions and it occurred outside the 48-72 h window and thus did not affect the primary endpoint.	Minor	Stop vancomycin, new TDM and restart after concentration is known.
788-1	AZ Sint-Jan	16/06/2022	Other	The patient received a wrong infusion rate for one of the continuous infusions and it occurred inside the 48-72 h window and thus did affect the primary endpoint.	Major	Stop vancomycin until new TDM and restart after 22-hour interruption based on new renal function.
788-2	AZ Sint-Jan	22/06/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as SOC	Minor	None
788-3	AZ Sint-Jan	23/06/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as standard-of-care.	Major	New TDM sample 24 hours after start vancomycin
788-3	AZ Sint-Jan	24/06/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as standard-of-care.	Major	Stop vancomycin for 9h and restart at lower dose
788-5	AZ Sint-Jan	25/06/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as SOC	Minor	New TDM sample 24 hours after start vanco
788-5	AZ Sint-Jan	24/06/2022	Trial assessments	Loading dose not given before maintenance dose.	Minor	Loading dose was administered four hours after start maintenance dose.

788-6	AZ Sint-Jan	5/07/2022	Other	The patient received a wrong infusion rate for one of the continuous infusions and it occurred outside the 48-72 h window and thus did not affect the primary endpoint.	Minor	New TDM taken on 2022-07-06 around 11:00
788-6	AZ Sint-Jan	5/07/2022	Other	Continuous infusion: a vancomycin level was not entered in the dosing calculator, but the omitted concentration was <20% different from the last measured level.	Minor	Retraining during MV#1
788-6	AZ Sint-Jan	6/07/2022	Other	Interruption of administration of vancomycin for 10 hours with no documented reason; outside the 48-72 h window.	Minor	None
788-7	AZ Sint-Jan	6/07/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as SOC	Minor	New TDM sample 24 hours after start vancomycin
788-10	AZ Sint-Jan	6/08/2022	Other	At 24 hours after initiation, the infusion had been interrupted for 22 hours, resulting in subtherapeutic vancomycin concentrations. The discontinuation may have been intentional, although this was not documented.	Major	None
788-12	AZ Sint-Jan	30/08/2022	Other	The patient received a wrong infusion rate for one of the continuous infusions and it occurred outside the 48-72 h window and thus did not affect the primary endpoint.	Minor	Prescription vancomycin was stopped immediately on 2022-08-31 5am14. A new lab was taken (creatinine, vancomycin). Finally the original vancomycin dose (1500 mg over 24h) was restarted on 2022-08-31 in the morning after input into InsightRX.
788-14	AZ Sint-Jan	14/09/2022	Other	The calculations performed in InsightRX were not stored, making it impossible to monitor the AUC.	Minor	None
788-16	AZ Sint-Jan	5/10/2022	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as SOC.	Minor	No action, dose adjustment based on early blood sample
788-20	AZ Sint-Jan	29/12/2022	Other	The calculations performed in InsightRX were not stored, making it impossible to monitor the AUC.	Minor	None
788-22	AZ Sint-Jan	23/01/2023	Trial assessments	Difficult story over the weekend 20-22/01/23, unclear what happened, presumably vancomycin administration until 21/01 around 2pm and then new dose administered, so not interrupted. Hours are correct in insightRX, dose 2g was adjusted based on TDM 28, presumably it was falsely elevated as nurse did not flush before and after blood drawing (only stopped vanco) => tdm of 28 flagged in InsightRX, after consultation with the CI and so omitted	Minor	Consultation CI
788-23	AZ Sint-Jan	23/01/2023	Trial assessments	A single repeat blood sample for vancomycin concentration measurement was not taken in time despite defined as standard-of-care.	Major	No action, dose adjustment based on early blood sample.

788-25	AZ Sint-Jan	12/02/2023	Trial assessments	Whether a loading dose was administered is unclear.	Major	No loading dose recorded under vancomycin dosages in the eCRF
788-26	AZ Sint-Jan	20/02/2023	Trial assessments	Infusion interrupted on 20/2 from 10 am - 1.30 pm	Minor	Documented InsightRX and REDCap
788-26	AZ Sint-Jan	18/02/2023	Other	The calculations performed in InsightRX were not stored, making it impossible to monitor the AUC.	Minor	None
788-27	AZ Sint-Jan	22/02/2023	Trial assessments	Vanco infusion 21-02-2023 with start in the evening is administered over 12 hours instead of 24 hours	Minor	Vanco therapy was interrupted and restarted based on TDM
788-31	AZ Sint-Jan	4/03/2023	Other	The calculations performed in InsightRX were not stored, making it impossible to monitor the AUC.	Minor	None
788-33	AZ Sint-Jan	19/03/2023	Other	The calculations performed in InsightRX were not stored, making it impossible to monitor the AUC.	Minor	None

11. Completion of the study

Site	Not active yet	Active	Closed	Number of subjects included	Data of first inclusion	Date of site closure (LSLV)
Ghent University Hospital	☐	☐	☒	121	12/11/2021	07/11/2023
AZ Sint-Jan Bruges	☐	☐	☒	34	15/06/2022	24/04/2023

12. Discussion and overall conclusions

This RCT showed that AUC/MIC-based MIPD, using a Bayesian tool, outperformed conventional TDM-guided dosing in achieving predefined AUC/MIC targets under continuous infusion during the 48-72h interval. Although the use of continuous infusion was previously associated with faster and higher target attainment, MIPD still markedly improved attainment, indicating meaningful added benefit.²⁰

Consistent with reports from trough-based dosing, supratherapeutic exposures at 48-72h were more common with standard-of-care, whereas AUC/MIC-guided dosing narrowed the AUC distribution [10]. Subtherapeutic exposure at 48-72h was uncommon in the standard-of-care arm, indicating minimal underdosing and a well-performing TDM protocol at the lower efficacy boundary, which likely constrained the additional benefit of MIPD.

Institutional dosing and TDM practices influenced the effect of MIPD on AUC-based target attainment, with higher standard-of-care targets for severe infections (25-30 mg/L) at one centre accentuating differences in favour of AUC-guided MIPD. Although no formal site-dependent effect modification was observed in the non-predefined post-hoc analysis, the descriptive post-hoc analysis highlights how institutional protocols shape apparent MIPD effect. The significant subgroup effect observed in orthopaedics in the predefined subgroup analysis may relate to the frequent use of higher standard-of-care targets (25–30 mg/L in 28/32 patients).

We did not find any signal for reduced AKI with MIPD. The BENEFICIAL RCT in severely ill children, however, reported a numerically but not statistically significant reduction in AKI in the intervention group.²¹ The overall incidence of AKI was low in our study. Both groups largely consisted of patients with normal baseline serum creatinine levels, which may have limited the inclusion of patients with pre-existing renal impairment. In addition, the use of continuous infusion, associated with a lower AKI risk compared with intermittent administration, may have contributed to the low observed AKI incidence.²² Adverse events aligned with vancomycin's known profile. Vancomycin flushing syndrome, a rapid infusion-related reaction, occurred only in the intervention arm, but the small numbers suggest random variation. Two of three events arose during or immediately after the loading dose, before AUC calculation, arguing against causality. No serious adverse events occurred; AUC/MIC-based MIPD appeared safe.

The increased target attainment rate observed at 48–72h was sustained through the subsequent 72–96h interval, aligning with previous observations for intermittent infusion in adults and children, as well as with the results of the BENEFICIAL RCT.^{21,23–25} Moreover, the mean proportion of time within the therapeutic range was also significant higher, further supporting improved overall exposure.

Fewer dose adjustments were needed in the intervention group, but the difference was not clinically relevant and did not reduce the number of blood samples.

Cumulative dose and AUC over the full treatment course did not differ significantly between groups, likely because short courses limited the impact of brief supratherapeutic episodes. In this context, MIPD primarily improved control of exposure within the therapeutic window rather than reducing overall drug exposure. Unlike findings in critically ill paediatric patients showing higher early AUCs with AUC/MIC-targeted MIPD, we observed no difference in cumulative AUC, likely reflecting our focus on total rather than early exposure.²⁶

To our knowledge, this RCT is the first to assess the prospective use of AUC/MIC-based MIPD of vancomycin in hospitalized adults. A notable strength is the use of the Colin et al. model, which demonstrated strong predictive performance in a prior validation study at both sites.^{17,27} Another major strength is the trial's pragmatic design and the inclusion of a heterogeneous cohort, which aimed to closely reflect real-world clinical practice and enhances the generalizability of the findings.

Our study has some limitations. First, our dosing strategy relied only on a posteriori optimization using available TDM concentration results. A priori dose prediction, using popPK priors together with patient covariates, could have enabled earlier individualization, but was not feasible without 24/7 pharmacist availability for dose calculations. Second, we applied an AUC/MIC > 400 efficacy threshold consistent with *Staphylococcus aureus* guidelines, although this target was derived from intermittent infusion and its validity for continuous infusion remains uncertain.^{28,29} We also extrapolated this threshold to less virulent bacteria to maintain consistency with previous studies. Third, target attainment was evaluated assuming a MIC of 1 mg/L, reflecting the lack of routine MIC testing in clinical practice; this may not fully represent pathogen susceptibility in targeted therapy. Forth, serum or plasma concentrations were measured, which may not reflect target-site exposure.

Further research should assess the clinical outcome and cost-effectiveness of MIPD in patients and should also include patients with pre-existing renal impairment and in higher-risk groups (e.g. those prone to AKI or suboptimal target attainment, including the critically ill). Because our multi-ward study population was highly heterogeneous, we intentionally limited clinical outcome evaluation to AKI.

In conclusion, this first RCT evaluating AUC/MIC guided MIPD for continuous vancomycin infusion in general ward adults showed that MIPD significantly improved target attainment and was safe. The incidence of AKI was comparable between groups, although the study was not powered to detect differences in nephrotoxicity. These findings demonstrate the value of MIPD to optimize vancomycin exposure and highlight the need for further research into its clinical benefits, particularly in predefined patient subgroups and in strategies incorporating a priori dose calculation.

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Appendix 1: Summary of the results of the clinical trial for laypersons

1. Clinical trial identification

Official title: Impact of model-informed precision dosing in adults receiving vancomycin via continuous infusion: a randomized, controlled clinical trial

Title for laypersons: Study on the impact of precision dosing of vancomycin in adults

EU reference number: 2021-003670-31

Acronym / Protocol code: BC-10433

ClinicalTrials.gov identifier: NCT05535075

2. Name and contact details of the sponsor

Sponsor: Ghent University Hospital

Contact details sponsor: C. Heymanslaan, 10, 9000 Ghent, Belgium

Coordinating Investigator: Prof. dr. Pieter De Cock, tel 09/332 29 69

3. General information

Vancomycin is an antibiotic with a narrow therapeutic-toxic margin. This means that there is little difference between the minimum and maximum target amount of vancomycin in the blood (= target concentration). Too low concentrations result in a reduced effect of the antibiotic. Higher concentrations often cause side effects, including renal toxicity.

Different factors lead to large differences in blood concentrations between patients. For example, the impact of disease (e.g. kidney disease) and treatment (e.g. medication that is best not taken together with vancomycin) should not be underestimated. Tailoring the doses of vancomycin to the needs of the patient poses enormous challenges.

Currently the dose of vancomycin is calculated at the start of therapy on the basis of a milligram per kilogram calculation, which is the same for all patients. Subsequently, the dose is adjusted based on a measured vancomycin blood concentration (if too high or too low). Despite this measurement, achieving and maintaining the target concentration (quickly) remains a major challenge.

In this study, we investigated the added value of a user-friendly computer program that calculated the dose of vancomycin in non-seriously ill adults compared to the current way of working. We specifically investigated whether the use of this computer program leads to the achievement of target concentrations in a shorter time, a reduction in the number and severity of side effects on the kidneys and a reduction in patient stress (e.g. fewer blood draws).

4. Population of subjects

A total of 155 patients was included in this study.

Inclusion criteria

- age: ≥ 18 years
- admitted to the participating ward units (non-critically ill patients)
- suspected or confirmed Gram positive infection
- planned to start or started on intravenous continuous infusion (CI) vancomycin treatment.
- if the patient was previously treated with vancomycin, the minimum interval to a previous vancomycin treatment episode is 48 hours
- informed consent signed by the patient or legal representatives
- not previously enrolled in this trial

Exclusion criteria

- extracorporeal treatment at inclusion

- serum creatinine level above 2.5 mg/dL at inclusion
- patient death is deemed imminent and inevitable

Summary of baseline demographics

	Standard-of-care arm	Intervention arm
N	78	77
Age (in years) at randomization		
Mean (SD)	61.8 (13.9)	62.6 (12.8)
Median (Range)	64.5 (20-84)	66 (21-84)
IQ range	55-71.8	56-71
Weight (in kg) at randomization		
Mean (SD)	82.4 (17.9)	75.5 (18.7)
Median (Range)	80.5 (45-141)	74.1 (41-131.5)
IQ range	70.1-94	61.4-85
Gender, n (%)		
Female	25 (32.1%)	33 (42.9%)
Male	53 (67.9%)	44 (57.1%)

SD: standard deviation

5. Investigational medicinal products used

Vancomycin is a commonly prescribed glycopeptide antibiotic drug to treat severe infections with Gram-positive pathogens.

6. Description and frequency of adverse reactions

Three patients experienced a severe but known side effect of vancomycin treatment, namely the vancomycin flushing syndrome (n=0 in standard-of-care arm; n=3 in intervention arm).

No patients developed a severe acute kidney injury (KDIGO stage 3 of AKI) during vancomycin treatment.

7. Overall results and comments on the outcome of the clinical trial

In this study, we could demonstrate that the use of a computer program results in a significantly faster attainment of target concentration and was safe for adults on general wards. There was no trend to reduced nephrotoxicity. These results show that using the computer program can help give vancomycin in the right amount to patients. They also suggest that more research is needed to see how much this approach improves patient outcomes, especially in specific groups of patients and when dosing is calculated in advance with the computer program.