Final Study Report

Study Title: ***A MULTICENTRIC, RANDOMISED CONTROLLED CLINICAL TRIAL TO STUDY THE IMPACT OF BEDSIDE MODEL-INFORMED PRECISION DOSING OF VANCOMYCIN IN CRITICALLY ILL CHILDREN***

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1. Introduction

Vancomycin is a commonly prescribed antibiotic to treat serious Gram-positive infections in children, predominantly in the empirical and directed treatment of hospital acquired central line associated bloodstream infections (HA-(CLA)-BSI) and healthcare associated sepsis (HAS).

National surveillance data report a HA-BSI incidence of 34.5 cases per 10000 patient days in neonatal intensive care units (NICUs) and pediatric intensive care units (PICUs) in 2016, of which 40 to 65% are CLA-BSI.[1] In 60 per cent of patients, HAS and CLA-BSI are caused by Staphyloccci commensals.[2,3] Data on HAS incidence in children are not available for Belgium. Based on the 2012 point prevalence Antimicrobial Resistance and Prescribing in European Countries (ARPEC) study, prevalence of sepsis in Belgian pediatric patients treated with vancomycin was 45%.[4] Prevalence of vancomycin use in Belgian pediatric patients was estimated in the ARPEC study to be around 6.7% (22% in level III NICUs, 20% in pediatric hemato-oncology units (PHOs), 10% in general neonatal medical wards, 6.3% in PICUs, 2.5% in general pediatric wards).[4]

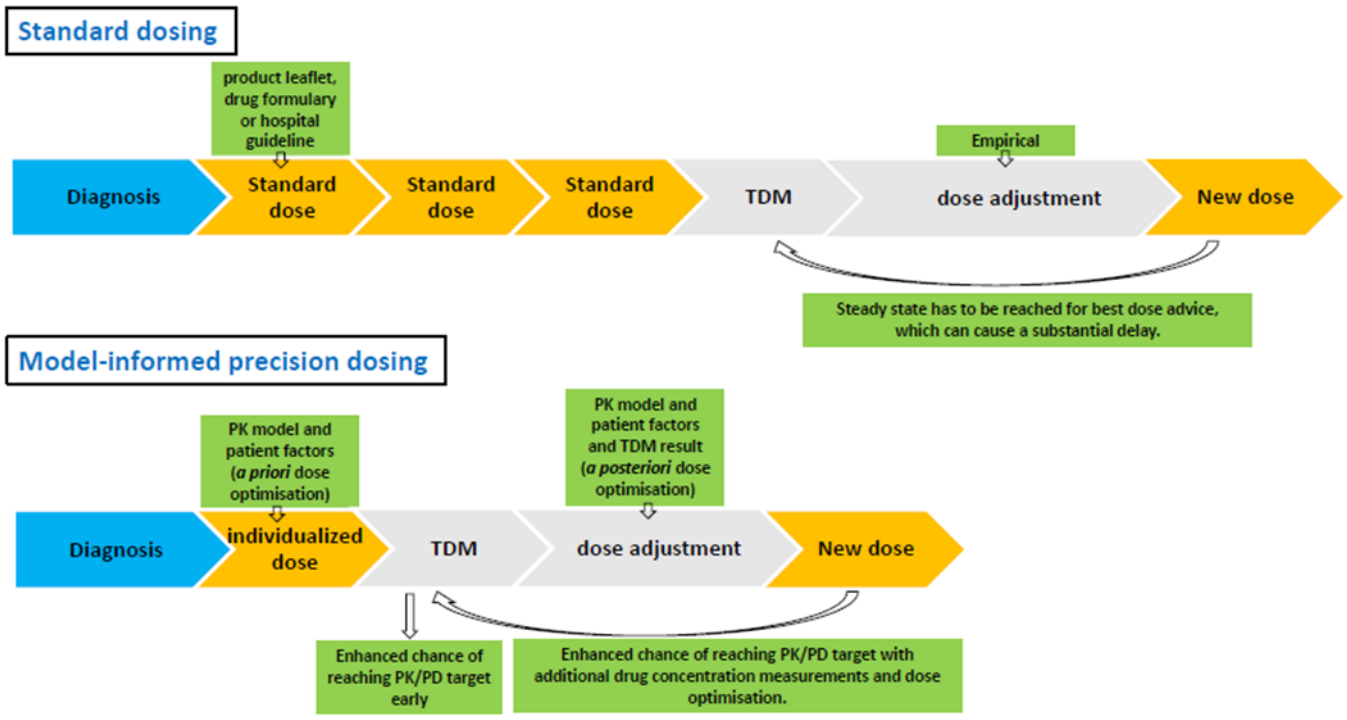
According to the last prevalence report from the European Antimicrobial Resistance Network, in 2017, 8.5% of invasive staphylococcal infections are due to methicillin-resistant Staphylococcus aureus in Belgium, with proportions of up to 44.4 % in some regions in the European Economic Area (EEA).[5]

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 24hour AUC/MIC for favourable clinical outcome in humans with methicillin-resistant Staphylococcus aureus and Enterococci infections is at least 400.[6] Instead, a 24h hour AUC of 600 µg/L*h is known to be independently associated with increased risk of acute kidney injury (AKI), indicating its narrow therapeutic index.[7] AKI is reported in up to 23.4% of critically ill children treated with vancomycin, with higher risks in those receiving mechanical ventilation and concomitant vaso-active and nephrotoxic drugs.[8] It is further known that (even mild) AKI is linked to significantly increased morbidity, mortality, hospital length of stay and costs.[9,10]

Growth, development and critical illness (including cancer) are known to have a massive impact on antibiotic PK/PD and complicate optimal drug dosing.[11] To date, vancomycin is commonly initiated, on a mg per kg basis, according to institutional guidelines. Both intermittent dosing and loading dose/continuous infusion dosing regimens are used. After reaching steady-state conditions (i.e. after the third or fourth dose for intermittent dosing regimens or 24h after start of a continuous infusion), therapeutic drug monitoring (TDM) is performed to ensure attainment of target concentrations.[6] Since traditional AUC/MIC calculations cause much patient burden and are labour- and cost-intensive, in routine practice, trough (Cmin) concentrations are measured as a 'surrogate' single-point parameter for target AUCs, just before the next intermittent dose or during infusion for continuous dosing regimens.[6] If necessary, empiric dose adjustments are performed, aiming at a Cmin

concentration range of 10 to 15 mg/L for intermittent infusions and a concentration range of 15 to 20 mg/L for continuous infusions. (Figure 1).[12]

Figure 1 : Standard versus model-informed precision dosing (adapted from Tängden et al. Intensive Care Med. 2017;43(7):1021-1032)



The current dosing approach has a number of drawbacks. First, reported Cmin target attainment rates in critically ill children are abominable (after start: 5.7 to 62%; after dose adjustment: 44 to 63%), with several days needed to reach target concentrations.[13-23] Delay in appropriate antibiotic therapy in patients with severe sepsis and septic shock leads to increased morbidity and mortality.[24,25] Growing evidence exists that subtherapeutic antibiotic dosing can lead to emergence of resistance of colonising bystander organisms.[26] Second, Cmin level monitoring as surrogate for target AUCs has its limitations as recent studies have documented a high degree of variability as well as therapeutic discordance between both.[27, 28] In essence, current evidence suggests that Cmin monitoring in children frequently results in supratherapeutic AUCs, and increased risk of nephrotoxicity.[6,7] Third, multiple blood drawings for TDM and biochemical tests may lead to iatrogenic anemia, increased patient burden, infection risk and healthcare costs.[29,30] Fourth, poor adherence to proper Cmin timing of sampling is common and may lead to erroneous dose adjustments, therapy failure and toxicity.[31]

PK modelling involves the development of mathematical models to describe a drug PK behavior. Once available, these models can be used to predict in 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, renal function) known as prior information. Then, after obtaining a single level, a revision of PK parameter estimates is provided. 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).[12,31] For vancomycin, Bayesian AUC guided MIPD in adults has been shown to lead to significantly decreased nephrotoxicity, lower total vancomycin doses, reduced per-patient blood sampling, and shorter length of therapy, without compromising efficacy, when compared to trough-only monitoring.[6,7,32] In critically ill neonates, MIPD guided starting doses increased early target attainment from 41 to 72% without any case of vancomycin-related toxicity.[33]

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).[6,34]

Bayesian MIPD is widely applied now, and is being considered the gold standard for vancomycin in some countries like the Netherlands and Australia.[35,36,37] However, to date, it largely mainly remains a complex task requiring intervention from "happy few" specialists in those countries with solid knowledge of clinical pharmacology, PK modelling, and clinical guidelines.[38]

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.[6]

2. Objectives of the study

The overall objective of this project was to investigate the large-scale utility of MIPD of vancomycin at point-of-care in ICU children. This evaluation included a comparison with the more standard approach on clinical, patient-/clinician-oriented, and cost outcome measures.

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/MIC (400-600) between [24 to 48] 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 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 24h AUC/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;
- AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator reduces the time to clinical cure, 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 ward unit length-of-stay, 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 hospital length-of-stay, 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 all cause 30 day mortality, 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 to first target attainment, 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 in patients with clinical cure, 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 24h AUC/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 reduces the number of dose adjustments during vancomycin 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;
- AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator, reduces the proportion of patients with (worsening) acute kidney injury as

assessed using KDIGO criteria, during 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, reduces the proportion of patients with (worsening) acute kidney injury as assessed using KDIGO criteria, during treatment with vancomycin, when compared to the use of standard-of-care dosing regimens with therapeutic drug monitoring;
- Number of trough sampling time errors during vancomycin treatment was also explored in the comparator arm

3. Investigational Medicinal Product

3.1 Name and description of intervention(s)

3.1.1. 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 be implemented in the MIPD dosing calculator.[39] It is a meta-analysis PK model, pooling PK data from premature neonates to elderly, ICU and obese patients (n=2554 patients). It was built using the largest human PK dataset in neonates (n>493) and children included (n=660). In this model, current weight, postmenstrual age and serum creatinine are input variables for dose forecasting, eventually in combination with individual vancomycin measurements.

AUC-based dose estimation

In the interventional arm, vancomycin starting doses and dose adjustments were based on a priori and a posteriori (Bayesian) MIPD dose calculations. Dosing regimens were suggested by MIPD software end-users and implemented by the attending physician. Choice for an intermittent or loading dose/continuous infusion dosing regimen was at the discretion of the attending physician/site preference.

MIPD software end-users and attending physician were allowed to be the same person.

Starting (1st) dose calculation

An a priori dose calculation targeting a 24h AUC of 400 to 600 between 24 and 48h after start treatment were performed using current weight, postmenstrual age and measured serum creatinine (input variables in the Colin et al model). Starting doses could deviate maximum 50% of institutional dosing guidelines.

2nd dose calculation

24h AUC were re-estimated, immediately after administration of the starting dose using 1 or 2 samples, targeting a 24h AUC of 400 to 600 between 24 and 48h after start treatment.

Follow-up dose calculations

Follow-up AUC-based dose calculations, using repeat measurements as per standard-of-care, also targeted a 24h AUC of 400 to 600 between 24 to 48h after dose adjustment.

3.1.2. Vancomycin

Vancomycin is a commonly prescribed glycopeptide antibiotic drug with activity against most Gram positive pathogens including methicillin-resistant Staphylocci and multidrug resistant Staphylococcus epidermidis.[40]

Vials for intravenous administration are available on the Belgian market in 500 mg and 1 G quantities. Three generic brands are currently on the Belgian market.[40,41,42]

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 a posteriori dosing is performed and within the marketing authorisation. [40,41,42]

4. Study Protocol Summary

4.1 Study design

This study was a prospective, multicentric, individual randomized clinical trial in neonatal and pediatric intensive care and pediatric hemo-oncology ward units across Belgium. Patients were randomized to the standard-of-care comparator or intervention arm.

4.2 Inclusion criteria

1. age: 0-18 years

2. admitted to ICU or PHO unit

3. suspected or confirmed Gram positive infection

4. planned to start on intravenous intermittent or continuous infusion vancomycin treatment (if the patient was treated with vancomycin before inclusion : the minimum interval to previous vancomycin treatment episode is 48 hours)

5. informed consent signed by parents or legal representatives

6. not previously enrolled in this trial

note: a patient restarted on vancomycin within the 30 day study period is considered not a new enrollment and should receive the treatment assigned for the first episode)

4.3 Exclusion criteria

1. extracorporeal treatment at inclusion (extracorporeal membrane oxygenation, dialysis, body cooling)

2. neonatal or pediatric RIFLE category failure at inclusion (Day 0)

3. Known chronic kidney disease as defined by the KDIGO definition as: structural or functional abnormalities of the kidney regardless of GFR for < 3 months in duration or GFR < 60ml/min/1.73m² for ≥ 3 months in duration. eGFR is estimated using the modified Schwartz equation

note: non-limitative list for a structural abnormality of the kidney : autosomal recessive polycystic kidney disease, bilateral kidney dysplasia, unique dysplasia of the kidney, nephrotic syndrome)

4. patient death is deemed imminent and inevitable

4.4 Primary endpoint

- Proportion of patients reaching target 24hAUC (400-600) between 24 and 48h after start

4.5 Secondary endpoints

- Proportion of patients with (worsening) AKI during vancomycin treatment

AKI was evaluated using modified neonatal and paediatric Risk Injury, Failure, Loss (RIFLE) AKI criteria.

- Proportion of patients reaching target 24hAUC (400-600) between [48 to 72] h after start treatment
- Time to clinical cure
- Ward unit length-of-stay
- Hospital length-of-stay

- 30 day mortality

4.6 Tertiary endpoints

- Number of (additional) blood samples during vancomycin treatment
- Cumulative number of (additional) blood samples during treatment in patients with reported clinical cure
- Proportion of patients reaching target 24hAUC (400-600) between [72 to 96] h after start treatment
- Number of dose adjustments during vancomycin treatment
- Cumulative vancomycin dose during vancomycin treatment
- Cumulative AUC during vancomycin treatment
- Proportion of patients with (worsening) AKI during vancomycin treatment using Kidney Disease Improving Global Outcomes (KDIGO) criteria (all children)
- Number of trough sampling time errors during vancomycin treatment

4.7 Randomisation and blinding

Trial randomisation

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. Randomisation was stratified by ward unit and hence by ward unit type (NICU, PICU, PHO) Random permuted blocks was created with a computer random number generator with variable sizes to avoid that the treatment allocation could be predicted.

The stratified randomisation 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. This web-based software programme enables randomisation by site and other stratification factors. The REDCap software randomised patients based on an allocation table that was provided by the statistician.

Before a patient was randomised, the baseline characteristics (at least the stratification factor ward unit) of the patient needed to be entered in REDCap.

Following randomisation and during the 30 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 D30 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

within the 30 day study period if still receiving or re-started on vancomycin. In case the patient was in the interventional arm, all details on dosing, serum creatinine and weight from the patient's medical file should have been used in the dosing software before making dose predictions for vancomycin.

Blinding

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

4.8 Monitoring and quality measures

Regular on-site and remote monitoring was performed by the sponsor's CTU Hiruz according to ICH GCP and all applicable national and international laws and guidelines.

Prior to commencing recruitment, the monitor met the study team by a trial initiation visit o review trial specific procedures such as the protocol, safety reporting procedures, ICF procedures, ISF content, PI's responsibilities, e-CRF 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 e-CRF 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. After last patient last visit per site, a close-out visit was planned at each site to ensure all open action items are addressed and the study could be closed at the centre.

5. Study analysis

5.1 Sample size calculation

Primary outcome: Proportions of patients reaching the therapeutic target 24h AUC/MIC (400-600 mg*h/L) between [24 to 48] h after start of treatment

Sample size calculation for the primary analysis was performed in SAS version 9.4 using the power procedure. 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 [24 to 48] h after start of treatment is 50% in the standard-of-care dosing group and 70% 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. Potentially, a learning effect will cause contamination.

Sample size was increased by taking into account some contamination. When assuming 20% contamination from intervention to control, and 5% contamination from control to

intervention, a dilution of the odds ratio (OR) is expected from 2.33 (70% versus 50%) to 1.90 (69% versus 54%).
When it became apparent that the sample size corresponding to this diluted OR could not be met within the project timelines, an analysis was performed after inclusion of 299 patients, to assess the initial contamination rates stated above. This analysis indicated there was an overestimation of contamination rates in the initial sample size calculation. We observed only 4% contamination from intervention to control, and 2.3% contamination from control to intervention. Based on these observations, we lowered the contamination rates assumed for the sample size with 25%, taking into account uncertainty around the observed contamination rates and the potential learning effect, without impacting power of the study. Hence, the assumed contamination rates were lowered from 20% to 15% for intervention-to-control contamination, and from 5% to 3.75% for control-to-intervention contamination.
When assuming 15% contamination from intervention to control, and 3.75% contamination from control to intervention, a dilution of the OR is expected from 2.33 (70% versus 50%) to 2.0 (69.25% versus 53%).
In total, 281 participants were required to achieve 80% power at a two-sided significance level of 5%, to detect an OR of 2.0 (b= 0.69) when the proportion in the control group is 53% (odds=1.13, intercept= 0.12) using logistic regression. An assignment ratio of 1 was applied.

Assuming a drop-out rate of 15%, a total sample size (both groups) of 332 patients was required.

Proportion of patients with (worsening) AKI during vancomycin treatment
The heterogeneity in reported AKI rates in patients treated with vancomycin is high but prevalences of 23.4% in critically ill children treated with vancomycin have been reported, with higher risks in those receiving mechanical ventilation and concomitant vaso-active and nephrotoxic drugs.[43] Furthermore, it is known that trough concentrations >15 mcg/L and AUC >= 800 mcg*h/L are independently associated with a >2.7-fold increased risk of AKI (Fiorito (2018); Le (2014)). We expected a large proportion of our patients in the control arm to have trough concentrations >15 mcg/L and AUC >= 800 mcg*h/L.
When assuming 15% contamination from intervention to control, and 3.75% contamination from control to intervention, the OR was expected to dilute from 0.219 (4% versus 16%) to 0.281 (4.45% versus 14.2%. A total sample size of 281 participants yields 84% power at the two-sided 5% significance level, to detect an OR of 0.28 (b=-1.27) when the proportion in the control group was 14.2% (odds=0.166, intercept= -1.80) using logistic regression. An assignment ratio of 1 was applied.

No interim analysis was planned for this study and no efficacy interim analysis was performed.

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 for binary data was applied, reaching the target AUC/MIC between 24 and 48 h after the start of vancomycin as a categorical predictor variable and randomization group (interventional versus the standard-of-care arm) as a categorical predictor for interest. Because of the limited number of subjects per ward unit, it was not appropriate to include a

term forward unit in the model. The factor type of ward (NICU, PICU, PHO) contains only three categories and was added as a covariate in the model. The primary endpoint was tested for superiority. The primary analysis is the intention-to-treat analysis, preferably performed because it avoids bias associated with non-random loss of participants. All participants 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 odds ratio (OR), together with the estimated proportion per group.

Intercurrent events

The ICH E9 (R1) addendum on estimands and sensitivity analysis in 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 in Table 1.

Table: Intercurrent events for the primary outcome and corresponding strategy according to ICH E9 (R1) for the main and protocol-compliant estimand

	Main estimand	Protocol-compliant estimand
Death	Composite strategy – Subjects who die will be considered to have an unfavorable outcome	
Discontinuation of vancomycin treatment because of clinical cure	Composite strategy – Subjects will be considered to have a favorable outcome	
Discontinuation of vancomycin treatment because of adverse event	Composite strategy – Subjects will be considered to have an unfavorable outcome	
Discontinuation of vancomycin treatment because of clinical failure	Composite strategy – Subjects will be considered to have an unfavorable outcome	
Patient treatment focus changed to palliation	While on treatment strategy – Estimated AUC prior to the discontinuation of vancomycin treatment The "while on treatment strategy" is not expected to cause bias because 1) 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) 2) Reaching the target earlier than the 24h to 48h interval is more difficult	

Discontinuation of vancomycin treatment because of change in antimicrobial therapy within 48h after start vancomycin	While on treatment strategy – Estimated AUC prior to the discontinuation of vancomycin treatment The "while on treatment strategy" is not expected to cause bias because 1) 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) 2) Reaching the target earlier than the 24h to 48h interval is more difficult	
Deferred consent not followed by an informed consent to continue the study, but with an informed consent for use of already collected data.	Hypothetical strategy – What would have happened if these subjects did not have this IE?	
Treatment switch (MIPD and standard-of-care or vice versa)	Treatment policy strategy – Observed outcomes are used regardless of whether or not this IE occurred	Hypothetical strategy – What would have happened if these subjects did not have this IE?
Early discontinuation of calculator	Treatment policy strategy – Observed outcomes are used regardless of whether or not this IE occurred	Hypothetical strategy – What would have happened if these subjects did not have this IE?
Serious protocol deviation with possible impact on primary endpoint	Treatment policy strategy – Observed outcomes are used regardless of whether or not this IE occurred	Hypothetical strategy – What would have happened if these subjects did not have this IE?

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 predictors used for the imputation model included:

Type of ward (NICU/ PICU/PHO)

Type of consent (A priori consent; Deferred consent at randomization)

Indication for vancomycin treatment: indication categorized in

Bloodstream infection/ bacteraemia

Systemic inflammatory response syndrome with no specific focus & Febrile neutropenia or other form of manifestation of infection in immunocompromised host (e.g., HIV, chemotherapy, etc.) with no clear anatomical site

Other

Combined with variable Sepsis (Yes/No)

Mechanical ventilation support at randomization (Yes/No)

Number of nephrotoxic medications at baseline

Age, serum creatinine (mg/dL) and weight at baseline; the cumulative vancomycin dose (mg/kg) within 48h-interval and duration of treatment.

Time since start of the study in that specific ward unit, to take into account the potential learning effect

The intercurrent events "Discontinuation of vancomycin treatment because of change in antimicrobial therapy within 48 after start vancomycin" (Yes/No) and "Treatment switch/Early discontinuation of calculator /Serious protocol deviation with possible impact on primary endpoint" (Yes/No)

When no blood samples were available and the 24h AUC/MIC between 24h and 48h after start vancomycin could not be calculated, or when randomization of a patient was based on deferred consent not followed by an informed consent to continue the study, but with an informed consent for use of already collected data, the available data were used to apply multiple imputation.

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

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

Additional estimand for the primary endpoint: Adjusted analysis

The unconditional Relative Risk, the Risk Difference and the proportion of patients reaching the 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. [44] In order to reduce the variability of the estimation of the treatment effect and thus obtain narrower Cis and more power, the model the following potentially prognostic baseline covariates (these covariates are a selection of the baseline covariates to be included in the imputation model) were included:

– Type of ward

– Baseline serum creatinine (mg/dL)

– Weight

– Age

Ninety-five percent CIs around the proportions and the unconditional relative risk were computed using the Boot MI method as described by Schomaker et al.: Two thousand bootstrap samples (including missing data) D_b^* 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".[45] Thus, there were 5 imputed data sets for each bootstrap sample D_b^*. Point estimates for the Relative Risk 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 relative risk.

Additional analysis for the primary endpoint: Protocol-compliant estimand

To answer the research question "What would have happened if no major protocol deviations occurred?", the unconditional relative risk, the risk difference and the proportions of patients reaching the primary endpoint were estimated in line as described in "Additional analysis/estimator for the additional estimand for the primary objective", but for the subjects that do not belong to the protocol-compliant analysis set because one of the following intercurrent events occurred:

– Treatment switch

– Early discontinuation of calculator

– Major protocol deviation

The outcome was made missing. As such, a hypothetical approach was applied, answering the research question: "What would have happened if the intercurrent event did not occur?".

A list of possible protocol deviations was a priori listed by the data monitors, project manager, and data manager. The chief investigator classified the severity of the protocol deviations into major and minor. A major protocol deviation was defined as having a possible impact on the primary endpoint.

Subgroup analyses

Subgroup analysis for interaction

A subgroup analysis was performed for the stratification factor type of ward unit. Statistical methods were similar to those described in "Primary outcome analysis". Type of ward was added as a categorical predictor variable. An interaction term between type of ward unit and the randomization group was included in the model.

A second subgroup analysis was performed for the type of dosing regimen (continuous versus intermittent). The type of dosing regimen and ward type were added as categorical predictor variables. An interaction term between the type of ward unit and randomization group (interventional arm versus standard-of-care arm) was included in the model.

Since subjects that are part of a twin were randomized individually, the power of the study is not impacted by the presence of twins. As a sensitivity analysis, a generalized estimating equation with an exchangeable working correlation structure was planned to account for the presence of twins.

Analysis on a subgroup of patients

Analysis on a subgroup of the data. A subgroup analysis of the patients with confirmed infection at baseline. Statistical methods were the same as those described in "Primary outcome analysis," but applied only to the subgroup with confirmed infection.

Sensitivity analyses

Sensitivity analysis 1

For the primary analysis, low model prior weight (0.3) was used to estimate the AUC. To assess the sensitivity of the results to this choice, a first 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

Sensitivity analysis 2

Due to the nature of the intervention being the use of an MIPD calculator in combination with early sampling, the number of available early samples was expected to be higher in the intervention group compared to the control group.

While these samples provide useful information to estimate the primary endpoint (reaching the target AUC/MIC between 24h and 48h after start vancomycin) more precisely, this availability of samples was expected to be imbalanced between both treatment groups and holds a risk for possible bias. Therefore, a second MIPD sensitivity analysis was performed where all early samples are omitted. Early samples were considered as samples taken within 6 hours after the start of the vancomycin treatment.

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.

Sensitivity analysis 3

To assess the robustness of our results against the assumption of independent observations, a sensitivity analysis which takes into account the possibly correlated outcomes of children "nested within twins or triplets" was planned.

Since subjects that are part of a twin were randomized individually, the power of the study is not impacted by the presence of twins. The following sensitivity analysis was planned in case ten percent of the subjects or more have a twin or triplet sibling included in the study: a logistic generalized estimating equation with randomization group (interventional versus the standard-of-care arm) as categorical predictor of interest, ward type as categorical predictor and an exchangeable working correlation structure.

5.4 Statistical methods for the secondary endpoints

The secondary binary outcomes (worsening) AKI and 30-day all-cause mortality were examined using a logistic regression model, similar to that used for the primary analysis. For time to clinical cure, a cox proportional hazards model stratified for type of ward unit was used. Ward unit and hospital length-of-stay were evaluated using a plug-in estimator with negative binomial regression. The secondary and tertiary outcomes related to AUC (48-72h 24h AUC, 72-96h 24h AUC) were estimated using a similar method as described for the primary outcome as well as the proportion of patients with (worsening) AKI during vancomycin treatment using modified AKI KDIGO criteria.

The secondary endpoint "Proportion of patients reaching target 24h AUC (400-600 mg·h/L) between [48 to 72] h after start treatment" and the tertiary endpoint "Proportion of patients reaching target 24h AUC (400-600 mg·h/L) between [72 to 96] h after start treatment" were analysed similarly as described for the primary endpoint. The intercurrent events and corresponding strategy for the other secondary endpoints are summarized below.

Estimand	Strategy for accounting intercurrent events	Endpoints
Treatment policy	Treatment policy strategy (the data collected for the variable of interest are used regardless of whether or not this intercurrent event occurs): All intercurrent events for which the endpoint could be observed Hypothetical strategy (censoring) (What would have happened if these subjects did not have this Intercurrent event?): Deferred consent not followed by an informed consent to continue the study, but with an informed consent for use of already collected data. Composite strategy: Death (unfavorable outcome) For the key secondary endpoint "time to clinical cure", the intercurrent event "Patient-treatment focus changed to palliation" is treated as a competing risk (censoring was applied).	-All cause 30-day mortality -Time to clinical cure -Ward unit length-of-stay -Hospital length-of-stay
While on treatment	While on treatment strategy: Discontinuation of vancomycin treatment Composite strategy: Death (unfavorable outcome)	-Proportion of patients with (worsening) AKI during vancomycin treatment

	Treatment policy strategy: Treatment switch (MIPD and standard-of-care or vice versa) Early discontinuation of calculator Hypothetical strategy: Deferred consent not followed by an informed consent to continue the study, but with an informed consent for use of already collected data.	

Table: Intercurrent events for the secondary outcomes and corresponding strategy according to ICH E9 (R1)

5.5 Statistical methods for the tertiary endpoints

The analyses of the tertiary outcomes were considered as exploratory. No p-values were reported and no correction for multiple testing was applied.

Outcome measure	Statistical method
• *Number of (additional) blood samples during vancomycin treatment* • *Cumulative number of (additional) blood samples during treatment in patients with clinical cure* • *Number of dose adjustments during vancomycin treatment*	Negative binomial regression with randomization arm (intervention arm versus standard-of-care arm) and ward type (NICU, PICU, PHO) as categorical predictor variables is applied. The standardized mean outcome per randomization arm is calculated using the plug-in method. Subjects with missing data is part of the population for which the standardized estimate is calculated. The intervention effect is expressed as a percentage increase or reduction of the outcome for Intervention versus Standard-of-care. Bootstrapping was used to create 95% confidence intervals for the mean per randomization arm and the percentage difference in the outcome.
	Statistical methods were similar to those described in 'Primary

• *Proportion of patients reaching target 24h AUC/MIC between [72-96]h after start vancomycin treatment*	analysis/estimator for the main estimand for the primary objective'. The intervention effect is expressed using the OR conditional on type of ward.
• *Cumulative vancomycin dose during vancomycin treatment* • *Cumulative AUC during vancomycin treatment*	Linear regression with randomization arm (intervention arm versus standard-of-care arm) and ward type (NICU, PICU, PHO) as categorical predictor variables was applied. The standardized mean outcome per randomization arm was calculated using the plug-in method. Subjects with missing data was part of the population for which the standardized estimate is calculated. The intervention effect was expressed as the mean difference in outcome for Intervention versus Standard-of-care. Bootstrapping was used to create 95% confidence intervals for the mean per randomization arm and the estimated difference.
• *Proportion of patients with (worsening) AKI (KDIGO-based criteria) or death*	Statistical methods were similar to those described for the secondary endpoint "proportion of patients with (worsening) AKI or death"
• *Number of trough sampling errors*	Negative binomial regression with randomization arm (intervention arm versus standard-of-care arm) and ward type (NICU, PICU, PHO) as categorical predictor variables was applied. The standardized mean outcome for the standard-of-care arm is calculated using the plug-in method.

Table: Statistical methods for tertiary endpoints

5.6 Evaluation criteria for Acute Kidney Injury

	Paediatric		Neonatal	
Class	Creatinine based classification	Urine output	Class	Urine output
Risk	1·5 to 2 fold rise in baseline serum creatinine or eGFR decrease by 25%	<0·5ml/kg/h for 8 h	Risk	<1·5 ml/kg/h for 24 h
Injury	2 to 3 fold rise in baseline serum creatinine or eGFR decrease by 50%	<0·5 ml/kg/h for 16h	Injury	<1 ml/kg/h for 24h
Failure	>3 fold rise in baseline serum creatinine or eGFR decrease by 75%	<0·3 ml/kg/h for 24h or anuria for 12h	Failure	<0·7 ml/kg/h for 24h or anuria for 12h
Loss	Failure >4 weeks		Loss	Failure >4 weeks
ESRD	persistent failure > 3 months		ESRD	persistent failure > 3 months

ESRD, end-stage renal disease

Table Modified neonatal and paediatric Risk Injury, Failure, Loss (RIFLE) AKI criteria

Serum creatinine criteria			Urine output criteria	
Stage	Paediatric definition	Neonatal definition	Paediatric definition	Neonatal definition
1	≥0·3 mg/L rise within 48 h or ≥1·5–1·9 × rise from baseline	≥0·3 mg/L rise within 48 h or ≥1·5–1·9 × rise from baseline	<0·5ml/kg/h for 8 h	<1·5 ml/kg/h for 24 h
2		Unchanged	<0·5 ml/kg/h for 16h	<1 ml/kg/h for 24h

	≥2–2·9 × rise from baseline			
3	≥3 × rise from baseline or ≥4·0 mg/L or eGFR<35 ml/min per 1·73 m2 or RRT initiation	≥3 × rise from baseline or ≥2·5 mg/L or RRT initiation	<0·3 ml/kg/h for 24h or anuria for 12h	<0·7 ml/kg/h for 24h Or anuria for 12h

RRT, renal replacement therapy

Table. Modified Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury criteria

6. Independent Ethics Committee and Competent Authority

The protocol has been reviewed and approved by the Ethics Committee of the Ghent University Hospital, designated as the central Ethics Committee, after consultation with the local Ethics Committees, and the Federal Agency for Medicine and Health Products (FAMHP).

OVERVIEW APPROVED DOCUMENTS		
Initial submission: - Protocol v.1.0 dd. 17-Jul-2020 - ANNEXE 1 v.1 dd. 19-Jun-2020 - ANNEXE 2 v.1 dd. 19-Jun-2020 - SmPC (Summary of Product Characteristics): Vancomycin Mylan 02/2018 - Beneficial ICF Parents v.1.0 dd.14-Jul-2020 (AR, BR, EN, FR, NL, TR) - Beneficial ICF child v.1.0 dd. 14-Jul-2020 (AR, BR, EN, FR, NL, TR) - Beneficial Deferred consent v.1 dd.14-Jul-2020 (AR, BR, EN, FR, NL, TR)	**Approval date Central EC: Not approved**	**Approval date FAMPH: 2020-10-01**

Submission after remarks LEC and CEC: - Protocol v.2.0 dd. 30-Oct-2020 - ANNEXE 1 v.2 dd. 30-Oct-2020 - ANNEXE 2 v.2 dd. 30-Oct-2020 - ANNEXE 3 v.1 dd. 30-Oct-2020 - Beneficial ICF Parents v.2.0 dd. 30-Oct-2020 (AR, BR, EN, FR, NL, TR) - Beneficial ICF child v.2.0 dd. 30-Oct-2020 (AR, BR, EN, FR, NL, TR) - Beneficial Deferred consent v.2.0 30-Oct-2020 (AR, BR, EN, FR, NL, TR)	**Approval date Central EC: 2020-11-20**	**Approval date FAMPH: NA**
Non-Substantial Amendment #1: - Addition Hôpital Erasme Brussels	**Approval date Central EC: 2020-12-23**	**Approval date FAMPH: NA**
Substantial Amendment #2 - Protocol v.3.0 dd. 20-Jul-2021 - ANNEXE 1 v.3 dd. 01-Jul-2021 - Beneficial ICF Parents/LAR v.3.0 dd. 01-Jul-2021 (AR, EN, FR, NL, TR) - Beneficial ICF child v.3.0 dd. 01-Jul-2021 (AR, EN, FR, NL, TR) - Beneficial Deferred consent v.3.0 dd. 01-Jul-2021 (AR, EN, NL); v3.0 dd. 15-04-2021 (FR); v3.0 dd.x-x-2021 (TR)	**Approval date Central EC: 2021-08-25**	**Approval date FAMPH: 2021-08-19**
Substantial Amendment #3 - Protocol v.4.0 dd.2023-03-20 - ANNEXE 3 v.2 dd. 2023-03-30 ➢ Adding additional recruiting site ZNA Middelheim ➢ Change of PI at HUDERF from Prof. dr. Biarent Dominique to Dr. Vens Daphné Vania - Small modifications/clarifications protocol	**Approval date Central EC: 2023-07-13**	**Approval date FAMPH: 2023-06-05**
Substantial Amendment #4 - Protocol v.5.0 dd.2023-10-18	**Approval date Central EC: 2023-11-20**	**Approval date FAMPH: 2023-11-08**

- ANNEXE 3 v.3 dd. 2023-10-18		

7. Results

7.1 Subject enrollment and demographics

Due to a recalculation of the sample size as a result of lower observed contamination rates, the initial enrolment number of 390 subject was reduce to 332. (Substantial Amendment #4)

Site	Not active yet	Active	Closed	Number of subjects included	Date of first inclusion	Date of site closure (LPLV)
Ghent University Hospital NICU ward	☐	☐	☒	61	07/01/2021	14/12/2023
Ghent University Hospital PICU ward	☐	☐	☒	28	28/12/2020	08/12/2023
Ghent University Hospital PHO ward	☐	☐	☒	25	30/01/2021	18/08/2023
Brussels University Hospital NICU ward	☐	☐	☒	23	13/02/2021	28/10/2023
Brussels University Hospital PICU ward	☐	☐	☒	6	12/04/2021	9/04/2023
Brussels University Hospital PHO ward	☐	☐	☒	6	28/06/2021	24/03/2022
AZ Sint Jan Bruges NICU ward	☐	☐	☒	20	12/02/2021	27/05/2023
Queen Fabiola University Children's Hospital (HUDERF) PICU ward	☐	☐	☒	15	25/03/2021	10/12/2023
Leuven University Hospital NICU ward	☐	☐	☒	58	06/04/2021	18/11/2023

Leuven University Hospital PHO ward	☐	☐	☒	24	18/05/2021	23/08/2023
Saint Luc University Hospital (UCL) NICU ward	☐	☐	☒	33	23/03/2022	29/11/2023
Saint Luc University Hospital (UCL) PICU ward	☐	☐	☒	7	14/07/2021	22/6/2023
Saint Luc University Hospital (UCL) PHO ward	☐	☐	☒	21	07/06/2021	20/01/2023
Erasmus Hospital NICU ward	☐	☐	☒	5	21/07/2021	23/9/2022

In the ITT population, baseline characteristics were similar between the standard-of-care and intervention group (Table 1). Of the 314 patients, 185 (59·0%) were patients admitted to the NICU, 55 (17·5%) patients admitted to the PICU and 74 (23·5%) patients admitted to the PHO unit. Most common indication for vancomycin treatment was bloodstream infection in 113 patients (36%) and 158 (50·3 %) of these patients had a documented infection at baseline. Identified Gram-positive organisms at baseline were detected in 125 patients (39·8%) and are listed in the table "Table: Identified pathogens at baseline". Vancomycin resistance was reported in one patient with *Bacillus cereus* according vancomycin by European Committee on Antimicrobial Susceptibility Testing Breakpoints.

	Standard-of-Care arm (n=156)	**Intervention arm (n=158)**
Postnatal age (months)	26·4 (50·0); 0·84 (0·4-26·8)	28·8 (52·5); 0·74 (0·3-32·1)
Sex **Girl** **Boy**	 63 (40·4%) 93 (59·6%)	 72 (45·6%) 86 (54·4%)
Weight (kg)	10·0 (14·9); 3·5 (1·3-12·3)	10·2 (14·9); 3·1 (1·2-14·3)
Birth weight (kg)*	1·9 (1·2); 1·4 (0·9-2·8)	1·7 (1); 1·3 (0·8-2·3)
Gestational Age (weeks)*	32 (6); 31 (27-37)	32 (5); 31 (27-36)
Postnatal age (days)*	22 (29); 14 (7-23)	21 (29); 12 (6-22)
Current weight (kg)*	2·0 (1·2); 1·5 (1·0-2·9)	1·7 (1·0); 1·3 (0·9-2·5)
Height (cm)	71·7 (41·0); 51·5 (41·0-92·0);48	70·8 (44·0); 49·0 (28·5-176·0);56

Serum creatinine (mg/L)	0·44 (0·20); 0·41 (0·30-0·53)	0·48 (0·24);0·42 (0·3-0·62)
Ward unit		
NICU	93 (59·6%)	92 (58·2%)
PICU	28 (18·0%)	27 (17·1%)
PHO	35 (22·4%)	39 (24·7%)
Vaso-active support	18 (11·5%)	17 (10·8%)
Mechanical ventilation	49 (31·4%)	42 (26·6%)
Number of concomitant nephrotoxic drugs		
0	94 (60·3%)	107 (67·7%)
1	40 (25·6%)	28 (17·7%)
2	13 (8·3%)	17 (10·8%)
3	5 (3·2%)	4 (2·5%)
>4	4 (2·5%)	2 (1·2%)
Indication for vancomycin treatment		
Bloodstream infection (%)	51 (32·7%)	62 (39·2%)
Systemic inflammatory response syndrome with no specific focus (%)	57 (36·5%)	53 (33·5%)
Febrile neutropenia or other form of manifestation of infection in immunocompromised host with no clear anatomical site (%)	12 (7·7%)	17 (10·8%)
Pulmonary infection	11 (7·1%)	10 (6·3%)
Gastro-intestinal infection (%)	9 (5·7%)	9 (5·7%)
Skin and soft tissue infection (%)	6 (3·8%)	3 (1·9%)
Infection of the central nervous system (%)	5 (3·2%)	1 (0·6%)
Other (%)	5 (3·2%)	3 (1·9%)
Documented infection**	84 (53·8%)	74 (46·8%)
Documented infection with Gram + pathogen	63 (40·4%)	61 (38·6%;)
Concomitant antibiotics	142 (91·0%)	146 (92·4%)

Data are presented as mean (SD), median (IQR); missing or n (%)· PICU, paediatric intensive care unit; NICU, neonatal intensive care unit; PHO, paediatric hemato-oncology ward unit·*collected in patients <6 months of age; ** documented infection was defined as an infection with a pathogen grown in blood or sterile site or an abcess or volume of infected tissue e.g. pneumonia, soft tissue.

Table 1: Baseline characteristics of the intention-to-treat population

Pathogen	**Standard-of-Care group (n=156)**	**Intervention arm (n=158)**
Coagulase negative Staphylococcus	36	30
Methicillin-Sensitive Staphylococcus aureus	17	13
Viridans Group Streptococci	0	6

Enterococcus spp.	3	2
Bacillus spp.	2	2
Beta-haemolytic Streptococci (Group A, B, C or G)	2	2
Streptococcus pneumoniae (or Pneumococcus)	0	3
Staphylococcus aureus (not further specified)	1	1
Methicillin Resistant Staphylococcus aureus	1	0
Lacticaseibacillus Rhamnosus	1	0
Staphylococcus spp (not further specified)	0	1
Corynebacterium amycolatum	0	1

Table 2: Identified pathogens at baseline

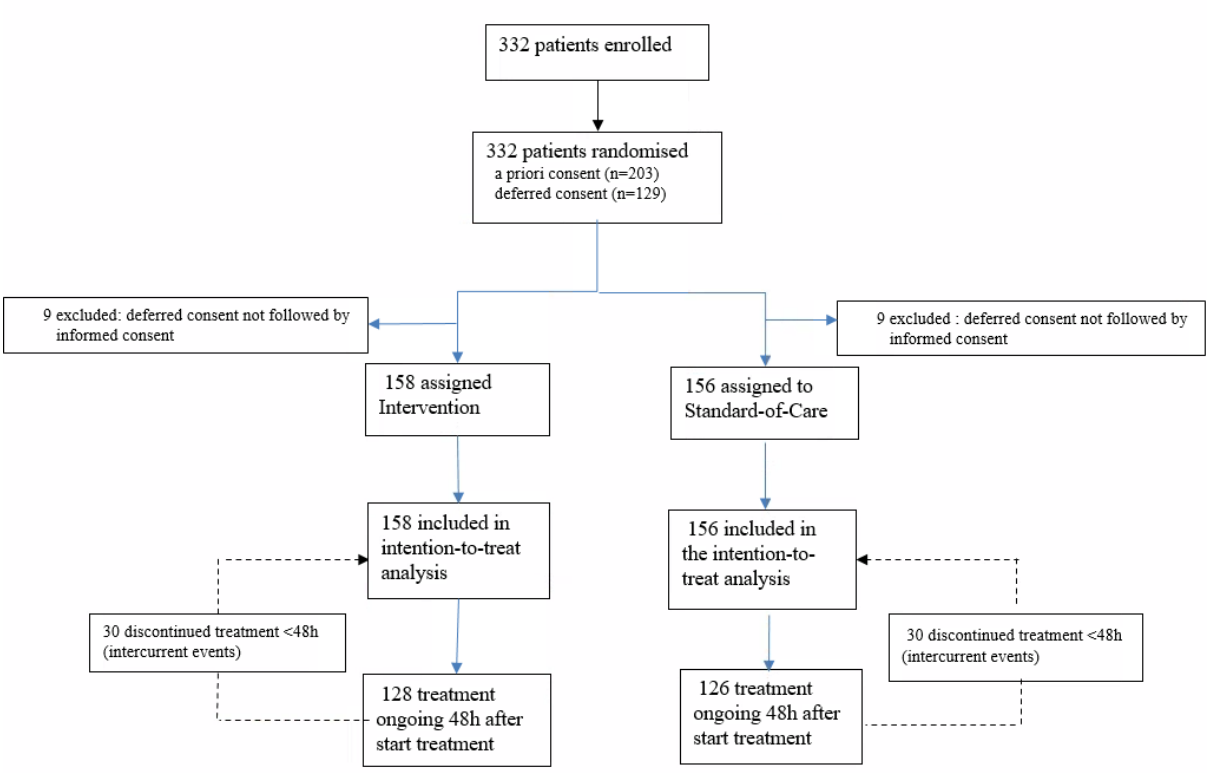


Figure 1: Trial profile for the primary endpoint

7.2 Study specific results

Between 28th of December 2020 and 14th of December 2023, 332 patients were randomised, with 165 patients in the standard-of-care arm and 167 in the intervention arm. Enrolment by site is shown below.

Site	Standard-of-Care group (n=164)	Intervention arm (n=168)
AZ Sint-Jan, Bruges, NICU	10	10
Hopital Erasme, NICU	3	2
Hopital universitaire Reine Fabiola, PICU	8	7
Cliniques universitaires de Saint-Luc, NICU	17	16
Cliniques universitaires de Saint-Luc, PHO	10	11
Cliniques universitaires de Saint-Luc, PICU	3	4
UZ Brussel, NICU	11	12
UZ Brussel, PHO	3	3
UZ Brussel, PICU	3	3
UZ Gent, NICU	30	31
UZ Gent, PHO	12	13
UZ Gent, PICU	15	13
UZ Leuven, NICU	28	30
UZ Leuven, PHO	11	13

NICU, neonatal intensive care unit; PHO, paediatric hemato-oncology ward unit; PICU, paediatric intensive care unit

Table 3: Enrolment by site

For 203 patients, a priori informed consent was collected; for 129 patients, a deferred consent approach was used. 18 patients were excluded from the analysis since a deferred consent was not followed by a informed consent. The ITT population consisted of 314 patients, with 156 in the standard-of-care group and 158 patients in the intervention group (Figure 1). Thirty patients in each group experienced an intercurrent event for the primary outcome.

	Standard-of-Care arm (n=156)	Intervention arm (n=158)
Discontinuation of vancomycin treatment because of clinical cure	5 (3·2%)	7 (4·4%)

Discontinuation of vancomycin treatment because of adverse event	1 (0·6%)	2 (1·3%)
Patient treatment focus changed to palliation	1 (0·6%)	1 (0·6%)
Discontinuation of vancomycin treatment because of change in antimicrobial therapy within 48h after start vancomycin treatment	18 (11·5%)	17 (10·8%)
Deferred consent not followed by informed consent to continue the study, but with an informed consent for use of already collected data	0 (0%)	1 (0·6%)
Other	5 (3·2%)	2 (1·3%)

Data are n (%).

Table 4: Reporting of intercurrent events for the primary endpoint

For the composite secondary outcome (worsening) AKI or death, 5 patients in the standard-of-care arm and 4 patients in the intervention arm were handled as intercurrent event.

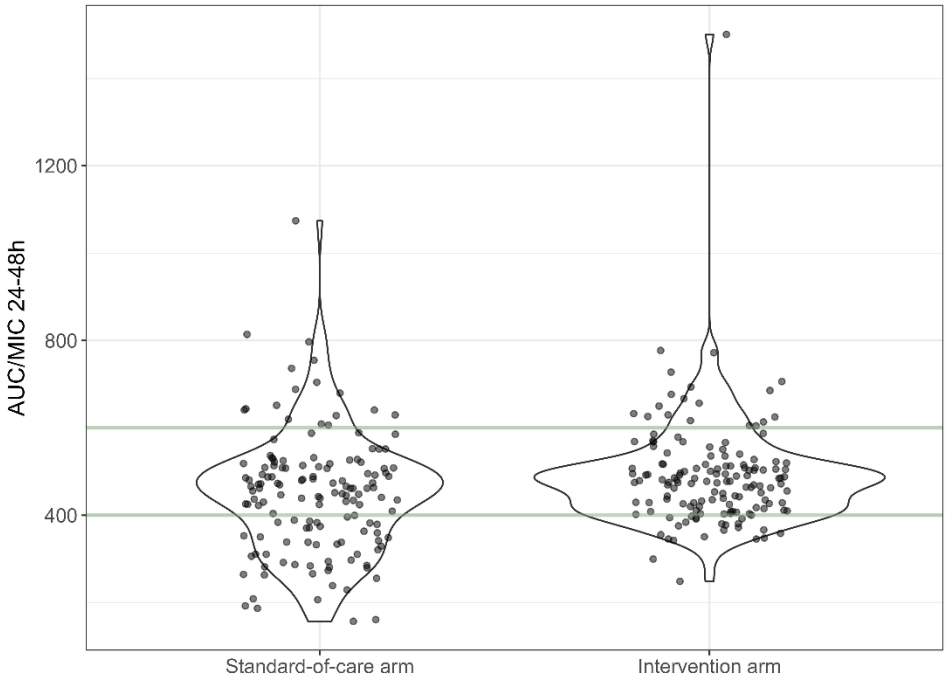
	Standard-of-Care arm (n=156)	**Intervention arm (n=158)**
Proportion of patients with (worsening) AKI Deferred consent not followed by informed consent to continue the study, but with an informed consent for use of already collected data	0 (0%)	2 (1.3%)
Mortality	5 (3.2%)	2 (1.3%)
30-day all-cause mortality Deferred consent not followed by informed consent to continue the study, but with an informed consent for use of already collected data	0 (0%)	2 (1.3%)

Data are n (%).

Table 5: Reporting of intercurrent events for the key secondary endpoints for safety

The safety population consisted of the same patients as in the ITT population.

In the ITT analysis, 82 (53·9%) patients in the standard-of-care group and 112 patients (71·8%) in the intervention group achieved the target 24h AUC between 24 and 48 hours after start of treatment (relative difference in proportion: 35·7% [95% CI: 3·0-81·4]; absolute difference in proportion: 18·9% [95% CI: 1·7-34·7]; OR: 2·21 [95% CI: 1·36-3·59]; p=0·001) (Table 6) (Figure 2).

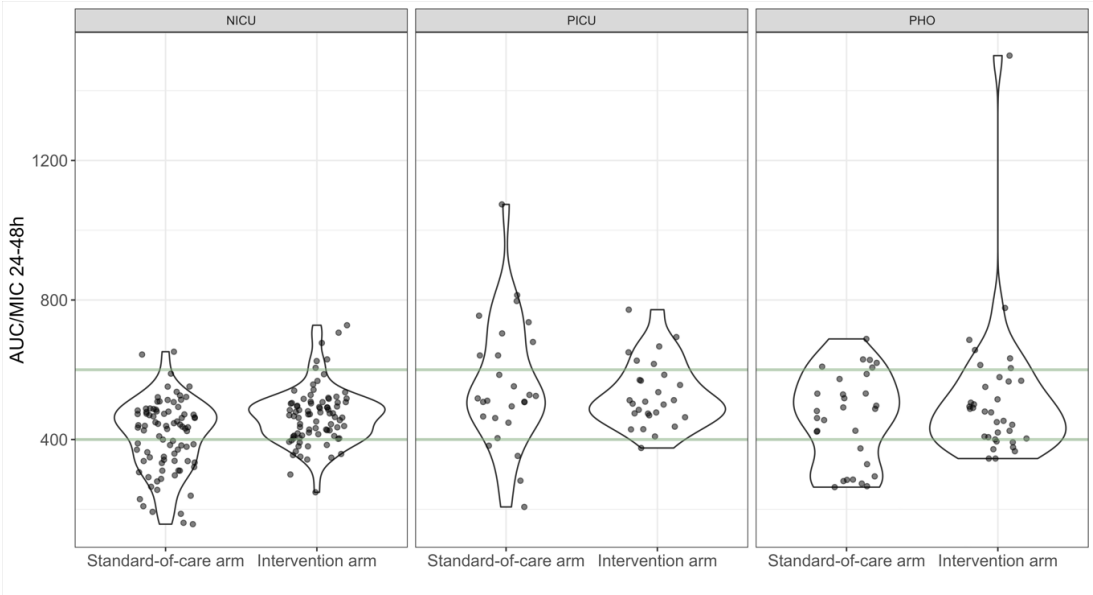


The solid horizontal green line represents the target range of AUC/MIC 400-600.

Figure 2. Violin plot for standard-of-care and intervention arm showing distribution of AUC/MICs (assuming a MIC of 1 mg/L) in the interval 24-48h after start of vancomycin treatment.

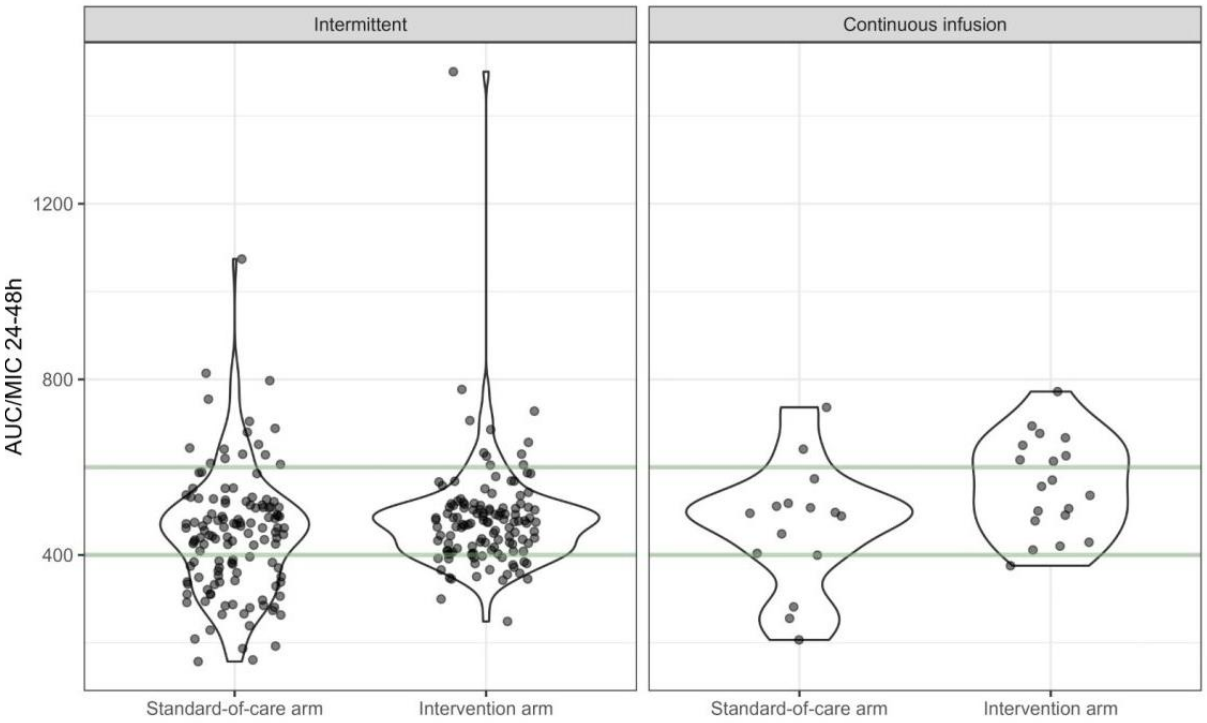
The protocol-compliant estimand of the primary outcome was also significantly in favor of the intervention group with 79 (54·5%) versus 100 (73·0%) of patients in the standard-of-care group and intervention group (relative difference in proportion: 33·6% [95% CI: 1·6-75·8]; absolute difference in proportion: 18·3% [95% CI: 0·3 to 33·5%]; OR: 2·42 [95% CI: 1·45 to 4·05]; p=0·001), as was the case for the two sensitivity analyses (Table 7). The estimates of treatment effect for subgroup analysis in all subgroups were similar to the main analysis, except for the subgroup on continuous infusions (Table 6). Subgroup analysis revealed that the proportion of target attainment between 24h to 48h after start of treatment were significantly higher in intervention group compared to standard-of-care group in patients from

NICU (absolute difference in proportion: 21·3% [95% CI: -13·6% to 43·9%]; OR: 2·92 [1·51 to 5·64]; p=0·001) (Figure 3, table 6), in patients on intermittent dosing (absolute difference in proportion: 22·3% [95% CI: 4·4-39·0]; OR: 2·73 [95% CI: 1·61 to 4·62]; p<0·001) (Figure 4, table 6) and in boys (OR: 2·81 [95% CI: 1·43-5·55]; p=0·003).



NICU, neonatal intensive care unit; PICU, paediatric intensive care unit; PHO, paediatric haemato-oncology ward unit

Figure 3. Violin plot for standard-of-care and intervention arm per ward type showing distribution of AUC/MICs (assuming a MIC of 1 mg/L) in the interval 24h to 48 h after start of treatment

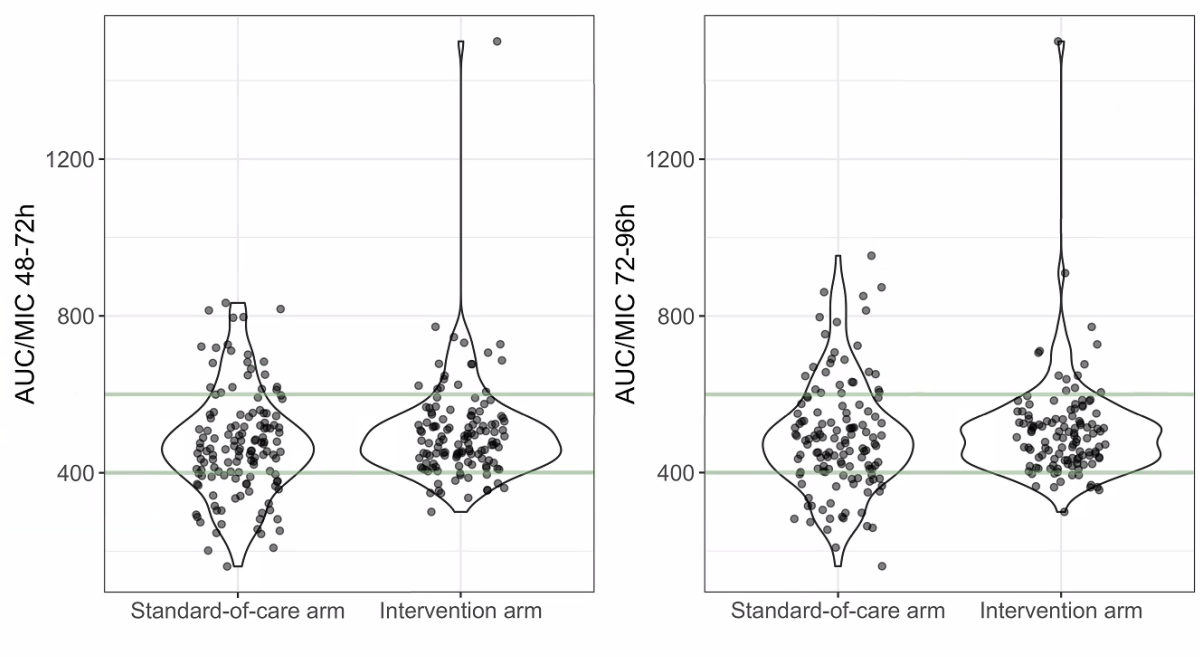


The solid horizontal green line represents the target range of 24hAUC/MIC 400-600.

Figure 4. Violin plot for standard-of-care and intervention arm per type of dosing regimenshowing distribution of AUC/MICs (assuming a MIC of 1 mg/L) in the interval 24h to 48h after start of treatment

The proportion of patients with AKI or death according to modified RIFLE criteria was numerically lower with 19 (12·4%) patients in the intervention group versus 26 patients in the standard-of-care group (16·9%) (absolute difference in proportion: -4·5% [95% CI: -11·6% to 3·5%]; OR: 0·67 [95 % CI: 0·34 to 1·33]; p=0·25), however not statistically significant (Table 6). 30-day all-cause mortality was overall low (3 patients (3·8%) in the intervention group versus 6 patients (1·9%) in the standard-of-care group) and was not statistically different between both groups (absolute difference in proportion: -1·9% [95% CI: -5·8% to 1·6%]; OR: 0·49 [95% CI: 0·12 to 2·06]; p=0·32) (Table 6). 89 patients (58·6%) in the standard-of-care group and 120 patients (77·4%) in the intervention group achieved the target 24h AUC between 48 and 72 hours after start of treatment (absolute difference in proportion: 20·5% [95% CI: 4·5 to 36·9%]; OR: 2·54 [95% CI: 1·52 to 4·26]; p<0·001) (Table 6; Figure 5).

A B



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

Figure 5. Violin plot for standard-of-care and intervention arm showing distribution of AUC/MICs (assuming a MIC of 1 mg/L) in the interval (A) 48-72h after start of vancomycin treatment, (B) 72-96 h after start of vancomycin treatment

Time to clinical cure showed a trend towards shorter period in the intervention group (OR:1·26 [95% CI: 0·99 to 1·6]; p= 0·056) but was also not statistically significant, as shown in the Kaplan-Meier plot of the cumulative incidence of the percentage of patients with clinical cure (Figure 6). Ward unit and hospital length-of-stay were not statistically different (Table 6; Figure 6).

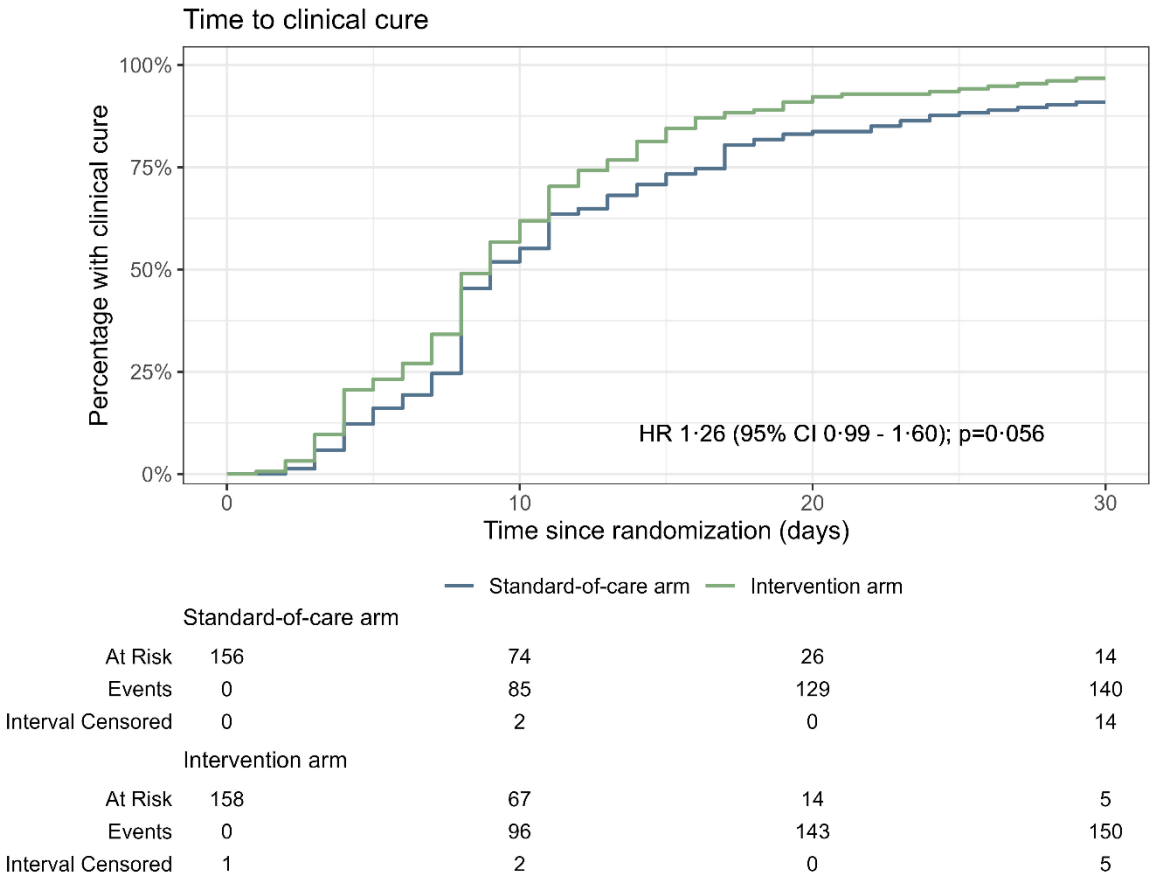


Figure 6. Estimates of the cumulative incidence of the time to clinical cure for the intention-to-treat population

Ninety-two patients (60·5%) in the standard-of-care group and 127 patients (81·9%) in the intervention group achieved the target 24h AUC between 72 and 96 hours after start of treatment (absolute difference in proportion: 22·2% [95% CI: 6·8 to 37·8%]; OR: 3·18 [95% CI: 1·85 to 5·47]) (Table 6, Figure 6).

Mean cumulative dose during vancomycin treatment was significantly lower in intervention group patients compared to standard-of-care group patients, being 325 milligram per kg (SD:334) versus 412 (SD: 421) milligram per kg (absolute difference in mean: -95 (IQR: -184 to -18)), respectively. In line with a significantly lower dose, mean cumulative AUC was also significantly lower in the intervention group being 3,429 mg·h/L (SD:2,544) versus 4,099 mg·h/L (SD: 3,510) respectively (absolute difference in mean: -711 (IQR: -1,497 to -109)) (Table 6).

Mean number of blood samples during vancomycin treatment were 4·2 (SD: 3·9) and 4·9 (SD: 3·5) in the standard-of-care group and intervention group, respectively (absolute difference in mean: 0·6 [95% CI: -0·3 to 1·4]; mean ratio 1·15 [95% CI 0·95 to 1·36]) ; mean number of additional blood samples during vancomycin treatment were 2·9 (SD: 2·9) and 3·4 (SD: 2·6) in

the standard-of-care group and the intervention group, respectively (absolute difference in mean: 0·5 [95% CI: -0·1 to 1·1]; mean ratio 1·18 [95% CI: 0·97 to 1·42]).

Mean number of sampling time errors in the standard-of-care group for intermittent infusions was 1·7 (SD: 2·2).

Outcome	**Standard-of-Care arm (n=156)**	**Intervention arm (n=158)**	**Absolute difference in mean or proportion, % (95% CI)**	**Odds ratio/Hazard Ratio or relative difference (95% CI)**	**P value**
Primary outcome					
Proportion of patients reaching 24h AUC/MIC target between 24-48h after start of treatment	82 (53·9%); 4	112(71·8%); 2	18·9% (1·7% to 34·7%)	2·21(1·36 to 3·59)	0·001
Protocol-compliant estimand	79 (54·5%); 11	100 (73·0%); 21	18·3% (0·3% to 33·5%)	2·42 (1·45 to 4·05)	0·001
Subgroup analyses primary outcome					
Type of ward unit					
NICU (n=185)	50 (54·9%); 2	70 (77·8%); 2	21·3% (-13·6% to 53·9%)	2·92 (1·51 to 5·64)	0·001
PICU (n=55)	15 (53·6%)	20 (74·1%)	23·5% (1·8% to 43·4%)	2·48 (0·78 to 7·90)	0·12
PHO (n=74)	17 (51·5%); 2	22 (56·4%)	7·6% (-27·2% to 40·6%)	1·32 (0·51 to 3·39)	0·56
Type of dosing regimen at start treatment					
Intermittent infusion (n=276)	72 (53·3%); 4	101 (74·8%); 2	22·3% (4·4% to 39·0%)	2·73 (1·61 to 4·63)	<0·001
Continuous infusion (n=38)	10 (58·8%)	11 (52·4%)	-2·5%(-48·6% to 45·7%)	0·83 (0·22 to 3·15)	0·78

Patients with documented infection (n=158)	47 (57·3%); 2	50 (67·6%)	11·6% (-13·0% to 33·1%)	1·66 (0·84 to 3·25)	0·14
Secondary outcomes					
Proportion of patients with (worsening) AKI or death*	26 (16·9%); 2	19 (12·4%); 5	-4·5% (-11·6% to 3·5%)	0·67 (0·34 to 1·33	0·25
Protocol-compliant estimand	26 (17·8%); 10	16 (11·4%); 18	-6·3% (-11·6% to 3·5%)	0·53 (0·26 to 1·09)	0·08
30-day all-cause mortality	6 (3·8%)	3 (1·9%); 2	-1·9% (-5·8% to 1·6%	0·49 (0·12 to 2·06)	0·32
Proportion of patients reaching 24h AUC/MIC target between 48-72h after start of treatment	89 (58·6%); 4	120 (77·4%); 3	20·5% (4·5% to 36·9%)	2·54 (1·52 to 4·26)	<0·001
Time to clinical cure, days	9 (8 to 11)&	9 (8 to 10)&		1·26 (0·99 to 1·6)	0·06
Ward unit length-of-stay, days	21·6 (10·4); 30 (11-30)	21·7 (10·1); 28·5 (13-30); 2	0·3 (-1·6 to 2·3)	1·02 (0·93 to 1·11)§	0·94
Hospital length-of-stay, days	24·1 (8·8); 30 (18-30)	23·1 (9·4); 30 (16-30); 2	-0·8 (-2·5 to 1·1)	0·97 (0·90 to 1·05)§	0·32
Tertiary outcomes					
Number of blood samples during vancomycin treatment	4·2 (3·9); 3 (2-6)	4·9 (3·5); 4 (2·75-6); 2	0·6 (-0·3 to 1·4)	1·15 (0·95 to 1·36) §	
Number of additional blood samples during vancomycin treatment	2·9 (2·9); 2 (1-4)	3·4 (2·6); 3 (2-5); 2	0·5 (-0·1 to 1·1)	1·18 (0·97 to 1·42) §	
Cumulative number of blood samples in subgroup of patients with clinical cure (n=290)	3·9 (3·2); 3 (2-5)	4·9 (3·5); 4 (2·25-6)	0·9 (0·1 to 1·6)	1·18 (0·97 to 1·46) §	

Number of dose adjustments during vancomycin treatment	2·8 (2·8); 2 (1-4)	2·2 (2·1); 2 (1-3) ; 2	-0·6 (-1·2 to -0·1)	0·78 (0·63 to 0·97)§	
Proportion of patients reaching 24h AUC/MIC target between 72-96h after start of treatment	92 (60·5%); 4	127 (81·9%); 3	22·2% (6·8% to 37·8%)	3·18 (1·85 to 5·47)	
Cumulative dose during vancomycin treatment (mg/kg)	412·2 (421·5); 258·4 (136·1-538·1)	324·7 (333·6); 241·4 (113·2-422·9); 2	-94·8 (-183·6 to -17·7)		
Cumulative AUC during vancomycin treatment (mg*h/L)	4,099·1 (3,509·9); 3,191·9 (1,606·1-5,146·8); 6	3,429·4 (2,544·3); 2,822·5 (1,397·7-4,595·5) ; 5	-710·6 (-1496·9 to -109·5)		
Number of trough sampling errors	1·7(2·2); 1(0-2) ; 6	NA	NA		
Proportion of patients with (worsening) AKI or death**	23 (14·9%); 2	15 (9·7%); 4	-4·7% (-11·1% to 3·1%)	0·61 (0·3 to 1·24)	

Data are presented as mean (SD), median (IQR); missing or n (%). AUC, Area-Under-the-Concentration Time curve; MIC, Minimal Inhibitory Concentration; AKI, acute kidney injury; NA, not applicable; *according to modified Risk Injury Failure Loss End-Stage (RIFLE) assessment criteria; **according to Kidney Diseases Improving Global Outcomes (KDIGO) assessment criteria &, median time to clinical cure (95% CI) §, Relative difference presented as a ratio

Table 6: Reporting of primary, secondary, and tertiary outcomes

Outcome	Standard-of-Care arm (n=156)	Intervention arm (n=158)	Odds ratio (95% CI)	P value
Primary outcome: proportion of patients reaching 24h AUC/MIC target between 24-48h after start of treatment				
Sensitivity analysis 1 : flattened prior 50%	82 (53·9%); 4	111 (71·2%); 2	2·21 (1·36 to 3·59)	0·001
Sensitivity analysis 2 : exclusion early samples	82 (53·9%); 4	100 (64·9%); 4	1·66 (1·04 to 2·66)	0·030
Sex-based subgroup analysis** :				
Boy (n=179)	52 (57·1%); 2	66 (77·6%) ; 1	2·81 (1·43 to 5·55)	0·003
Girl (n=135)	30 (49·2%); 2	46 (64·8%); 1	1·96 (0·96 to 4·01)	0·060
Secondary outcome: proportion of patients with (worsening) AKI* or death				
Sex-based subgroup analysis**:				
Boy (n=179)	15(16·1%)	9 (10·8%);3	0·55 (0·21 to 1·42)	0·21
Girl (n=135)	11 (18·0%);2	10 (14·3%);2	0·80 (0·30 to 2·17)	0·66
Secondary outcome: 30-day all-cause mortality				
Sex-based subgroup analysis**				
Boy (n=179)	4 (4·3%)	1 (1·2%); 1	0·26 (0·03 to 2·49)	0·23
Girl (n=135)	2 (3·2%)	2 (2·8%); 1	0·90 (0·12 to 6·91)	0·92

Data are presented as mean (SD), median (IQR); missing or n (%). Sensitivity analysis 1: 50% weight is given to the PK model for 24hAUC estimation; Sensitivity analysis 2 : early samples are omitted for 24hAUC estimation; AUC, Area-Under-the-Concentration Time curve; MIC, Minimal Inhibitory Concentration; AKI, acute kidney injury;*according to modified Risk Injury Failure Loss End-Stage (RIFLE) assessment criteria; ** not predefined analysis

Table 7: Sensitivity and subgroup analysis of primary outcome and key secondary outcomes for safety

Additional tables

Details on the start of vancomycin treatment, starting dose, TDM and reasons for cessation of vancomycin are shown below.

	Standard-of-Care arm (n=156)	**Intervention arm (n=158)**
Duration of first episode of vancomycin treatment	146 (119); 119 (57-176)	143 (113);122 (55-183);2
Proportion of patients with>1 episode of treatment	41 (26·3%)	27 (17·3%);2
Vancomycin method of administration Intermittent (%) Continuous (%)	 139 (89·7%) 17 (10·9%)	 137 (86·7%) 21 (13·3%)
Cumulative starting dose in first 24h (mg/kg)	54 (19); 53 (41-64)	52 (22);47 (34-66)
Switch during treatment from intermittent to continuous infusion	5 (3·2%)	3 (1·9%);2
Number of TDM samples during treatment	4·2 (3·9); 3(2-6)	4·9 (3·5); 4(2·5-6);2

Data are mean (SD), median (IQR); missing or n (%).

Table 8: Vancomycin treatment, dosing and sampling details for therapeutic drug monitoring; TDM, therapeutic drug monitoring.

	Standard-of-Care arm (n= 154)	**Intervention arm (n=155)**
Reasons for stop vancomycin		
clinical cure	78 (50·6%)	93 (60·0%)
change in antimicrobial therapy	61 (39·6 %)	53 (34·2%)
adverse event	1 (0·7%)	3 (1·9%)
patient treatment focus changed to palliation	1 (0·7%)	1 (0·6%)
Other	13 (8·4%)	5 (3·2%)

Data are n (%).

Table 9: Reasons for stop vancomycin treatment

8. Safety

Serious adverse events were reported in 8/158 (5·1%) in the standard-of-care group and 8/156 (5·1%) in the intervention group.

All but one severe adverse events (SAE) (n=16) were resolved; 1 patient died. No Serious Unexpected Serious adverse Reactions (SUSAR) were reported.

13 patients experienced the vancomycin flushing syndrome (n=7 in standard-of-care arm ; n=6 in intervention arm).

3 patients developed a severe acute kidney injury during vancomycin treatment (n=1 in standard-of-care arm; n= 2 in intervention arm). 1 patient died.

Subject ID	*Study Arm*	*SUSAR (Y/N)*	*Days since start treatment*	*Severity*	*Reportable event*	*Description of reportable event*	*Relationship to IMP (vancomycin)*	*Was the reportable event expected to IMP?*	*Relationship to vancomycin dose calculation (SOC/MIPD tool)*	*Was the reportable event expected to IMP dose calculation (SOC/MIPD tool)?*	*Outcome*	*The number of days from start of the adverse event to the date resolved / resolved with sequela*
232-7	*IV arm*	*N*	*1 day since start second Vancomycin treatment*	*Moderate*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Onset of vancomycin infusion syndrome (also known as red man syndrome) with itching rash in the face during the administration of first Vancomycin dose. This was successfully treated with one dose of an oral antihistaminic. The SAE occurred during a second vancomycin treatment episode within the study period of 30 days As the SAE occurred on a ward unit not participating in the study, the dosing was according the standard-of-care institutional guidelines. No SAE was registered in this patient while dosed with the dose calculator.*	*Definitely*	*Yes*	*Not related*	*No*	*Resolved*	*1*
232-30	*SOC arm*	*N*	*1*	*Mild*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome with onset of itchy rash of face and thorax during the first Vancomycin infusion. On the second dosing mild rash was noticed on the legs.*	*Definitely*	*Yes*	*Not related*	*No*	*Resolved*	*1*
233-2	*IV arm*	*N*	*1*	*Moderate*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Onset of vancomycin infusion syndrome (also known as red man syndrome) with itching erythematous rash in the face and upper torso at the end of infusion of the second vancomycin dose. Palpitations were associated due to emotional distress. SAE was immediately and successfully treated with one dose of an oral antihistaminic and one dose of intravenous corticoid.*	*Definitely*	*Yes*	*Not related*	*No*	*Resolved*	*1*

233-9	*SOC arm*	*N*	*1*	*Mild*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome with onset of rash on the face after the administration of first Vancomycin dose.*	*Definitely*	*Yes*	*Not related*	*No*	*Resolved*	*1*
233-10	*SOC arm*	*N*	*1*	*Mild*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome.*	*Definitely*	*Yes*	*Not related*	*No*	*Resolved*	*2*
233-16	*SOC arm*	*N*	*1*	*Mild*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome with body rash after administration of first Vancomycin dose.*	*Definitely*	*Yes*	*Not related*	*No*	*Resolved*	*1*
233-20	*SOC arm*	*N*	*11*	*Moderate*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome with onset of body rush, itcy eyes and feet's and dry cough. Tahycardia was also noticed.*	*Probable*	*Yes*	*Not related*	*No*	*Resolved*	*5*
233-22	*IV arm*	*N*	*1*	*Mild*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome with onset of rash on face and body after the first dose of Vancomycin. The patient also become agitate.*	*Definitely*	*Yes*	*Not related*	*No*	*Resolved*	*3*

238-9	*SOC arm*	*N*	*2*	*Mild*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome with high blood pressure (12/7) and tachycardia 193/min. Large vomiting episode (2 times). Erythema diffused over the whole body.*	*Probable*	*Yes*	*Possible*	*Yes*	*Resolved*	*4*
238-16	*IV arm*	*N*	*7*	*Severe*	*Neonatal or pediatric RIFLE class category failure*	*Initial report: Neonatal or pediatric RIFLE class category failure: Toxic trough concentration of vancomycin : 71.8 µg/mL and acute renal insufficiency. In the same time, our patient has pulmonary and digestive infection with E coli. Follow-up report: Other significant safety issue (including death) at the discretion of the investigator thought to be at least possibly related to the vancomycin dosing method. Respiratory failure on pneumonia > SIP Pneumonia and E coli urinary sepsis Vancomycin poisoning (Toxic trough concentration : 71.8 µg/mL and acute renal insufficiency.) Acute renal failure in a septic and toxic context > dialysis. Tetraplegia on inflammatory and haemorrhagic lesions from lower trunk to lower marrow > reduced recovery potential. ARCA (Autosomal recessive cerebellar ataxia) on 31/5 on respiratory arrest due to agitation (bitten tube). Pulmonary hemorrhage > comfort care > death.*	*Unlikely*	*No*	*Unlikely*	*No*	*Death*	*8*
238-21	*IV arm*	*N*	*2*	*Mild*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome with skin erythema and generalized pruritus following vancomycin infusion.*	*Definitely*	*Yes*	*Possible*	*Yes*	*Resolved*	*1*

239-10	*SOC arm*	*N*	*2 days since start second Vancomycin treatment*	*Mild*	*Neonatal or pediatric RIFLE class category failure*	*Neonatal or pediatric RIFLE class category failure.*	*Possible*	*Yes*	*Not related*	*No*	*Resolved*	*4*
242-11	*IV arm*	*N*	*1*	*Moderate*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome with redness, itching, circulation always remained good, always alert.*	*Definitely*	*Yes*	*Unlikely*	*No*	*Resolved*	*1*
242-13	*SOC arm*	*N*	*1*	*Moderate*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome with redness on the face and itching.*	*Definitely*	*Yes*	*Unlikely*	*No*	*Resolved*	*1*
242-14	*IV arm*	*N*	*1*	*Mild*	*Vancomycin flushing syndrome (also known as red man syndrome)*	*Vancomycin flushing syndrome with erythema face and trunk, limbs spared, itching. Other normal findings. Cardiorespiratory stable parameters.*	*Definitely*	*Yes*	*Unlikely*	*No*	*Resolved*	*1*
243-5	*IV arm*	*N*	*3 days since start second Vancomycin treatment*	*Severe*	*Neonatal or pediatric RIFLE class category failure*	*Neonatal or pediatric RIFLE class category failure with intermittent anuria.*	*Unlikely*	*Yes*	*Not related*	*Yes*	*Resolved*	*31*

9. Device deficiencies

NA

10. Protocol deviations

To ensure a consistent approach in reporting Protocol Deviations, a criteria list was developed for capturing these deviations in the electronic case report form. Registered Protocol Deviations were reviewed regularly during meetings between the project management team and monitors. During Investigator Meetings, the most frequently occurring deviations were presented and discussed. On-site retraining and close follow-up were implemented to minimize the occurrence of protocol deviations.

An overview of the protocol deviations and corrective actions is added as annexe to this document.

11. Discussion and overall conclusions

In 2020, 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 published revised guidelines for vancomycin therapeutic monitoring in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections. These revised guidelines now advocate for the routine use of AUC/MIC-based model-informed precision dosing (MIPD) in both adults and children, recommending a target AUC/MIC of 400-600 for therapeutic effectiveness 24 to 48 hours after the start of treatment, replacing single-point therapeutic drug monitoring.[46,47]

One of the main concerns with applying these recommendations to children, compared to adults, is the lack of pediatric prospective, comparative studies linking AUC/MIC-based MIPD with improved pharmacokinetic/pharmacodynamic (PK/PD) target attainment and clinical outcomes, including safety, as compared to traditional 'single-point' monitoring. Healthcare providers, therefore, carefully weigh the potential benefits of targeting a vancomycin AUC/MIC in children against the more resource-intensive MIPD process and any potential additional patient burden.[48]

The BENEFICIAL trial is the first multicenter, pragmatic, randomized controlled trial investigating the target attainment and clinical benefit of early AUC/MIC MIPD of vancomycin in critically ill children. The intervention consisted of a user-friendly MIPD dosing calculator for deriving starting and follow-up doses, combined with early sampling in the first hours after the start of treatment.

The "golden window" of antibiotic treatment for severe bacterial infections is within the first hours.[49] In this trial, we demonstrated a significantly increased AUC/MIC target attainment 24 to 48 hours after treatment initiation using MIPD, an effect that persisted throughout the treatment course (48-72h and 72-96h windows). This aligns with findings from a small, single-center randomized controlled trial in children receiving vancomycin as a continuous infusion, which used a broader AUC/MIC target range (400-800).[50] Growth, development, and dynamic pathophysiological changes during critical illness significantly impact vancomycin PK/PD and complicate optimal dosing over the course of therapy.[51] Implementing a fit-for-purpose PK/PD model in MIPD software that captures inter- and intrapatient variability in this population is essential for improving clinical outcomes. In this clinical study, we used a validated PK/PD model that accurately represented vancomycin disposition in the target patient population.[39]

Higher exposure rates are associated with increased nephrotoxicity.[54] We observed a statistically significant higher cumulative dose and corresponding cumulative exposure in the comparator arm compared to the intervention arm *(mean difference: 95 mg/kg and 711 mg*h/L, respectively; for comparison, a 1-month-old child typically receives a starting dose of 60 mg/kg/day, with the upper threshold of the target 24h AUC, assuming an MIC of 1 mg/L, being 600 mg**h/L).*[6,55] This increased dose requirement was also seen in a retrospective monocentric study of hospitalized children.[56] However, despite a clear trend toward reduced vancomycin-related acute kidney injury (AKI) in critically ill children using both RIFLE and KDIGO criteria, we were unable to demonstrate a statistically significant decrease in the proportion of patients with acute or worsening AKI or death. One possible explanation is that we used a pragmatic approach to assess AKI, relying on routinely collected data on serum creatinine and urine output. The sensitivity of the current assessment criteria to detect AKI in neonates—a large subgroup in our study population—is debated, and ongoing research is exploring alternative biomarkers.[57,58] Since this was a pragmatic study, we did not influence the frequency of serum creatinine measurements. Particularly in neonates, serum creatinine was not measured daily, which may have impacted the detection of renal toxicity. Longer treatment duration is also a risk factor for nephrotoxicity, and we speculate that the non-significant trend could also be partially explained by a trend toward shorter treatment courses as part of antimicrobial stewardship efforts.[59-62] Finally, the proportion of patients experiencing AKI in our comparator study group was lower than previously reported in the literature for critically ill children (range:17-26%).[8,63,64]

The time to clinical cure favored AUC/MIC-based dosing with near statistical significance (p-value=0.056). In this trial, we used a single AUC/MIC threshold for efficacy (>400) for all patients, as most patients are started empirically on vancomycin. This reflects current clinical practice, where clinicians use the same single-point monitoring target range for patients with different infections and pathogens. Recent evidence suggests that lower efficacy thresholds can be used in children with Gram-positive infections other than *Staphylococcus aureus*.[65] We hypothesize that lower thresholds for efficacy may have led to an increased clinical cure rate, particularly in neonates and hemato-oncology patients from the comparator group, in which subtherapeutic dosing (AUC/MIC < 400) was most pronounced during the 24-48h window.

Judicious use of routine invasive procedures could improve quality of life without compromising patient safety. It is also known that reduced blood loss due to sampling decreases the risk of developing iatrogenic anemia.[66] In this study, we did not observe

statistically significant differences in the number of blood samples between the two study groups, despite an average of one extra sample being required in the intervention group for clinical cure. This extra sample is related to the intervention, which required at least one (and preferably two) extra samples after the first dose for follow-up AUC/MIC dose calculations. Since there was no statistical difference in dose adjustments, which would also require an additional sample for follow-up, it is plausible that clinicians felt most comfortable adhering to ward-based guidelines on re-monitoring frequency (e.g., every 24 hours), leading to no net difference in sampling.

AUC/MIC-based MIPD dosing allows for blood samples to be taken at the most convenient time for the patient and caregiver.[67] Additionally, this approach means vancomycin concentrations can be measured from leftover samples obtained during routine clinical care for biochemical monitoring (i.e., opportunistic or scavenged sampling). Since no statistically significant reduction in additional samples was observed, we speculate that clinicians did not fully take advantage of combining blood samples, due to the additional organisational effort in a complex, high-stress environment.

Inappropriately timed trough samples lead to difficult-to-interpret results, often requiring a repeat sample or resulting in inaccurate interpretations by clinicians if not caught.[69] In our study, we found that trough sampling errors were frequently encountered in the comparator arm.

Strengths of this study include the aspect of early dose optimization (first and second doses), which was shown to be feasible and effective in patients with variable PK admitted to a complex, dynamic hospital environment. Additionally, the study's results are directly applicable to a large patient population due to its pragmatic design and the recruitment of a heterogeneous study cohort. Regarding organizational effort, we demonstrated that the 24/7 use of dosing software with a large team of users per hospital and interdisciplinary involvement is feasible and safe.

Overall Conclusion: In the BENEFICIAL trial, we demonstrated significantly increased PK/PD target attainment and a reduction in cumulative dose and corresponding AUC when using AUC/MIC-based MIPD. We also showed that sampling errors were frequent in the comparator arm with intermittent dosing, and that time to clinical cure favored the intervention arm with near statistical significance. The use of MIPD software was safe.

Whether broad-scale implementation of AUC-based MIPD in routine practice is advisable remains a topic for debate. In children, AUC >600 mg*h/L, cumulative AUC, treatment duration, and concomitant nephrotoxic medication have been linked to an increased risk of nephrotoxicity.[54,59,69,70] Since the consequences of acute kidney injury (AKI) in children are significant, with 70% of children experiencing AKI from nephrotoxic exposure showing residual damage 6 months later[71], we recommend the routine implementation of AUC/MIC MIPD for intermittent dosing in critically ill children with presumed or documented Gram-positive infections requiring longer treatment with additional risk factors for AKI or existing chronic kidney disease.

Limitations:

This study has several limitations. First, a fixed MIC value of 1 mg/L was used to calculate AUC/MIC, as the causative pathogen was often unknown and repeated MIC determinations are not feasible in routine clinical practice. Second, vancomycin exposure was assessed in serum or plasma, which may not accurately reflect drug concentrations at the site of infection. In critically ill children with sepsis, impaired tissue penetration may result in subtherapeutic concentrations at the infection site and potential treatment failure, even when systemic exposure appears adequate. Third, only the study statistician and parents were blinded; treating clinicians were aware of the group allocation, which may have influenced dose titration in the standard-of-care arm during the study (learning effect). However, we expect such risk of bias to be low as we accounted in the sample size calculation for contamination from the intervention to the standard-of-care arm and vice versa. Fourth, follow-up data on hearing were not collected, limiting our ability to assess ototoxicity - a known, albeit rare, adverse effect of vancomycin. Finally, the study period was limited to 30 days, resulting in censored data on ward and hospital length of stay for a substantial proportion of NICU patients.

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Appendix 1: Summary of results for lay persons

1. Clinical trial identification

EU reference number: 2019-004538-40

Study protocol/CIP code: BC-5429

2. Name and contact details of the sponsor

Sponsor: Ghent University or Ghent University Hospital

Contact details sponsor: Principal Investigator: Prof. dr. Pieter De Cock, Tel 09/332 29 69

Funder: Federal Healthcare Knowledge Centre.

3. General information

Vancomycin is an antibiotic with a narrow therapeutic-toxic margin. This means that the minimum and maximum required target concentrations in the blood differ only slightly. Too low concentrations result in a reduced effect of the antibiotic. Higher concentrations often cause serious side effects, including renal toxicity. Adjusting the dose of vancomycin for the sick child is therefore a huge challenge.

Currently the dose of vancomycin for all patients is calculated at the start of therapy based on milligram per kilogram. The dose is then adjusted according to a too high or too low dose of the concentration of vancomycin measured in the blood. Despite this measurement, it is still a major challenge to achieve the required target concentration (quickly).

In this study, we investigated the added value of a user-friendly computer program that calculates the dose of vancomycin for critically ill children. We specifically investigated whether the use of a computer program resulted in a faster calculation of the target concentrations, less frequent and less serious side effects on the kidney, less stress for the patient, a faster recovery and a shorter stay in hospital.

This project is financed by the Belgian Health Care Knowledge Centre (KCE) and includes critically ill children between the age of 0 and 18 years admitted to neonatal and pediatric intensive care and paediatric haematology/oncology departments of 7 Belgian hospitals. This study was approved by the Committee for Medical Ethics of Ghent University Hospital following consultation with the ethical committees of each Belgian centre where the study was carried out.

4. Population of subjects

A total of 332 patients was included in this study.

Inclusion criteria

- age: 0-18 years
- admitted to ICU or PHO unit
- suspected or confirmed Gram positive infection
- planned to start on intravenous vancomycin treatment (
- informed consent signed by parents or legal representatives
- not previously enrolled in this trial

Exclusion criteria

- extracorporeal treatment at inclusion
- severe acute kidney injury at inclusion
- known chronic kidney disease
- patient death is deemed imminent and inevitable

Demographics_table: Summary of baseline demographics

label	Standard-of-care arm	Intervention arm
Postnatal age (in months) at randomization		
N	156	158
Mean (SD)	26.39 (50.014)	28.81 (52.532)
Median (Range)	0.84 (0.0; 215.6)	0.74 (0.1; 207.7)
IQ range	(0.35; 26.83)	(0.26; 32.06)
Postnatal age (in days) at randomization		
N	156	158
Mean (SD)	803.25 (1522.444)	876.96 (1599.098)
Median (Range)	25.50 (1.0; 6562.0)	22.50 (2.0; 6321.0)
IQ range	(10.50; 816.50)	(8.00; 976.00)
Weight (kg)		
N	156	158
Mean (SD)	10.04 (14.914)	10.23 (14.913)

Demographics_table: Summary of baseline demographics		
label	Standard-of-care arm	Intervention arm
Median (Range)	3.54 (0.6; 71.6)	3.09 (0.4; 62.0)
IQ range	(1.30; 12.25)	(1.22; 14.30)
Birth weight (kg)		
N	83	86
Mean (SD)	1.88 (1.166)	1.65 (0.992)
Median (Range)	1.35 (0.6; 4.4)	1.30 (0.4; 3.9)
IQ range	(0.89; 2.75)	(0.80; 2.34)
Height (cm)		
N	108	102
Mean (SD)	71.72 (41.004)	70.83 (44.042)
Median (Range)	51.50 (30.0; 180.0)	49.00 (28.5; 176.0)
IQ range	(41.00; 92.00)	(36.50; 101.00)
Gender, n(%)		
N	156	158
Female	63 (40.4%)	72 (45.6%)
Male	93 (59.6%)	86 (54.4%)

Note: SD: standard deviation

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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

13 patients experienced a severe but known side effect of vancomycin treatment, namely the vancomycin flushing syndrome (n=7 in standard-of-care arm ; n=6 in intervention arm).

3 patients developed a severe acute kidney injury during vancomycin treatment (n=1 in standard-of-care arm; n= 2 in intervention arm). 1 patient died. No significant differences were observed between intervention and control group.

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 concentrations, a lower cumulative dose and lower drug concentrations of vancomycin over the entire treatment course and was safe. There was a trend to (albeit not statistically significant) reduced nephrotoxicity and time to clinical cure. Sampling errors with trough sampling monitoring frequently occur. No differences were noted in length of ward unit and hospital stay. Based on these study results, we suggest for routine implementation in critically ill children with severe infection requiring longer treatment and other risk factors for nephrotoxicity or pre-existing kidney disease.