A multicentric, randomised, controlled clinical trial to study the impact of bedside model-informed precision dosing of vancomycin in critically ill children – BENEFICIAL trial

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Abstract

Background

Vancomycin is a commonly prescribed antibiotic to treat serious Gram-positive infections in children. The efficacy of vancomycin is known to be directly related to the pharmacokinetic/pharmacodynamic (PK/PD) index of the area under the concentration-time curve (AUC) divided by the minimal inhibitory concentration (MIC) of the pathogen. In most countries, steady state plasma concentrations are used as a surrogate parameter for this target AUC/MIC, but this practice has some drawbacks. Hence, AUC-based dosing using model-informed precision dosing (MIPD) tools has been proposed for increasing target attainment rate and reducing vancomycin-related nephrotoxicity. Solid scientific evidence for these claimed benefits is lacking in children. This randomized controlled trial aims to investigate the large-scale utility of MIPD dosing of vancomycin in critically ill children.

Methods

Participants from 14 neonatal intensive care, pediatric intensive care and pediatric haemo-oncology ward units from 7 hospitals are randomly allocated to the intervention or standard-of-care comparator group. In the intervention group, a MIPD dosing calculator is used for AUC-based dosing, in combination with extra sampling for therapeutic drug monitoring in the first hours of treatment, as compared to standard-of-care. An AUC24h between 400 to 600 is targeted, assuming an MIC of 1 mg/L. Patients in the comparator group receive standard-of-care dosing and monitoring according to institutional guidelines. The primary endpoint is the proportion of patients reaching the target AUC24h/MIC of 400–600 between 24 and 48 hours after start of vancomycin treatment. Secondary endpoints are the proportion of patients with (worsening) acute kidney injury during vancomycin treatment, the proportion of patients reaching target AUC24h/MIC of 400–600 between 48 and 72 hours after start of vancomycin treatment, time to clinical cure, ward unit length-of-stay, hospital length-of-stay and 30 day all-cause mortality.

Discussion

This trial will clarify the propagated benefits and provide new insights into how to optimally monitoring vancomycin treatment in critically ill children.

Trial registration

Trial Registration: Eudract number:2019-004538-40, registered: 2020-09-08

Administrative Information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

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Role of sponsor {5c}	Responsibilities of the sponsor are: • Central data collection and verification of reportable events. • Reporting safety information to the Trial Steering Committee (TSC) • Expedited reporting of SUSARs to the Competent Authority (FAMHP) and EC within required timelines • Notifying investigators and reporting of SUSARs within required timelines. • Preparing standard tables and other relevant information for the Development Safety Update Report (DSUR) in collaboration with the Chief Investigator (CI) and ensuring timely submission to the regular authorities and EC. • Submission of the annual progress reports, including safety summary and deviations

Introduction

Background and rationale {6a}

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 and healthcare associated sepsis.

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.[1] 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.[2] 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.[3,4]

Growth, development and critical illness (including cancer) are known to have a massive impact on antibiotic PK/PD and complicate optimal drug dosing.[5] To date, vancomycin is commonly initiated, on a mg per kg basis, according to institutional guidelines. Both intermittent dosing regimens and continuous infusions are used. After reaching steady-state conditions (i.e. after the third to fifth 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.[1] 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.[1] 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.[6,7]

The current dosing approach has a number of drawbacks. First, reported Cmin target attainment rates in critically ill children are abominable, with several days needed to reach target concentrations.[6,8–11] Delay in appropriate antibiotic therapy in patients with severe sepsis and septic shock leads to increased morbidity and mortality.[13,14] Growing evidence exists that subtherapeutic antibiotic dosing can lead to emergence of resistance of colonising bystander organisms.[15] 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.[16,17] 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.[17,18] Fourth, poor adherence to proper Cmin timing of sampling is common and may lead to erroneous dose adjustments, therapy failure and toxicity.[19]

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.[20]

For vancomycin, Bayesian AUC based dosing using model-informed precision dosing tools (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.[1,2,19] In critically ill neonates, MIPD guided starting doses increased early target attainment from 41 to 72% without any case of vancomycin-related toxicity.[21]

The overall objective of this project is to investigate the large-scale utility of MIPD of vancomycin at point-of-care in critically ill children. This evaluation includes a comparison with the more standard approach on clinical, patient-/clinician-oriented measures.

Objectives {7}

Primary objective

This study will test 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.

Secondary objectives

This study also aims to test the following secondary hypotheses:

1/ 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;

2/ 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;

3/ 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;

4/ 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;

5/ 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;

6/ 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;

Tertiary objectives

This study also aims to test the following tertiary hypotheses:

1/ 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;

2/ 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;

3/ 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;

4/ AUC/MIC based vancomycin dosing, using a model-informed precision dosing calculator reduces the number of dose adjustments to first target attainment (24h AUC/MIC between 400–600 in the interventional arm; target concentrations for intermittent and continuous dosing regimens according to institutional guidelines) during treatment, when compared to the use of standard-of-care dosing regimens with therapeutic drug monitoring;

5/ 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;

6/ 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;

Finally, we also aim to measure a trough sampling error rate in the comparator arm.

The collected data are available for continuous PK/PD model refinement if necessary.

Trial design {8}

This study is a prospective, multicentric, individually randomized controlled clinical trial in neonatal, pediatric intensive care (N/PICU) and pediatric hemo-oncology (PHO) ward units across Belgium. Patients are randomized to the standard-of-care comparator or intervention arm with an allocation ratio of 1:1.

Methods: Participants, interventions and outcomes

Study setting {9}

This trial is recruiting patients in 14 ward units at 7 Belgian hospitals. A list of study sites can be found on Clinicaltrials.gov. Identifier: NCT046666948

Eligibility criteria {10}

Inclusion criteria:

- age: 0–18 years
- admitted to ICU or PHO unit
- suspected or confirmed Gram positive infection
- planned to start on intravenous intermittent (INT) 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)
- informed consent signed by parents or legal representatives
- 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)*

Exclusion criteria

- extracorporeal treatment at inclusion (extracorporeal membrane oxygenation, dialysis, body cooling)
- neonatal or pediatric Risk Injury, Failure, Loss (RIFLE) criteria category failure at inclusion (Day 0)
- known chronic kidney disease as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) definition as: structural or functional abnormalities of the kidney regardless of glomerular

filtration rate (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)

- patient death is deemed imminent and inevitable

Who will take informed consent? {26a}

Written informed consent for all trial participants will be obtained, by discussing with the parents or legal guardians the nature, objectives and the possible adverse events associated with their participation in the study. A copy of the information sheet and the signed and dated consent form will be supplied to the parent or legal guardian providing written consent, as well as any other documentation discussed through the consent process. For participants 12 years or older, a separate information sheet and assent form will be provided. All documents will be available in Dutch, English, French, Turkish, Arabic. Maximum effort will be made to obtain written informed consent prior to inclusion.

Antibiotic therapy in critically ill children is usual a matter of clinical urgency and prior consent is not always possible from parents or legal representatives. A deferred consent approach is allowed in the case that parents or legal guardians are unavailable for following assessments/procedures: assessment of trial eligibility (screening), collection of baseline data and dose administration details on the first dose (comparator and interventional study arm), a priori MIPD starting dose estimation (interventional study arm) and implementation of the MIPD dosing regimen and blood sampling after the administration of the starting dose. In such case, this deferred consent procedure will be documented in the patient file and maximum effort will be undertaken by the clinical team to start an oral (by phone) consent procedure as soon as possible (max. time constraint for obtaining informed consent: 24h after inclusion). An oral consent is asked by the treating physician in the presence of impartial witness and is documented on the consent form. At this stage, the parents or legal guardians will be given the option to consent for continuing the study or to withdraw from the study.

Written informed consent forms should, in any case, be signed by the parents or legal representatives at the first visit on site. At this stage, the parents or legal guardians will again be given the option to consent for continuing the study or to withdraw. If the parents or legal guardians do not wish to continue the study for a patient included in the study via a deferred consent procedure, permission to use the already collected study data is asked. If parents or legal guardians give their consent to use the already collected data, this will be documented on the informed consent form. No data will be entered in the eCRF study database before written informed consent is obtained.

The Principal Investigator at each participating site will retain the overall responsibility for the informed consent of the parents/legal guardians of participants at their site. Informed consent will be obtained by the principal investigator, the ward unit investigator or the attending physician at the departments involved. All principal, ward unit investigators and physicians at the participating sites will be duly authorised, trained and competent to participate according to the protocol approved by the central and

local ethical committees (EC), the competent authorities (CA), principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. The names of the principal and ward unit investigators/physicians to which delegation of consent has been granted, will be recorded with their signatures in the Investigator Site File (ISF).

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Additional consent (optional) from parents is asked for: collection and storage of the national insurance number, sharing personal data with the Federal Healthcare Knowledge Centre (funder) and other European research institutions for public health for supplementary research, use of the participant data to optimize the PK/PD model for vancomycin.

Interventions

Explanation for the choice of comparators {6b}

The overall objective of the study is to evaluate the clinical utility of MIPD in critically ill children. Therefore, a proper comparator is the current standard-of-care practice. In this comparator arm, the vancomycin starting dose are prescribed according to the institutional dosing regimen and dose adjustment nomograms. Dosing regimens are prescribed by the attending physician. Maintenance doses are based on the patient's weight and estimated kidney function and subsequently therapeutic drug monitoring of measured vancomycin concentrations.

Therapeutic drug monitoring of vancomycin is standard-of-care practice and in accordance to the marketing authorisation. Following standard-of-care principles currently apply:

- a trough sample is taken just before the second, third, fourth or fifth dose for intermittent dosing regimens and around 24 hours [timeframe: 12h-48h] after the start of loading dose for continuous dosing regimens (timing dependent on the institutional or local ward unit protocol) .
- if sub-or supratherapeutic concentrations are measured, the dosing regimen is changed and repeat samples are taken.
- repeat trough samples are taken just before the second, third, fourth or fifth new dose for intermittent dosing regimens and around 24 hours [timeframe: 12h-48h] after start infusion for continuous infusion dosing regimens until therapeutic concentrations are reached (timing dependent on the local ward unit protocol)
- whenever therapeutic concentrations are reached, a repeat sample is usually drawn every 3 to 7 day interval, or sooner (e.g. in case of changing renal function, suspected therapy failure, or major surgery) (dependent on the local ward unit protocol)
- More frequent sampling to ensure efficacious treatment, avoid toxicity to rule out sampling errors is performed at the discretion of the attending physician

Intervention description {11a}

In this study, the intervention combines the use of a MIPD dosing calculator for starting and follow-up dose calculation, in combination with extra sampling for therapeutic drug monitoring in the first hours of treatment, as compared to standard-of-care.(Fig. 1) The MIPD dose calculator for estimation of the starting dose and follow-up doses based on AUC24h assessment is the InsightRX Nova web application.[22] A target AUC24h/MIC is defined between 400 to 600, assuming an MIC of 1 mg/L. In case of severe infections, typically the higher end of the target range is used.

The vancomycin PK model by Colin et al. is used within this MIPD software package.[23] It is a meta-analysis PK model, pooling PK data from premature neonates to elderly, intensive care unit (ICU) and obese patients (n = 2554 patients). In this PK model, current weight, age and serum creatinine are covariates for dose forecasting, eventually in combination with individual TDM concentrations.(14) This model is chosen since it was one of the best predictive PK models in a retrospective fit-for-purpose validation using vancomycin PK data from two university hospitals.[24] The InsightRX software has a number of real-time checks and warnings implemented, e.g. warnings for duplicate doses or TDM measurements or warnings for out of range weight, serum creatinine or vancomycin blood concentration.

The above sampling standard-of-care principles are also applicable to the interventional arm. In the interventional arm, a deviation from the standard-of-care sampling time point (i.e. intermittent dosing: just before the intermittent dose; continuous dosing : standard-of-care timepoint depending on local ward unit protocol) is allowed within an interval of 3h before the standard-of-care sampling timepoint, in case this sample could be combined with a scheduled biochemical sample or another sampling timepoint is more convenient for the patient and/or nurse.

Extra samples are taken for patients in the interventional study arm. For intermittent dosing regimens, minimum 1 and maximum (but ideally) 2 extra samples are taken after administration of the starting dose, to allow for early and accurate AUC-based dose adjustment on subsequent doses. For continuous infusions, minimum 1 and maximum (but ideally) 2 extra samples are taken after administration of the loading dose, to allow for early and accurate AUC-based dose adjustment on subsequent supplementary loading doses and continuous infusion rates.

Calculated starting doses could deviate maximum 50% of institutional dosing guidelines. A maximum upward dose adjustment of 33% in total daily dose is allowed for both intermittent and continuous dosing regimens. Intermittent starting dosing intervals are restricted to 4 hourly, 6-hourly, 8-hourly, 12-hourly, 18 hourly and 24 hourly dosing intervals, which are similar to standard-of-care dosing intervals. A dose suggestion for continuous infusion regimens should always include a loading dose, administered over a 1 to 2 hour interval, immediately followed by a continuous infusion. Maximum allowed MIPD loading dose are 30 mg per kg

It is allowed to round the MIPD suggested dose to the nearest manageable dose for administration with a maximum allowed deviation of 10% of the minimum or maximum suggested dose to attain a 24h AUC between 400–600.

Dosing regimens are suggested by MIPD software end-users and implemented by the attending physician. Choice for an intermittent or loading dose/continuous infusion dosing regimen is at the discretion of the attending physician/site preference. MIPD software end-users and attending physician are allowed to be the same person.

Criteria for discontinuing or modifying allocated interventions {11b}

The patient and/or parent/legal guardian of the patient may withdraw consent at any time during the study. The patient will receive the standard-of-care treatment from moment of withdrawal of consent.

Reasons may include:

- Patient requiring extracorporeal treatment (renal replacement therapy, extracorporeal membrane oxygenation, body cooling) (mandatory to permanently stop the use of the MIPD dosing calculator)
- Patient developing acute kidney injury RIFLE class failure (mandatory to permanently stop the use of the MIPD dosing calculator)
- Treating physician’s decision due to other safety reasons than kidney injury
- Patient moved to another ward unit not participating in the study
- Patient transferred to a ward unit in a hospital not participating in the study
- Patient discharged from hospital to home
- Withdrawal of informed consent
- Other reason

Notes: If a patient is readmitted to one of the participating ward units, the study assigned dosing method needs to be followed within the 30 day study period if still receiving or re-started on vancomycin. In case the patient is in the interventional arm, all details on dosing, serum creatinine and weight from the patient’s medical file should be updated in the dosing software before making dose predictions for vancomycin.

A reason for premature discontinuation of vancomycin administration may be the treating physician’s decision due to safety reasons, e.g. kidney injury. If vancomycin is permanently stopped within a treatment episode according to standard-of-care treatment decisions (e.g. de-escalation of antibiotic treatment, switch of antibiotic since vancomycin is not an appropriate treatment choice for the identified pathogen of the infection),this is not considered a premature discontinuation. If vancomycin dosing is temporarily held (e.g. physician prefers to plan re-dosing of vancomycin after another TDM concentration becomes available), this is not considered as a premature discontinuation.

Strategies to improve adherence to interventions {11c}

All members of the study team are duly trained on GCP, the study protocol and their distinct responsibilities in this trial, e.g. patient screening, obtaining informed consent and MIPD dose calculations. Procedures, worksheets and step-by-step plans were developed as guidance throughout the 20-day study period. Eligible end-users per centre will be identified and registered per ward unit before start of patient recruitment. A software training session(s) by the investigator team will precede the registration as end-user and study collaborator. An on-call service for back-up support with dose calculation is planned in the initial period of recruitment and is provided by the team of the chief investigator. Feedback meetings for study coordinators, principal and ward unit investigators are organized on a regular basis.

Relevant concomitant care permitted or prohibited during the trial {11d}

N/a: when a participant requires extracorporeal treatment (dialysis, extracorporeal membrane oxygenation, body cooling), the trial intervention discontinues and the patient receives standard-of-care treatment. This is already been described in ‘Criteria for discontinuing or modifying allocated interventions’.

Provisions for post-trial care {30}

The sponsor provided an insurance, even without fault, to cover its liability as the requesting party in case of harm caused to the patient by participation in the study.

Outcomes {12}

Primary endpoint

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

Relevance:

The primary endpoint is therefore chosen, in line with European Medicines Agency recommendations on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95) and its addendum (EMA/CHMP/187859/2017), in which pediatric clinical data requirements were stipulated.[25,26] In summary, extrapolation of efficacy of the antibacterial agent across age ranges is considered possible for the majority of infectious diseases because treatment is aimed at the infectious organism and not the host per se. Consequently, differences in exposure (i.e. AUC) are to be considered as primary endpoint for optimizing vancomycin dosing in children.

Rationale of target 24h AUC range definition:

Successful treatment of methicillin-resistant Staphylococcus aureus (MRSA) and Enterococcal bacteremia is strongly correlated with a steady-state 24h AUC/MIC ratio of at least 400. Since MIC measurements are not standard-of-care in most institutions, sterile cultures are common in children and MIC measurements are prone to twofold errors, a MIC of 1 mg/L was chosen. Moreover, for pathogen isolates with an MIC of 2 mg/L (measured using the reference technique of broth macrodilution), it is presumed that the optimal AUC/MIC cannot be achieved safely, and an alternative agent is strongly encouraged.[1]

The 24h AUC threshold for toxicity is defined as 600 mg*h/L, and was derived from the recently revised consensus guidelines on therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections from the Society of Health-System Pharmacists, the Infectious Diseases, Society of America, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases.[1] It is in agreement with the published range of AUC thresholds for vancomycin nephrotoxicity (550–800 mg*h/L) in adults and children.[2]

Secondary endpoints

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

Relevance: Vancomycin is a known nephrotoxin. In adults, it has been demonstrated that AUC based dosing of vancomycin is associated with reduced incidence of AKI, when compared to standard-dosing of vancomycin and therapeutic drug monitoring. [1,2]

AKI classes are defined according to the neonatal (n) and pediatric (p) RIFLE criteria as shown in Table 1.[27–29]

The nRIFLE are used for children < 1 month of age (30 days); pRIFLE criteria are used in children ≥ 1 month of age (31 days). For eGFR, the modified bedside Schwartz formula is used : 0.413 * (height/serum creatinine) (in ml/min/1.73m2).

AKI is categorized in children 1 month and older if at least one of the criteria on serum creatinine, eGFR or urine output is attained. When the three criteria result in different stages of AKI, the higher stage is chosen. If height could not accurately be collected, only the fold rise criterion for creatinine is to be used (and not the eGFR decrease criterion).

Table 1
neonatal and pediatric Risk Injury, Failure, Loss AKI criteria

p RIFLE			n RIFLE	
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

Legend: ESRD, end-stage renal disease; n or p RIFLE: neonatal or pediatric Risk Injury, Failure, Loss AKI criteria; eGFR, estimated glomerular filtration rate; fold rise is calculated whenever the most recent value of serum creatinine is higher than the baseline value using the formula Y/X with X the original value and Y the most recent value

- Baseline creatinine is defined as the most recent serum creatinine (measured within a maximum of 120h before planned start vancomycin).
- Proportion of patients reaching target 24hAUC (400–600) between [48 to 72] h after start treatment
- Time to clinical cure
  Time to clinical cure is defined as the time interval (in days) from start to completion of the vancomycin vancomycin treatment, without recommencement of antibiotics for the same indication within 48h after stop. De-escalation or escalation of vancomycin for the same indication is considered as part of the antibiotic treatment course.
  Timeframe:date of randomization – stop date treatment

- Ward unit length-of-stay
  Timeframe:date of randomisation– date of discharge to another ward unit
- Hospital length-of-stay
  Timeframe: date of randomisation – date of hospital discharge
- 30 day mortality
  Time frame: date of randomization – 30 days after randomisation

Tertiary endpoints

• Number of (additional) blood samples to first target attainment during vancomycin treatment

An additional blood sample is defined as a sample for vancomycin TDM taken at another timepoint of routine biochemical monitoring samples. This endpoint will also count the (additional) sample(s) after the starting dose in the interventional arm.

Timeframe: start date treatment – stop date treatment

• Cumulative number of (additional) blood samples during treatment in patients with reported clinical cure

Timeframe: start date treatment – end date of treatment

• Proportion of patients reaching target 24hAUC (400–600) between [72 to 96] h after start treatment

• Number of dose adjustments to first target attainment

Target range definition:

- Interventional arm: 24h AUC : 400–600 mg*h/L
- Comparator arm: target concentration range for intermittent (trough concentration) and continuous dosing regimens according to institutional guidelines

Timeframe: start date treatment – stop date treatment

• Cumulative vancomycin dose during vancomycin treatment

Timeframe: start date treatment – stop date treatment + 48h to allow for vancomycin to be eliminated

• Cumulative AUC during vancomycin treatment

Timeframe: start date treatment – stop date treatment

• Number of trough sampling time errors during vancomycin treatment

Definition

trough concentrations are defined as samples obtained 23.5 to 24h, 17.5 to 18h, 11.5 to 12 h, 7.5 to 8h, 5.5 to 6h, 3.5 to 4h after the previous dose for respectively 24 hourly, 18 hourly, 12hourly, 8hourly, 6hourly and 4hourly dosing regimens.

• Proportion of patients with (worsening) AKI during vancomycin treatment using KDIGO criteria (all children)

AKI classes are defined according to the neonatal (n) and pediatric (p) Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The nKDIGO are used for children < 1 month of age (30 days); pKDIGO criteria are used in children ≥ 1 month of age (31 days).

• PK/PD model refinement

Relevance: meta-analysis of PK/PD data is useful for further update of available PK/PD models.

Participant timeline {13}

Table 1
Schedule of enrolment, interventions and trial assessments

	Screening	Baseline	Day 0 to end of vancomycin treatment	Day 0 to D30
Eligibility assessment	X			
Informed consent	X			
Patient characteristics		X		
Pathogen characteristics				X
Vancomycin dosing			X	
Concomitant nephrotoxic and vasopressor medication			X	
Concomitant antibiotic use				X
Blood sampling			X	
Weight			X	
Urine output			X	
Serum creatinin			X	
n or pRIFLE category	X		X	
Time to clinical cure				X
Ward unit stay				X
Hospital length of stay				X
Mortality				X
Safety assessments			X	X
Compliance	X	X	X	X
End of trial assessments				X

Legend: n or p RIFLE: neonatal or pediatric Risk Injury, Failure, Loss AKI criteria

Sample size {14}

The outcome on which this sample size calculation is based upon are (i) the proportion of patients reaching target 24hAUC/MIC between 24 and 48h after start vancomycin treatment and (ii) the proportion of patients with (worsening) AKI during vancomycin treatment.

Proportion of patients reaching target 24hAUC/MIC between 24 and 48h after start vancomycin treatment

Sample size calculation for the logistic regression on the primary outcome was performed in SAS version 9.4 using the power procedure.

The sample size calculation was based on the assumed proportions of patients reaching the therapeutic target AUC/MIC (400–600) between [24 to 48] h after start of treatment are 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.[30] When assuming 20% contamination from intervention to control, and 5% contamination from control to intervention, a dilution of the effect size is expected from 70% versus 50%, corresponding to an odds ratio of 2.33, to 69% (AUC/MIC based vancomycin dosing) versus 54% (standard-of-care), corresponding to an odds ratio of 1.90.

When it became apparent that this sample size 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 (contamination of control to intervention arm: 2.3%; contamination of intervention to control arm: 4%. Based on this information, we could lower the contamination rates with 25% (contamination rate of control to intervention arm from 5–3.75% and contamination rate of intervention to control arm from 20–15%), taking into account uncertainty around observed contamination rates and the potential learning effect, without impacting power of the study.

When assuming 15% contamination from intervention to control, and 3.75% contamination from control to intervention, a dilution of the effect size is expected from 70% versus 50%, corresponding to an odds ratio of 2.33, to 69.25% (AUC/MIC based vancomycin dosing) versus 53% (standard-of-care), corresponding to an odds ratio of 2.0.

In total 281 participants are required to achieve 80% power at a significance level of 5%, to detect an OR of 2 (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 will be applied.

Assuming a drop-out rate of 15%, a total sample size (both groups) of 332 patients is required. No interim analysis is planned for this study.

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.[31] Furthermore 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.[32,33] We expect a large proportion of our patients in the comparator having trough concentrations > 15 mcg/L and AUC > 800.

When assuming 15% contamination from intervention to control, and 3.75% contamination from control to intervention the effect size is expected to dilute from 4% versus 16%, corresponding to an odds ratio of 0.219, to 4.45% (AUC/MIC based vancomycin dosing) versus 14.2% (standard-of-care), corresponding to an odds ratio of 0.281.

In total 281 participants yields 84% power at a significance level of 5%, to detect an OR of 0.28 (b=-1.27) when the proportion in the control group is 14.2% (odds = 0.166, intercept= -1.80.) using logistic regression. An assignment ratio of 1 will be applied.

Recruitment {15}

During the start-up phase of the study, the principal investigator and ward unit investigator(s) will identify the most efficient workflow and personnel for eligibility screening per ward unit. Personnel will be team members from the clinical and/or study nurse team, designated by the principal investigator. The consulted resource for inclusion and exclusion criteria check is the patient's medical file, in which only the required information with regard to eligibility (in-and exclusion criteria) will be sought. The attending physician of the participating ward unit, principal or ward unit investigator will sign off for eligibility.

If deemed appropriate by the principal investigator, email reminders with inclusion-and exclusion criteria of the study will be periodically sent from the trial management group to the principal and ward unit investigators and/or other study collaborators. A nurse information sheet in Dutch and French will be prepared to inform nurses at participating ward units about the study objectives of the study, to ask for actively reminding attending physicians to check trial eligibility whenever a vancomycin treatment is imminent, and to explain the relative importance of registration of dosing and sampling details. Whenever possible, this information sheet will also be communicated through banners on the ward unit computers. A similar information sheet in Dutch and French will be developed and distributed to laboratory physicians, if deemed appropriate by the principal investigator.

Parents or legal guardians from potentially eligible patients will receive both an oral explanation of the study as well as a Participant Information Sheet, providing a plain language text in Dutch, French,, English, Turkish, or Arabic with a Participant Consent Form. Whenever possible, team members from the clinical team will inform parents or legal guardians on beforehand about the study whenever there is a high chance of their child being eligible (e.g. bone marrow transplant patient on the hemo-oncology unit with multiple catheters).

Eligible patients can enter the study only after written informed consent is obtained or after deferred consent is documented. No data will be collected from patients whose parents (legal representatives)

did not consent for participation in this study, except for the patients in which a deferred consent approach is applicable. A screening log will be kept per ward unit.

Assignment of interventions: allocation

Sequence generation {16a}

Patients will be randomly allocated to the interventional arm or standard-of-care arm at inclusion. The study is a parallel-group RCT with a 1:1 allocation ratio. Randomisation will be stratified by ward unit and hence by ward unit type (NICU, PICU, PHO). Random permuted blocks will be created with a computer random number generator with variable sizes to avoid that the treatment allocation can be predicted. The stratified randomisation will be performed using the randomization module of Research Electronic Data Capture (REDCap).

Concealment mechanism {16b}

Before a patient can be randomised, the baseline characteristics (at least the stratification factor ward unit) of the patient need to be entered in REDCap. At each participating site, the ward unit investigator, clinical research coordinator or a delegated person will do the randomization by clicking the “randomize” button of the REDCap randomisation module. REDCap will automatically document the allocation and store all the records and the randomisations. If REDCap would not be available (due to f.e. internet problems, login problems, scheduled update procedures, …), a back-up procedure with envelopes based on a randomization list generated by the statistician will be used.

Implementation {16c}

The allocation sequence is generated in SAS version 9.4 by the statistician and imported in REDCap.

Enrolment and allocation of participants is performed by a trained person guided by the previously developed

REDCap randomization tool.

Assignment of interventions: Blinding

Who will be blinded {17a}

Participants or legal representatives are blinded for the allocation to the intervention or standard-of-care arm until the end of the study. The biostatisticians are blinded until after the data analysis.

Procedure for unblinding if needed {17b}

N/a: no circumstances in which unblinding is permissible are determined.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Vancomycin treatment

Vancomycin dosing details are recorded by the attending nurse on an (electronic) vancomycin administration and sampling registration sheet. If accidently one or more doses are not recorded, maximum effort will be undertaken for retrieval of the information (e.g. ask the attending nurse who administered the drug); if not retrievable the planned dose and start and stop timing are registered.

If a patient is still prescribed vancomycin following discharge from the participating ward unit to a ward unit not participating in the study or home, maximum effort to continue collecting dosing details is made.

If a patient is restarted on vancomycin after being discharged from the participating ward unit to a ward unit not participating in the study, maximum effort to continue collecting dosing details is made.

Blood sampling for vancomycin concentration measurement

Accurate vancomycin sampling times are recorded by the attending nurse (when administering the drug) on the (electronic) administration and sampling registration form.

Weight

Standard-of-care assessment – at least once a week for patients younger than 1 month (30 days) and at least once every two weeks for patient 1 month (31 days) and older.

Serum creatinine

Serum creatinine measurements for patients ≥ 1 month are collected on a regular basis as per standard-of-care to allow AKI category assessment in both study arms using serum creatinine and eGFR during vancomycin treatment. If the patient is transferred to a non-intensive care setting while still on vancomycin treatment (e.g. general pediatric ward), at least once weekly serum creatinine measurements are collected.

When serum creatinine or urine output criteria result in different stages of AKI, the higher stage is chosen.

Urine output

If measured, data on urine output is used, to allow AKI category assessment in both study arms during vancomycin treatment. If not measured as standard-of-care, the other AKI criteria based on serum creatinine or eGFR are used.

Concomittantly administered nephrotoxic and vasopressor/inotropic comedication

Concomittantly administered nephrotoxic and vasopressor comedication during vancomycin treatment are recorded

Concomittant antibiotic use

Concomittant systemic antibiotic use are recorded. Antibiotic compounds that are not used as antibiotic treatment but in another indication (e.g. erythromycin as gastroprokinetic agent) are not recorded.

Safety assessments

Following SAEs occuring until 48h after last vancomycine study administration (maximum D30 + 48h in case vancomycin is administered on day 30 after randomisation), is reported in both study arms:

- neonatal or pediatric RIFLE class category failure
- vancomycin flushing syndrome
- Other significant safety issues (including death) at the discretion of the investigator thought to be at least possibly related to the vancomyin dose calculation should also be collected until D30 or D30 + 48h in case vancomycin is administered on day 30 after randomization

These safety events are assessed on a continuous basis. In case of withdrawal of consent, safety events are recorded until the last study related vancomycin administration + 48h. These safety events are recorded in the patient file (standard-of-care) and eCRF.

Date of ward unit discharge and reason

If patients are moved to different ward units within the hospital, these dates are recorded.

Date of hospital discharge and reason

Isolated pathogen(s), site of infection and reported sensitivity (sensitive, intermediate, resistant)

All cause 30 day mortality and reason

Vital status is recorded, including date and cause of death.

Protocol compliance

Protocol deviations are recorded from randomization until end of trial in a protocol deviation log, either provided by the sponsor or in the eCRF. If applicable, the paper protocol deviation log will be kept in the investigator site file (ISF) at each site.

Data reported in the eCRF are used to calculate other data points. Following data is not collected in source documents:

- Time to clinical cure – calculated using the date of randomisation and date of clinical cure
- The total number of (additional) blood samples taken to first target attainment– calculated using the date of randomisation and number of (additional) vancomycin measurements between start and reported time of target attainment
- Cumulative number of blood samples during therapy in patients with reported clinical cure – counting the number of (additional) vancomycin measurements in patients with reported clinical cure
- Ward unit length-of-stay – calculated using date of admission to ward unit and date of ward unit discharge
- Hospital length-of-stay – calculated using date of admission and date of hospital discharge
- AKI classification according to KDIGO criteria with collected data on serum creatinin and dialysis
- Number of trough sampling time errors: evaluation from recorded vancomycin dosing and TDM details in case of intermittent dosing regimen in patients in the comparator arm

AUC estimation

Estimation during vancomycin treatment – interventional arm

Starting (1st) dose calculation

An a priori dose calculation targeting a 24h AUC of 400 to 600 between 24 and 48h after start treatment is performed using current weight, postmenstrual age and measured serum creatinine.

2nd dose calculation

24h AUC is 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 target a 24h AUC of 400 to 600 between 24 to 48h after dose adjustment.

Posthoc estimation in comparator and interventional arm

24h AUC between 24h and 48h (primary endpoint), 48h and 72h and 72h and 96h (secondary endpoints) is estimated posthoc for patients in the comparator arm using all the available vancomycin blood measurements per patient. Cumulative AUC is estimated from time 0 till 48h after stop treatment. This estimation is performed, after the patient end of trial assessment, using all available measurements per patient.

End of trial assessments

End of trial assessments is collected on Day 30. All efforts are made to capture the following end of trial assessments for included patients:

- D30 mortality
- Safety assessment* (instead of D30 : D30 + 48h in case of patients still receiving vancomycin treatment on D30)
- Whether or not patient's (still) receiving vancomycin*
- Reason and date end of trial.

Reason for end of trial and date of end of trial are registered for each patient. Possible reasons include:

- Protocol completion (Day 30),
- Patient Died
- Patient's withdrawal of informed consent

*unless the parents or legal guardians explicitly withdraw consent for this data collection.

Plans to promote participant retention and complete follow-up {18b}

The study team consisting of investigators, software end-users and study coordinators conduct rigorous patient follow-up and monitor protocol compliance. If a patient is withdrawn from the study or the study intervention is prematurely discontinued, the patient will receive standard-of-care treatment and maximum effort to continue collecting data until the end of trial is made.

Regular on-site and remote monitoring will be performed by the sponsor's clinical trial centre according to GCP and all applicable national and international laws and guidelines. Prior to commencing recruitment, the monitor will meet the study team by a trial initiation visit to review trial specific procedures such as the protocol, safety reporting procedures, ICF procedures, ISF content, PI's responsibilities, e-CRF completion guidelines and study timelines. Following written standard operating procedures (SOP), the monitors will verify on-site whether the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Data recorded in the eCRF will be evaluated for accuracy in relation to source documents. The monitor will provide a monitoring report after each visit for the sponsor and the investigator. The

frequency, extent and nature of monitoring will be defined in more detail in a monitoring plan. Depending on the quality of the data, additional monitoring visits may be necessary according to the sponsor's discretion. After last patient last visit per site, a close-out visit will be planned at each site to ensure all open action items are addressed and the study can be closed at the centre.

Protocol deviations are recorded from randomization until end of trial in a protocol deviation log in the eCRF. If applicable, a proposed plan of action for resolution will also be documented on the protocol deviation log.

Critical issues that significantly affect patient safety, data integrity and/or study conduct should be reported to the CI and sponsor immediately. The CI and sponsor will subsequently communicate and discuss this with the EC.

Early termination of the study may be necessary in case of major non-compliance or premature trial discontinuation. If standard clinical care at the centre differs from standard clinical care described in the protocol, this will not be considered as protocol deviations as long as the standard care of the local hospital is followed.

Data management {19}

Data will be collected using REDCap. REDCap is provided and maintained by Vanderbilt University; a license for use was granted to the clinical trial centre of the sponsor (Health, Innovation and Research Institute). REDCap is a web-based system. The data is accessed through a web browser directly on the secure REDCap server. The server is hosted within the UZ Gent campus and meets hospital level security and back-up requirements.

Privacy and data integrity between the user's browser and the server is provided by mandatory use of Transport Layer Security, and a server certificate issued by the Trans-European Research and Education Networking Association. All study sites will have access to REDCap. Site access is controlled with IP restriction. The study site staff is responsible for data entry in REDCap. Login in REDCap is password controlled. Each user will receive a personal login name and password and will have a specific role which has predefined restrictions on what is allowed in REDCap. Futhermore, users will only be able to see data of participants of their own site. Any activity in the software is traced and transparent via the audit trail and log files. A data management plan will be developed to document the data management process in more detail.

Data validation rules will be added to maximize immediate validation of the data at entry. In addition, complex edit checks will be programmed by the data manager to check for inconsistencies within data. Any inconsistencies will be queried to the responsible persons at site. Query management and reconciliation will be carried out in REDCap.This will be documented in a data validation plan.

Data analysis will be performed by a statistician.

Patients that are included in the study, will be assigned a unique study number upon their randomisation in REDCap (the randomisation database). On all documents submitted to the coordinating centre, sponsor or CI, patients will only be identified by their study number. The subject identification list will be safeguarded by the site. The name and any other directly identifying details will not be included in the study database.

The unique study number, generated in the REDCap randomisation database will also be used to identify patients in the web-based CE labelled MIPD platform. Site access for the MIPD platform is controlled with password control. The study site staff is responsible for data entry in the MIPD platform. Each user will receive a personal login name and password and will have restricted access to data of individual patients of the ward unit and/or centre. Any activity in the software is traced and transparent via the audit trail and log files). A contract with the software company will include GDPR compliance requirements.

The unique study number will also be used for data collection in the eCRF, the study database in REDCap. No data will be entered in the study database before written informed consent is obtained.

If parents or legal guardians withdraw from the study after written consent is obtained, all data collected until the time of withdrawal will be kept in the study database. The details of withdrawal should be clearly documented in the patient's medical records and in the eCRF.

Confidentiality {27}

All investigators and trial site staff must comply with the requirements of the of the Belgian and European Privacy legislation (https://www.dataprotectionauthority.be/legislation-and-standards) on the protection of privacy in relation to the processing of personal data, with regards to the collection, storage, processing and disclosure of personal information.The data access in the MIPD platform is via a web browser directly on a secure server. The server meets General Data Protection Regulation (GDPR) security and back-up requirements. This same study number is to be used in the MIPD software. Access to the data is limited to the minimum number of individuals necessary for central back-up on dosing advice, quality control, audit and analysis. The data will be retained for least 20 years after end of trial. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirement(s). A contract with the software company will include GDPR compliance requirements.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Blood samples for vancomycin concentration or serum creatinine measurement are drawn as per standard of care for both intervention as comparator study groups. One or two supplemental samples are drawn in patients randomized to the intervention arm for vancomycin concentration measurement.

Statistical methods for primary and secondary outcomes {20a}

Primary outcome analysis

A logistic regression for binary data will be applied, reaching the target AUC/MIC between 24h and48h after start vancomycin as categorical predictor variable and randomization group (interventional versus the standard-of-care arm) as categorical predictor for interest. Because of the limited number of subjects per ward unit it is not approporiate to include a term for ward unit in the model. The factor type of ward (NICU, PICU, PHO) contains only three categories and will added as a covariate in the model.[34]

The primary analysis will be the intention-to-treat analysis, preferably performed because it avoids bias associated with non-random loss of participants. All participants will be included in the analysis in the groups to which they were originally assigned, regardless of what subsequently occurred. Imputation techniques will to be used for outcome data that are missing.[35] The intervention effect will be expressed by using the odds ratio (OR), together with the estimated proportion per group.

Secondary outcome analysis

- *Proportion of patients with (worsening) acute kidney injury during ward unit stay*:
- *Proportion of patients reaching target 24h AUC/MIC between [48–72]h after start vancomycin treatment*
- *30 day all cause mortality*

Statistical methods will be similar to those described in ‘Primary outcome analysis’. We will express the intervention effect by using the odds ratio (OR), together with the estimated proportion per group.

- *Time to clinical cure*

Statistical methods will be similar to those described in ‘Primary outcome analysis’. A Cox proportional hazards model with randomization group (interventional arm versus standard-of-care arm) and ward type (NICU, PICU, PHO) as categorical predictor variables will be used to compare the hazard.

- *Ward unit length of stay*
- *Hospital length of stay*

Negative binomial regression with randomization group (interventional arm versus standard-of-care arm) and ward type (NICU, PICU, PHO) as categorical predictor variables will be applied. We will express the intervention effect as a percentage increase or reduction of the number of days in the unit or hospital.

Interim analyses {21b}

N/A

Methods for additional analyses (e.g. subgroup analyses) {20b}

A subgroup analysis will be performed for the stratification factor type of ward unit. Statistical methods will besimilar to those described in ‘Primary outcome analysis’. Medical discipline will be added as a categorical predictor variable. An interaction term between medical discipline and randomization group will be included in the model. A second subgroup analysis will be applied on the patients with confirmed infection at baseline. Statistical methods will be the same as to those described in ‘Primary outcome analysis’, but applied only on the subgroup with confirmed infection. A third subgroup analysis will be performed for the type of dosing regimen (continuous versus intermittent). Type of dosing regimen and ward type will be added as a categorical predictor variables. An interaction term between type of ward unit and randomization group (interventional arm versus standard-of-care arm) will be included in the model.

Since subjects that are part of a twin will be 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 will be applied to account for the presence of twins.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

The primary analysis will be the intention-to-treat analysis, preferably performed because it avoids bias associated with non-random loss of participants. All participants will be included in the analysis in the groups to which they were originally assigned, regardless of what subsequently occurred. Multivariate imputation by fully conditional specification will be used to apply multiple imputation of missing data.

The predictors used for the imputation model will include (but are not limited to): randomisation group, ward unit, type of consent, indication for vancomycin treatment, admission diagnosis, mechanical ventilation, nephrotoxic medication, a priori estimation of the AUC (PK model-based value based on serum creatinine, age and weight, duration of treatment and vancomycin dose). Primary analysis will be based on the multiple imputed data. As a sensitivity analysis, the results will be compared with the analysis on the protocol-compliant sample.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Additional consent (optional) from parents is asked for: sharing personal data with the Federal Healthcare Knowledge Centre and other European research institutions for public health for supplementary research, use of the participant data to optimize the PK/PD model for vancomyin. Access to Study Data by KCE is fully defined in the contract between KCE and the Sponsor and the research

agreement template is publicly available on the KCE website. Link: https://kce.fgov.be/en/resources-for-investigators

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Principal Investigator (PI):

- Checking for reportable events during study period intervention and follow-up.
- Using medical judgement in assigning seriousness, causality and expectedness using the Reference Safety Information approved for the trial.
- Ensuring that all reportable events (including SUSARs) are recorded and reported to the Sponsor, chief medical advisor and chief investigator and within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that they are chased with Sponsor, Chief Investigator and Chief Medical Advisor if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that reportable events are recorded and reported in line with the requirements of the protocol.
- Coordinating role during study recruitment if more ward units per participating centre
- Checking research protocol compliance

Ward unit investigator

- Checking for reportable events during study period intervention and follow-up, in close collaboration with principal investigator.
- Checking protocol compliance
- Ensuring that reportable events are recorded and reported in line with the requirements of the protocol.
- Coordinating role during study recruitment within the ward unit, in close collaboration with the principal investigator

Chief Medical Advisor (CMA)

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs/SARs where it has not been possible to obtain local medical assessment.
- Immediate review of all SUSARs.

- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
- Preparing of the annual progress reports, including safety summary and deviations
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR). (If applicable)
- Subcoordinating role during study recruitment for recruitment sites in the French speaking region

Chief Investigator (CI)

- Trial coordination, together with project manager
- Responsible for training of end-users on software
- Back-up for MIPD dosing software support, together with project manager
- Registration of end-users, in collaboration with the project manager
- Immediate review of all SUSARs, in close interaction with the chief medical advisor.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
- Preparing of the annual progress report, including safety summary and deviations in close collaboration with the project manager and chief medical advisor
- Final reporting to Funder

Sponsor:

- Central data collection and verification of reportable events in e-CRF
- Reporting safety information to the Trial Steering Committee (TSC)
- Expedited reporting of SUSARs to the Competent Authority (FAMHP) and EC within required timelines.
- Notifying Investigators of SUSARs that occur within the trial.
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
- Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the FAMHP and REC.
- Submission of the annual progress reports, including safety summary and deviations

Trial Steering Committee (TSC):

- Follow-up on patient recruitment
- In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data

The trial management group is chaired by the chief investigator and consists of : the trial manager, data manager, biostatistician, clinical trial center representative of the sponsor and study monitors. This group minimally meets every two weeks.The TSC is chaired by the chief investigator and is composed of: the trial manager, clinical trial centre representative of the sponsor, chief medical advisor, biostatistician, a patient representative, representatives of the participating study sites, precision dosing, pharmacometrics and laboratory medicine specialists and a representative of funder. The TSC meets twice a year.

Composition of the data monitoring committee, its role and reporting structure {21a}

N/a: There is no separate data monitoring committee because minimal risk is associated with the study. MIPD of vancomycin is already within marketing authorization. Safety data are periodically reviewed by the trial management and TSC. SAEs are ad hoc reviewed by the medical advisor of the study.

Adverse event reporting and harms {22}

The following events are considered reportable events:

Significant safety issues (including death) at the discretion of the investigator thought to be at least possibly related to the vancomyin dosing method until D32 in both study arms

Following SAEs until 48h after last study vancomycin administration (maximum D30 + 48h in case vancomycin is administered during the whole study period since randomisation) in both study arms:

- neonatal or pediatric RIFLE class category failure
- vancomycin flushing syndrome

All reportable events will be recorded in the patient file and in the e-CRF between first dose administration of vancomycin and 48h after the last administration of vancomycin and must be sent by email to the sponsor, the chief medical advisor and the chief investigator within 24 hours of the research staff becoming aware of the event.

Assessment of seriousness, causality and expectedness for trials involving IMPs must be made by the PI or another authorised physician. If an authorised physician from the reporting site is unavailable, initial reports without causality and expectedness assessment should be sent to the sponsor, the chief medical advisor and the chief investigator by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

Any change of condition or other follow-up information should be sent to the sponsor, the chief medical advisor and the chief investigator as soon as it is available or at least within 24 hours of the information

becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

SUSARs will be subject to expedited reporting to the Federal agency for medicines and health products (FAMHP).

If any urgent safety measures are taken, the principal investigator or chief investigator will inform the sponsor immediately and in any event no later than 3 days from the date the measures are taken. The sponsor gives written notice to the FAMHP and the central EC of the measures taken and the circumstances giving rise to those measures. This reporting will be done in accordance with the European Medicines Agency (EMA) guidelines.

The CI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the competent authority (FAMHP in Belgium), EC and sponsor. This DSUR will include all SAE's. The report will be submitted 1 year (+ maximum 60 days) after the Development International Birth Date, and will subsequently be submitted each year until the study is declared to have ended.

Frequency and plans for auditing trial conduct {23}

The trial conduct is evaluated by the monitors. One sponsor audit by the funder is planned.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Amendments should not be implemented without prior review and documented approval/ favorable opinion form the Ethics Committee (EC) and the Federal Agency for Medicines and Health Products (FAMPH) except when necessary to eliminate an immediate hazard to trial subjects or when the change involves only logistical or administrative aspects of the trial.

Dissemination plans {31a}

After registration the outline of the study protocol and the contact details will be publicly available at ClinicalTrials.gov. We will publish the protocol of the study as an open-access paper in a peer-reviewed medical journal after approval of the final version of the protocol and the amendments by all parties involved. After completion of the study a final CSR will be prepared based on a locked analysis data set and a table with the final study analyses performed by the statistician as outlined in the Statistical Analysis Plan (SAP). All trial investigators will be given access to the final CSR. Dissemination of the study findings will be in accordance with the EU General Data Protection Regulation (GDPR) of 14 April 2016 and the Belgian Law of 22 August 2002 on patients' rights.

After completion of the study all parents or legal guardians and children older than 12 will be notified about study results by a specifically designed newsletter.

Dissemination to the broader public will be performed through the websites of the participating centres. In preparing the manuscript of the research findings the CONSORT guidelines and the checklist (http:/www.consort-statement.org/) will be followed to ensure that the CSR meets the standards required for submission to high quality peer reviewed journals. The data are owned by the Sponsor and shall be free to publish or publicly present the results of the Study. The study will be published on behalf of the 'Beneficial study investigators'. Prior to submission of any publication, the sponsor will provide co-authors a 20-day period for allowing review and constructive commenting of a manuscript, including review for any designated Confidential Information.

Details of the published study report will be made available to all parties involved after acceptance of the manuscript. We aim to have the CSR submitted for publication in a high-quality peer-reviewed journal within 18 months after completion of the study.

All case report forms and other data (including without limitation, written, printed, graphic, video and audio material, and information contained in any computer database or computer readable form) created or developed during the course of the Study (the "Data") shall be the property of the sponsor.

The results of the study will also be published on clinicaltrials.gov. Open access publication, scope of the journal and editorial facilitators to disseminate the study findings will be considered by the consortium for the final selection of the targeted journal. Any funding or logistical support will be acknowledged within the journal in the appropriate section of the manuscript. Review and publication rights will be respected according to the journal policy. The trial protocol and the statistical code for generating the results will be submitted as separate appendices to the full study report files and will be publicly available at the journal website after acceptance for publication.

Discussion

N/a: no other issues need to be covered.

Trial status

Protocol version 5.0

Date of start recruitment: 28/12/2020

Approximate date of trial completion: 24/02/2024

Abbreviations

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
AKI	Acute Kidney Injury
AUC	area under the concentration-time curve
CA	Competent Authority
CI	Chief Investigator
Cmin	Trough concentration
CRF	Case Report Form
CRO	Contract Research Organisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	Ethics Committee
eGFR	Estimated Glomerular Filtration Rate
EMEA	European Medicines Agency
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FAMPH	Federal Agency for Medicines and Health Products
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HAS	Healthcare-associated sepsis
ICU	Intensive Care Unit
ICF	Informed Consent Form

ABBREVIATION	DEFINITION
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMA-AIM	Belgian Intermutualistic Agency
IMP	Investigational Medicinal Product
INT	Intermittent
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials
KCE	Belgian Healthcare Knowledge Centre
KDIGO	Kidney Disease: Improving Global Outcomes
MA	Marketing Authorisation
MIC	Minimal Inhibitory Concentration
MIPD	model-informed precision dosing
MS	Member State
NICU	Neonatal Intensive Care Unit
NIMP	Non-Investigational Medicinal Product
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
PHO	Pediatric Hematology and Oncology
PI	Principal Investigator
PICU	Pediatric Intensive Care Unit
PIS	Participant Information Sheet
POC	Point-of-care
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
RCT	Randomised Control Trial
REDCap	Research Electronic Data Capture

ABBREVIATION	DEFINITION
RIFLE	Risk Injury, Failure, Loss (RIFLE) criteria
RIZIV-INAMI	National Institute of Sickness and Disability Insurance
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOC	Standard of care
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAR	Target Attainment Rates
TDM	Therapeutic Drug Monitoring
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
VAN	Vancomycin

Declarations

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Collaboration group: BENEFICIAL

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Beneficial Trial consortium:

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Authors' contributions {31b}

PADC: chief investigator with overall trial responsibilities.

RC: lead methodologist responsible for sample size calculation, statistical analysis plan and data analysis

AA: project manager responsible for EC file submission, submission to competent authorities, and project management and study conduct

HDP: project manager responsible for project management and submission to competent authorities

LV: data manager responsible for writing data management plan and data cleaning

PDP: sub-investigator responsible for protocol review

DVDL: chief medical advisor mainly responsible for safety assessment/reporting in collaboration with the chief medical advisor

All authors read and approved the final manuscript

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Belgian Health Care Knowledge Centre (KCE) Trials is a funding programme for non-commercial clinical trials financed by the Belgian public authorities. These clinical trials address issues that are usually neglected by industry despite their high societal importance.

KCE is responsible for the selection and funding of the clinical trials, but does not conduct them itself.

Hospitals, universities or non-commercial research institution take on the sponsorship and coordination responsibilities.

More info: https://kce.fgov.be/en/kce-trials

Although KCE provides funding for the trial, KCE shall under no circumstances be considered as sponsor of the Study or assume any responsibilities or liabilities in connection therewith, and sponsor or co-sponsor shall make no representations whatsoever in this respect.

Availability of data and materials {29}

Only the chief investigator, project managers, data managers, statisticians and study monitors will have access to the final trial dataset. Access to Study Data by KCE is fully defined in the contract between KCE and the Sponsor and the research agreement template is publicly available on the KCE website. Link: https://kce.fgov.be/en/resources-for-investigators

Ethics approval and consent to participate {24}

Approved by the Ethics Committee UZ Ghent: BC-05429 and FAMPH. Written informed consent to participate will be obtained from all participants or their legal representatives.

Consent for publication {32}

N/a: no details, images or videos relating to an individual person are included in the study protocol. A model informed consent is provided.

Competing interests {28}

The authors declare that they have no competing interests.

Authors' information (optional)

N/a

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Figures

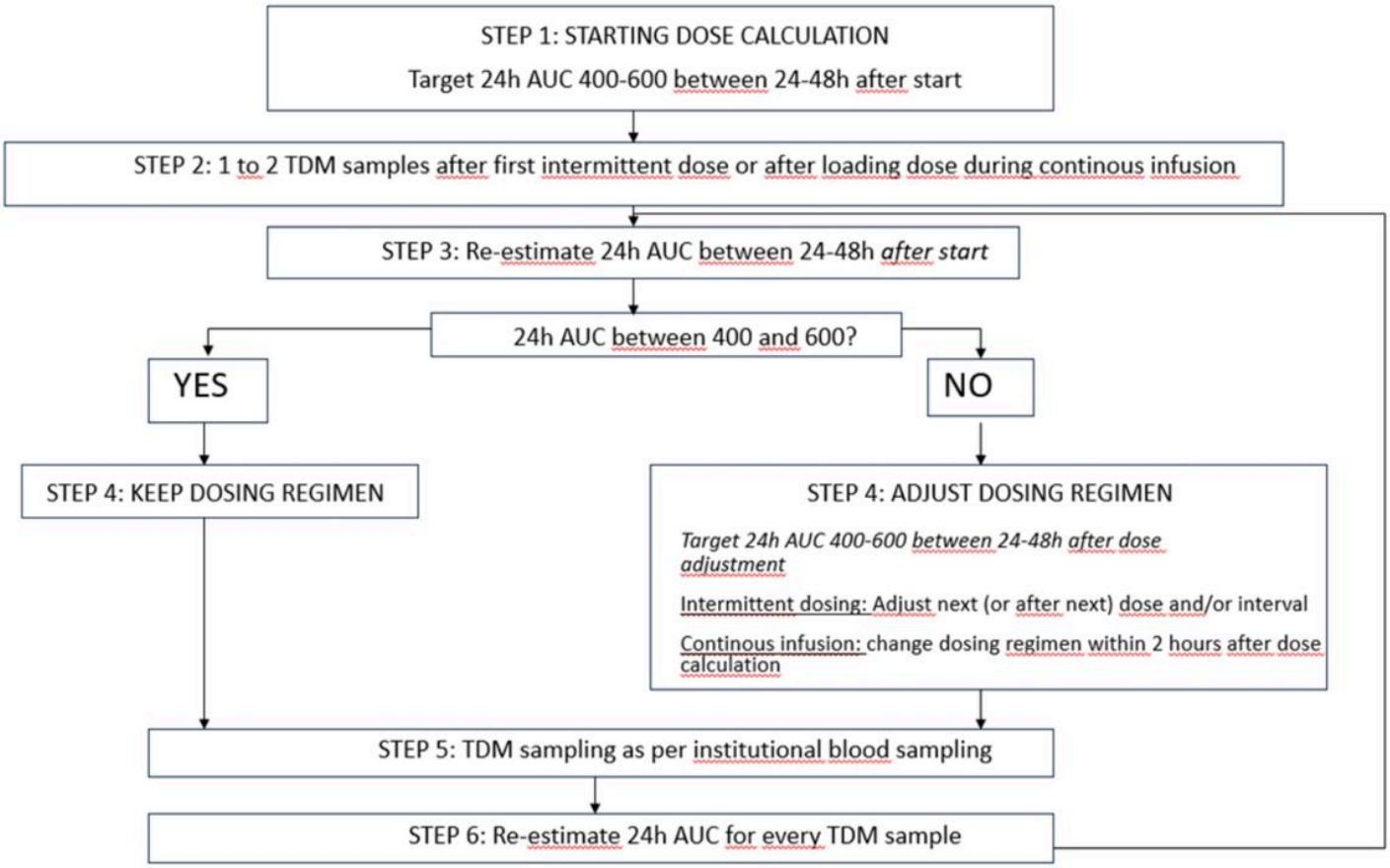

Figure 1

Dose calculation and dose adjustment in the intervention arm

Legend: AUC, Area-Under-the-Concentration-time curve; TDM, Therapeutic Drug Monitoring

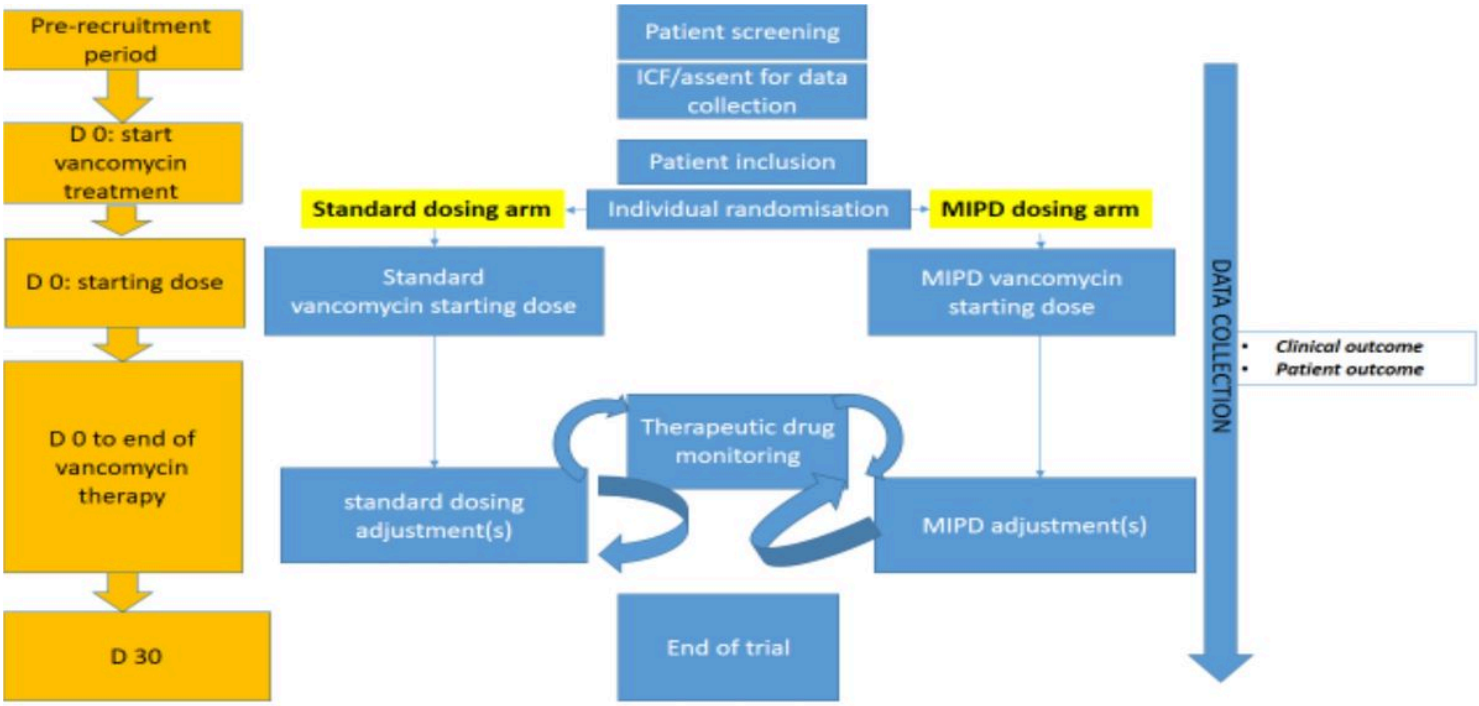

Figure 2

Study flowchart

Legend: ICF, informed consent ; MIPD, model-informed precision dosing

Supplementary Files

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