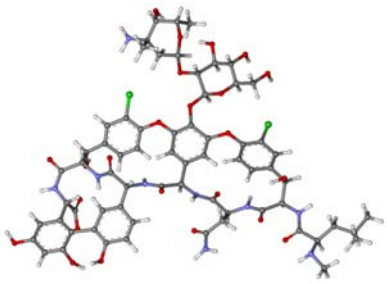
Université catholique de Louvain
Louvain Drug Research Institute

Centre hospitalo-universitaire
de Mont-Godinne

Continuous Infusion of Vancomycin in non-ICU Patients: Why, How and What's the Benefit?



Els Ampe, Pharm.

Thesis submitted in view to obtain the degree of
Doctor in Biomedical and Pharmaceutical Sciences
(orientation "Clinical Pharmacy")

Co-promotors:
Professor Youri Glupczynski
Professor Paul M. Tulkens

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Foreword and Acknowledgments

When I finished my Hospital Pharmacy education at the *Katholieke Universiteit Leuven* (KU-Leuven), clinical pharmacy was only beginning its developments in Belgium. However, I got the unique opportunity to join the *Université catholique de Louvain* (UCL) to be one of the first Belgian pharmacist making a PhD thesis in Infectious Disease based on a Clinical Pharmacy approach.

I had the opportunity to work with the Infectious Disease Management Team of the Cliniques Universitaires de Mont-Godinne (now CHU Mont-Godinne) where I learned a lot about Infectious Diseases during the tours in the Microbiology Laboratory and in different wards. Soon, we were able to determine what my research project would focus on. It was a difficult but also challenging task for a pharmacist because many aspects of antibiotic therapy were already well covered by the infectious disease physicians.

Pharmacists interested in Infectious Diseases often specialize in subareas by focusing on pharmacovigilance, pharmaco-economics or clinical pharmacology and pharmacokinetics. The latter seemed a good starting point as (i) there were perceived but not fully analyzed issues about the quality of therapeutic drug monitoring (TDM) of antibiotics at that time, and (ii) the Cellular and Molecular Pharmacology group to which I was member through my nomination as "Assistant universitaire" was deeply involved in basic research on pharmacology, pharmacodynamics, and pharmacokinetics of antibiotics.

So, the basic starting point of my thesis was now set, and I started to analyze the performance of TDM of vancomycin and amikacin, which would eventually lead me to what is now the topic of this Thesis.

I want to emphasize that it would have been impossible to accomplish this Thesis project without the help and support of many people.

I want to address special thanks to:

- Mon promoteur, le Professeur Paul M. Tulkens pour m'avoir donné la possibilité d'entamer un des premiers projets de recherche dans ce domaine. Merci, Mr. Tulkens, d'avoir cru en ce projet, de m'avoir fait confiance et d'avoir investi tant d'énergie à le rendre réalisable. Je vous remercie également pour l'encadrement scientifique tout au long de ce projet. J'ai vraiment été encouragée par votre enthousiasme éternel et votre passion pour la science, plus particulièrement pour la pharmacologie et la pharmacie clinique.
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I want also to thank the external members of the jury for having accepted to participate to the evaluation of Thesis: Professor Hartmut Derendorf, PhD. (Distinguished Professor of Pharmaceutics at the University of Florida) and Professor Frédérique Jacobs (Chef de service de maladies Infectieuses de l'Hôpital Erasme de l'Université Libre de Bruxelles). Your well known and very appreciated activities in the field of anti-infective pharmacology are the best guarantee of the quality of my work and I look forward hearing from you how it could be improved.

J'ai eu la chance de travailler avec de nombreuses autres personnes venant d'horizons divers et d'avoir bénéficié de leur compétence et leur aide dans la collecte et l'analyse des données. Je remercie particulièrement Vincent Lorant pour son aide dans l'analyse des données qualitatives. Les collègues actifs en Pharmacie clinique et en Pharmacologie des antibiotiques m'ont aussi aidé à valider les documents utilisés. J'adresse des remerciements particuliers à Anne Spinewine, Jean-Marc Feron, Catherine Bouland, Stéphane Carryn, Séverine Noirhomme, Karine Berthoin, Laurence Galanti, Patricia Gillet, Catherine Berhin, Martial Vergauwen, Cédric Baude et Joseph Mathieu.
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General Introduction

In light of the increasing resistance of micro-organisms towards antibiotics and the limited number of new antimicrobial agents in clinical development, the optimal use of available drugs is more then ever important [1]. New insights have emerged from the study of the pharmacokinetics/pharmacodynamics (PK/PD) of antibiotics [2;3], several of which led to successful implementation in new clinical practices, such as the once daily dosing of aminoglycosides [4-7] or dose adaptation based on MIC for fluoroquinolones [8;9]). Infectious disease management teams in which medical doctors and clinical pharmacists collaborate have delivered important work in this context (see [7;10] typical examples).

We focused our attention on vancomycin. This antibiotic was originally isolated by Eli-Lilly from a soil sample coming from Borneo and containing the actinomycete *Nocardia Orientalis* [11]. The molecule was found to have in vitro activity against *Staphylococci* [12] and animal studies showed a low level of toxicity [13]. The drug was eventually approved and used in clinical practice in 1958 for the treatment of Gram-positive infections. Methicillin, licensed in 1960, resulted in the decline of vancomycin use but the appearance of methicillin resistance in the 1980s renewed interest in vancomycin [14;15]. Today, vancomycin is at the forefront of clinical use for the treatment of infections caused by Gram-positive organisms resistant to β-lactams [16;17], although its restricted use has been largely advocated [18;19].

The chemical structure of vancomycin (Figure 1.1.) was confirmed in 1978 (CAS registry number 1404-93-9, molecular formula C66H75C12N9O24; molecular weight 1449 g/mol). The main properties of vancomycin related to its chemistry and mode of action have been summarized in 4 key review articles [15;20-22] from which we have extracted the following information.

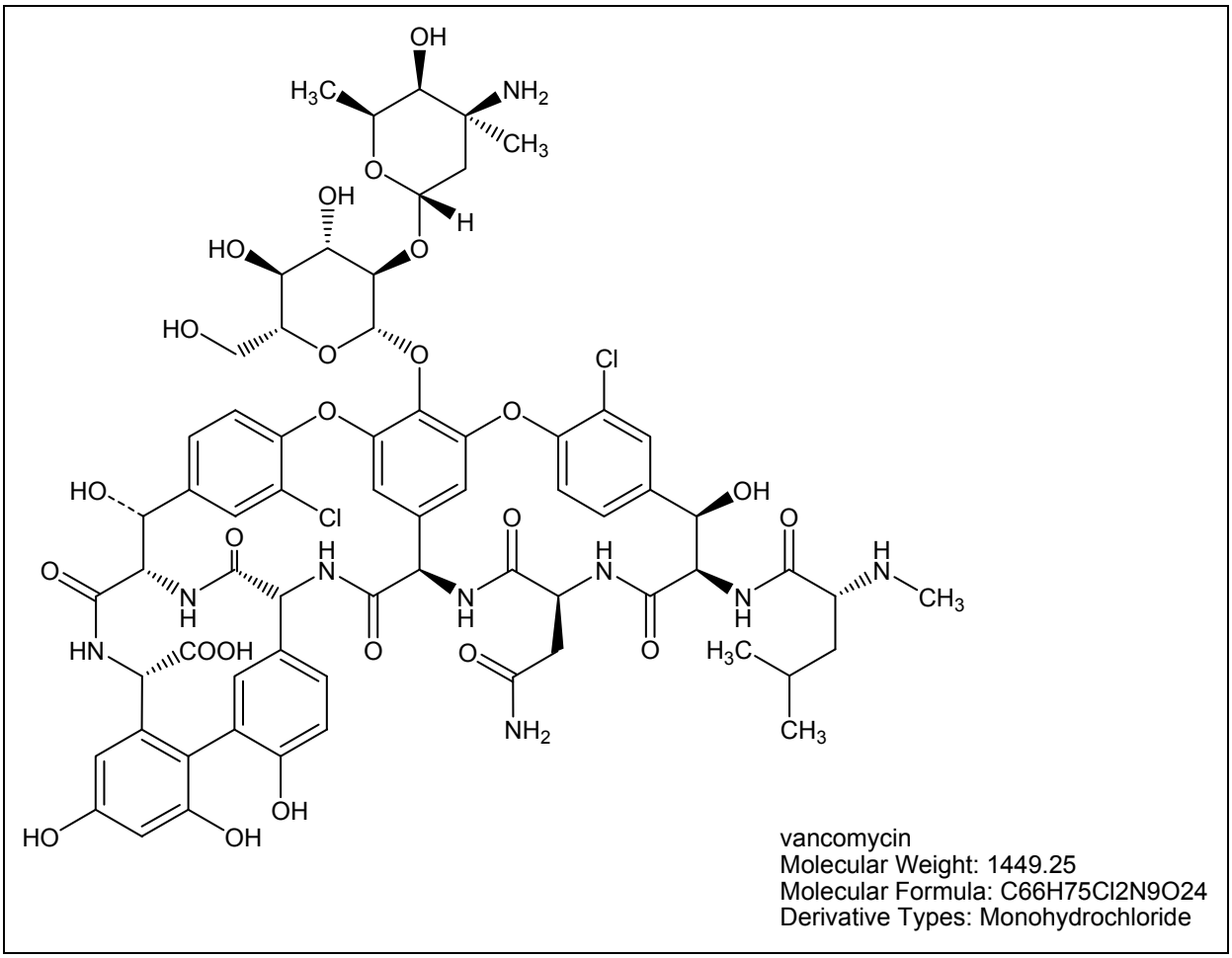

Figure 1: structural formula of vancomycin

The molecule consists of a heptapeptide core (in which two peptides bear a chloride) substituted with vancosamine and glucose sugars. The heptapeptide core is responsible for the pharmacological activity of the molecule, whereas the sugars are thought to modulate its hydrophylicity and its propensity to form dimers. As a result of its large size, vancomycin is unable to cross the outer membrane of Gram-negative bacteria explaining inactivity against these organisms. Inability to penetrate inside bacteria limits vancomycin activity to extracellular targets. Vancomycin inhibits the late stage of cell wall peptidoglycan synthesis by binding to the D-Ala-D-Ala termini of the pentapeptide ending precursors localized at the outer surface of the cytoplasmatic membrane. It forms a high affinity complex with the D-Ala-D-Ala by forming hydrogen bonds with the heptapeptide core. The strength of this bond is enhanced by vancomycin dimerization. The steric hindrance around the pentapeptide termini blocks the reticulation of peptidoglycan by inhibiting the activity of transglycolsylases responsible for attaching the new disaccharide-pentapeptide subunit to the nascent peptidoglycan and of transpeptidases catalysing the formation of interpeptide bridges.

Vancomycin shows a volume of distribution (V_d) of about 0.7 L/kg, an half-live about 6-12 h, about 50 % protein binding, and a moderate post antibiotic effect. Because of lack of intestinal resorption, vancomycin is exclusively administered by the intravenous route for systemic infections.

The most pertinent PK/PD index predicting vancomycin efficacy is the ratio between the 24 h Area under the serum concentration curve (AUC_{24h}) and the MIC of the offending organism [2], with a value of 350-400 for severe lung infections caused by *Staphylococcus aureus* [23].

Vancomycin is commercialized as a hydrochloride salt and is most soluble at pH 3 to 5. Solubility and stability decreases at increasing pH. Reconstitution of commercially available vancomycin is made in water with further dilution in Glucose 5% or saline up to maximally recommended concentrations up to 10 mg/L.

Since its introduction in clinical practice, vancomycin has been subject of extensive debate [24]. Initial concerns rose for reasons of renal toxicity which seemed to be caused to some extent by impurities in the first commercial preparations leading to the nickname ‘Mississippi mud’ [25]. Renal toxicity greatly improved after marketing more pure preparations. In the meantime monitoring of blood levels for reason of toxicity had become routine clinical practice [26].

The other important part of the debate was about concerns of efficacy in deep seated infections with high inocula due to its slow killing rate [2] associated with inter-individual differences in pharmacokinetics [27] and limited tissue penetration [28-30]. The raising MICs of Gram-positive organisms for vancomycin (commonly referred to as "MIC creep" [31;32]) has only further fuelled this debate and several publications have questioned whether vancomycin remains a viable treatment option today [33-37].

Despite all these limitations, no clinical studies have proven global and clear superiority for alternative agents and vancomycin still remains the drug of choice for the majority of infections caused by methicillin resistant Gram-positive infections [38;39].

Measurement of serum vancomycin concentrations by therapeutic drug monitoring is widely recommended in routine practice as it is supposed to allow for dose readjustment on an individual patient level in order to optimize efficacy and avoid toxicity [40;41].

Extensive pharmacokinetic studies in a variety of patient populations have been conducted [42-48]. Commercial drug assays have allowed clinicians to target serum vancomycin concentrations in routine practice. There is some controversy that has resulted from conflicting evidence regarding the use of serum vancomycin concentrations to predict and prevent drug induced toxicity and as a measure of effectiveness in treating infections [49]. Further, data derived from more recent studies appear to suggest that vancomycin has little potential for nephrotoxicity or ototoxicity when used at conventional dosages unless it is used concomitantly with known nephrotoxic drugs or at very high dosages [50]. Several studies did not find a clear correlation between vancomycin levels and toxicity.

The use of a nomogram is an alternative method for dosage adjustments, with the original one and still widely used proposed by Moellering *et al*. [51]. Several others have been proposed but not fully clinically validated and often point to too low trough levels (10–15 mg/l), which, as we shall see, is not consistent with current recommendations.

Recent North American guidelines recommend conventional twice daily dosing (BID) for vancomycin with through levels around 15-20 mg/L [17;40] because of recent pharmacokinetic insights about the risk of subtherapeutic doses in face of less susceptible organisms. This practice, however, has some important limitations. Firstly, higher trough levels have been associated with significantly higher rates of nephrotoxicity [52-54] and it is therefore important to detect them. Secondly, the omission of peak levels withdraws information about the exact AUC obtained, although, as stated above, it is AUC_{24h}/MIC that governs the overall activity of the drug.

BID was the common practice in our institution but with therapeutic monitoring of both peak and through levels to meet the criticisms raised against "trough level only" determinations. The following recommendations were in place: standard doses of 1g every 12 h (to be modulated according to the renal function and TDM results); target peak and trough levels of 30-40 mg/L and 5-10 mg/L respectively.

Based on its PK/PD index, continuous infusion (CI) of vancomycin should be equally effective compared to its BID schedule. The AUC_{24h} of an intravenously administered drug depends, indeed, only on the ratio between the total drug daily dose and drug creatinine clearance, irrespective of is schedule of administration.

Actually, CI of vancomycin is more and more applied in Europe with recent reports showing implementation in all Belgian institutions having answered to a recent survey (about 30 % of respondents), and mostly in the ICU setting [55]. As discussed in this Thesis, CI of vancomycin has been shown to be at least clinically equivalent and probably less nephrotoxic than BID, especially if considering the need of high dosage. Moreover, it offers practical advantages for nursing as it reduces time spent for drug administration and sampling and makes these activities more easy manageable as they can be scheduled together with other routine activities. It allows clinicians to get reliable information about serum levels in individual patients and to make a reliable estimation of the AUC. Together with information about the MIC of the offending organism this allows to tailor treatment at an individual patient level.

When we began our work, several reports point out to major quality issues concerning the routine practice of TDM [37;56], and there were indications that this could be the case in our Institution. A reliable system allowing correct dose adaptation was, therefore, considered mandatory.

In this Thesis, we used a combined qualitative and quantitative approach.

Quantitative methods are well known and widely used in the medical context and will, therefore, not be further introduced here.

Qualitative methods may be not so well known although they are increasingly applied in various disciplines. Qualitative research adds to quantitative methods by going beyond numbers and aiming at gathering an in-depth understanding of human behavior and the reasons that govern such behavior [57-59]. The qualitative method investigates the why and how of decision making, not just what, where and when. Hence, smaller but focused samples are more often needed than large samples. We applied a grounded theory method (GT; [60]) which is a systematic methodology involving the discovery of theory through the analysis of data. Grounded theory method is a research method which operates almost in a reverse fashion. Rather than beginning with a hypothesis, the first step is data collection, through a variety of methods. From the data collected, the key points are marked with a series of codes, which are extracted from the text. The codes are grouped into similar concepts in order to make them more workable. From these concepts, categories are formed, which are the basis for the creation of a theory, or a reverse engineered hypothesis. This contradicts the traditional model of research, where the researcher chooses a theoretical framework, and only then applies this model to the phenomenon to be studied [61;62].

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Administration of β-lactams and vancomycin by continuous infusion: rationale, clinical evidence, choice of molecules, and practical and economical considerations

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Abbreviations:

AUC: Area Under Curve.

AUIC: Area Under the Inhibitory activity-time Curve.

CI: Continuous Infusion.

CSF: Cerebrospinal Fluid.

II: Intermittent Infusion.

ICU: Intensive Care Unit.

MIC: Minimum Inhibitory Concentration.

MRSA: Methicillin-resistant Staphylococcus aureus.

Contents

Abstract

Continuous infusion (CI) is gaining popularity for β-lactams and vancomycin. Pharmacokinetic/pharmacodynamic considerations show that this mode of administration could be more rational than conventional discrete administrations (twice- or thrice-a-day) as these antibiotics are primarily time-dependent under their actual conditions of use and if considering organisms with MICs within the limits of the EUCAST breakpoints. For vancomycin, the activity of which is primarily dependent upon the AUC/MIC ratio, discrete administration or CI should yield similar activity. Yet, CI offers several advantages in terms of nursing and monitoring. The present review examines the pharmacological basics of CI and critically asses the problems related to drug stability (for β-lactams) and compatibility with other drugs administered by the same intravenous line. We then review the available biological and clinical literature concerning CI of β-lactams and vancomycin, and provide practical recommendations for actual used in the clinical setting. Our conclusion is that CI of β-lactams and of vancomycin is an efficient way to use these antibiotics that could be implemented widely in clinical practice if paying due attention to stability issues (for β-lactams [thus, excluding carbapenems for which only extended infusion [3-4h] seems acceptable]) and compatibility issues (for both β-lactams and vancomycin).

Introduction

The ever-increasing levels of resistance of the main bacterial pathogens combined with the difficulties in discovering and bringing to regulatory approval new antibiotics have urged the need to optimize the use of available antimicrobial agents. In this context, a re-appraisal of the conventional modes of administration, many of which were developed and approved at a time when such optimization seemed quite a futile exercise, becomes critical. Research on pharmacokinetics and pharmacodynamics (PK/PD) of antibiotics has indeed shown clearly that several modes of administration or dosages could be suboptimal, leading to insufficient activity, selection of less susceptible isolates, while not necessarily protecting against undesired toxicity. Typical examples include (i) aminoglycosides, for which a shift from dividing the daily dose in multiple administrations to once-daily dosing is now common practice [1], (ii) fluoroquinolones, for which a reappraisal of dosages based on PK/PD considerations and more realistic breakpoints [2] has been useful to maintain activity in difficult-to-treat patients, and (iii) β-lactams, for which application of PK/PD principles has led to the development of continuous and extended infusion regimens [3;4].

The present review focuses on the administration of β-lactams and vancomycin by continuous infusion (CI). This has already been the subject of many reviews, and practical applications are growing in number and popularity. Our aim has, therefore been, to define the conditions in which CI of these two classes of antibiotics can be advantageous and safe, compared to other modes of administration, and to propose guidelines for its implementation in clinical practice. Our review is based on a systematic analysis of published literature of last past 40 years considering the rational for continuous or extended infusion of β-lactams and vancomycin, its feasibility in terms of drug stability and compatibility with other medications commonly used in hospitalized patients, and the actual clinical experience. For these purposes, literature search of PubMed (biological and clinical studies) and SciFinder (chemical investigations) was performed to cover original

publications and reviews over the 1970 to 2013 period with search vocabulary including "continuous infusion", "β-lactams", "vancomycin", "stability", and corresponding to both clinical trials and laboratory investigations for studies on drug stability and compatibility. The search was supplemented by reviewing the references cited in all key papers.

The concept of continuous infusion

CI of antimicrobial agents has been studied since 1950. Penicillin was the first antibiotic studied using this method of administration in dogs [5]. Investigators noted that penicillin was most effective when the serum concentrations at the site of infection remained above those necessary to kill the bacteria. In order to achieve maximal efficacy, penicillin had, therefore, to be administered by CI or at 2-4 h intervals. More detailed PK/PD studies showed that the effectiveness of β-lactams tends to become maximal once their that concentrations exceeds by about 4-fold the MIC [6-9], making large peaks unnecessary. Coupled with the observation that β-lactams kill more slowly than aminoglycosides or fluoroquinolones, these studies explain why most investigators refer to these antibiotics as "time-dependent", creating a clear rationale for their use by CI [3;10-13]. Pharmacologically-speaking, it may, however, seem odd to dismiss the importance of the concentration/MIC ratio for β-lactams. Actually, every antibiotic, including β-lactams, displays a concentration-dependent activity pattern when explored in *in vitro* models over a wide range of concentrations (typically from 0.01 to 100-fold the MIC ([14]). However, the results of such investigations need to be examined in the context of the serum concentrations that are achieved *in vivo* (for systemic infections at least). This is illustrated in Figure 1, where one sees a concentration above 4-fold above the MIC of a susceptible organism is easily achieved with any clinically-used β-lactam for a large proportion of the dosing interval, providing a maximal effect with respect to concentration and leaving time to

become the major pharmacokinetic/pharmacodynamic (PK/PD) index to consider when examining the *in vivo* response.[1]

Vancomycin PK/PD index for efficacy has been the subject of longer debates, since this molecule was first reported to be primarily time- or even C_{max}-dependent [15] before being clearly recognized as being primarily being AUC_{24h}/MIC-dependent in animal studies [16]. The confusion stemmed from the fact that vancomycin has a considerably longer half-life than most β-lactams, making it difficult to design animal experiments distinguishing between the time during which the concentration remains above a defined concentration and the AUC. As such, the mode of administration (continuous or discontinuous) of vancomycin should, therefore, be unimportant, as long as the daily dosage (which determines the AUC_{24h}) remains sufficient. Nevertheless, the possibility of administering vancomycin by CI has attracted much attention because of its ease and of expected better penetration and activity in target tissues. Thus, the first aanimal study examining the treatment of meningitis with continuous infusion published in 1980 showed an increase in extravascular concentrations and of efficacy compared to short infusions [17;18].

Based on the principles discussed so far, many other antimicrobials showing either a time- or AUC_{24h}/MIC-dependent pattern could benefit from administration by CI. Yet, few drugs besides β-lactams and vancomycin have been studied in this context. Conversely, there are several antibiotics that should not benefit from CI for different reasons. CI will, for example not be of much benefit for antimicrobials with prolonged half-life as their serum concentration profiles will not be markedly changed by it. Some other antibiotics, such as fluoroquinolones, require a large C_{max}/MIC ratio to minimize the risk of selecting subpopulations with reduced susceptibility [19] and should, therefore, not be

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[1] This may no be true for organism showing elevated MICs, but those should be reported as non-susceptible if using appropriate breakpoints. This makes the use of EUCAST breakpoints important as they have been based on the pharmacokinetic/ pharmacodynamic considerations discussed here. If too high breakpoints are used, such as the value of 64 mg/L for piperacillin in the U.S.A, killing of organisms with high MICs may no longer be dependent upon time only but may become truly influenced by the concentration.

given by continuous infusion since this would imply a significant increase in daily dosage that may not be safe.

Aminoglycosides, which are both AUC_{24h}/MIC and C_{max}/MIC dependent, are better administered by discontinuous administration with long interdose intervals (24 h or more) because this reduces their toxicity [20]. The same applies to daptomycin, for which the simple change of twice-daily to once-daily administration has turned an unsuccessful drug into an approved one because of an increased potency and decreased toxicity [21]. Lipoglycopeptides, obtained from vancomycin by addition of lipophilic moieties, are truly concentration-dependent antibiotics (probably in relation to their multiples mode of action which go much beyond that of vancomycin [22]) and have prolonged half-lives, making their use by continuous infusion rather illogical.

Clinical experience with continuous infusion

The first clinical publications with CI of β-lactams and vancomycin date back now of 34 and 19 years, respectively [23;24]. Tables 1 and 2 show in a synoptic fashion the key informations (study setting, type of pathology, dosages used, serum concentrations obtained, clinical outcomes) gained from an systematic analysis of published clinical studies of β-lactams or vancomycin administered by CI. The studies have been ranked (i) by general design (CI compared to discontinuous administration [DA] or not); (ii) overall assessment of their intrinsic quality (based primarily on sample size and statistical power), (iii) the impact factor of the Journal where the study was published, and (iv) the amount of practical information that could be extracted from the reports for the performance of CI on a routine basis. Studies with pharmacokinetic outcomes only have been treated separately.

β-lactams

1. Penicillins

CI of penicillin G, flucloxacillin, oxacillin and ampicillin has been studied in a limited number of non-controlled observational studies in the outpatient setting [25-27], neonatology ([28;29]), and burned patients [30]. In these trials, CI appeared safe and achieved high clinical cure rates. One retrospective study compared oxacillin CI (n=78) with DA (n=28) in MSSA endocarditis. While no difference was seen in mortality or LOS, microbiological cure rate at 30 days was significantly higher in the CI group (odds ratio: 3.8). Several studies have been published on CI of piperacillin/tazobactam from which two show equivalent clinical and microbiological outcomes for a reduced cost compared to DA [31;32]. Studies showing superiority of CI found significant reduction of APACHE II scores in Gram negative sepsis even at lower doses than those administrated by DA [33], faster temperature normalization [34] and higher clinical cure rate in patients suffering from ventilator associated pneumonia caused by organisms with higher MICs (retrospective studies [35]). Taking into account that the EUCAST "R" breakpoint for piperacillin/tazobactam against *P. aeruginosa* is set at > 16 mg/L, two studies found that stable concentrations of 35 mg/L and 18 mg/L could be obtained after administration of 12 g/24h [36;37]. Measuring the MIC of the causative pathogen may be warranted in this context as it can be directly compared with the actual concentration and used as a guide for decision to either increase it or switch to another antibiotic. Lastly, CI of 4 g/day of temocillin has been compared to its conventional twice daily schedule and shown to yield stable total and free serum concentrations around 75 and 30 mg/ L, respectively [38].

2. Cephalosporins

As early as in 1979, Bodey *et al.* [23] found that cefamandole administered by CI was more effective than carbenicillin given by bolus injection in a subgroup of patients with persistent severe neutropenia. Later on, 5 trials compared ceftazidime CI vs. DA. Three showed equivalent cure rates for both modes of administration (ICU patients with

nosocomial pneumonia [39;40] and pediatric cystic fibrosis patients infected with *P. aeruginosa* infection [41]). However, lower doses were used in the CI arm and both CI and DA regimens achieved T>MIC > 90%. Conversely, one study [42] showed superiority for ceftazidime (combined with tobramycin) administered by CI in critically ill patients suffering from ventilator-associated pneumonia. However, both CI- and DA-treated patients received lower total daily doses than usually recommended (4g/day), which could have influenced results because the chances of attaining a sufficient the T>MIC value are then higher with CI. A fifth study [43] reported superior survival rates for CI ceftazidime compared to DA but it was underpowered to draw any definite conclusions.

In critically-ill adult patients suffering from Gram-negative infection, continuous infusion of cefepime versus an intermittent regimen resulted in greater bactericidal activity against organisms with higher MICs (>2 mg/ L) but the clinical outcome was not significantly modified [44]. Similar results were obtained in a study on CI of cefotaxime [45]. In study comparing ceftriaxone by CI vs. DA in critically ill patients with sepsis, a significant clinical and bacteriological advantages in favor of CI was observed in the subgroup of patients requiring > 4 days of antibiotic treatment [46].

Two studies have compared cefazolin CI vs. DA in surgical prophylaxis and found higher serum and tissue concentrations in the CI group [47;48]. In the last study, a *f*T>MIC>90% was also reached more frequently in the CI arm.

3. Carbapenems

As will be discussed later, CI of carbapenems is not recommended because of insufficient stability. Nevertheless, it has been used for imipenem in critically-ill patients suffering from pneumonia in comparison with DA [49] but with no difference between arms because a T>MIC = 100% was reached for all patients. Extended infusion has been more often used, with a retrospective study [50] observing superior clinical cure rates for meropenem (6 h infusion) compared to DA in critically ill patients suffering from VAP. A

second retrospective study showed equivalent outcomes for meropenem extended infusion at a lower dose (500 mg q6h 3-h) compared to DA at normal dosing (1g q8h) in critically ill patients with HAP due to *A. baumanii* [51]. Doripenem has been registered with the possibility of administration by extended infusion (4 h) to enhance its activity against organisms with elevated MICs [52;53].

Vancomycin

Since vancomycin PK/PD index for efficacy is primarily the AUC_{24h}/MIC ratio, no advantage of CI is expected in this context. An AUC_{24h}/MIC > 350 was associated with greater clinical success and an AUC_{24h}/MIC > 400 with faster bacterial eradication in patients receiving vancomycin for treatment of *Staphylococcus aureus* pneumonia [54]. In a prospective study in non-ICU patients from different wards, clinical success was associated with even higher AUC_{24h}/MIC > 451 [55]. In the first large, prospective, and randomized trial of patients with severe MRSA infections, no difference in clinical outcome or safety was found between CI and DA, but CI allowed for faster attainment of target serum levels, less variability of AUC_{24h} values, and lower costs [56]. Several other studies found equivalent outcomes for CI infusion of vancomycin versus DA in ICU patients [57-59], hospitalized non-ICU patients [60;61], and outpatients [62]. However, a retrospective matched cohort study in ICU patients with MRSA VAP showed a significantly lower mortality inpatients treated by CI [63], although confounding factors cannot be excluded.

The tendency toward higher doses of vancomycin to attain a PK/PD-target AUC_{24h}>400/MIC has reopened the debate on the safety profile of CI compared to DA of vancomycin. Of the nine studies conducted in this context, 6 found no difference for both modes of administration [56;59-61;64;65]. Two of these studies, however, found a slower onset of nephrotoxicity in the CI group [59;64]. Two trials using a high dose of vancomycin (40 mg/kg per day) for the treatment of osteomyelitis found less adverse reactions in the CI group with significantly less adverse events leading to treatment discontinuation in the CI

group [66;67]. More recently, one large retrospective study and a meta-analysis showed a lesser need for renal replacement therapy [68] and a significantly lower risk of nephrotoxicity for CI [69]. However, a recent, retrospective, non-controlled study with 129 patients found a nephrotoxicity rates of CI up to 29.5%, with a significant influence of the treatment duration (> 10 days) and plasma levels exceeding 30 mg/L [70], suggesting that more studies are needed in this context.

While improvements in efficacy are not expected safety issues remains unsettled, several other reasons support the CI of vancomycin. Thus, the original study of Wysocki *et al*. [56] indicated suggested that CI could be cheaper, logistically more convenient, and would also achieve target concentrations more rapidly and with lesser variability in AUC_{24h} than DA. In the context of busy ward activities, CI also offers the advantage of allowing simplifying the monitoring of vancomycin blood levels and its interpretation since sampling can be performed at any convenient time and readings can be immediately translated into AUC_{24h}/MIC values. In this respect, our views are contradicting the recently issued guidelines from the Infectious Diseases Society of America (IDSA), which only support the used of continuous infusion for vancomycin in "patients not responding to standard dosing methods" (BID)" [71].

Practical considerations

Chemical stability

In order to support the CI administration of a drug, it is necessary to establish that it is stable during the projected infusion time. Because there seems to be much confusion amongst health care professionals about this point, we describe here in some details the reasons and mechanisms of instability of β-lactams, while summarizing the data about the well known stability of vancomycin.

β-lactams

β-lactam antibiotics carry a long reputation of being unstable in aqueous media due to the rapid opening of the four-membered ring by hydrolysis, especially if the solutions are concentrated and brought to temperatures above 20°C as can be the case in hospital rooms or if containers are carried under clothes for outpatients. There are however large differences between the different families of β-lactams with respect to instability, depending on their particular chemical structures.

Contrary to common beliefs, it is not the inherent strain of the 4-membered ring itself that makes the β-lactam antibiotics fragile. Indeed, monocyclic β-lactams (such as aztreonam) are quite stable and resistant to hydrolysis, similarly to normal (i.e. non-cyclic) amides. This results from the stabilization of the amide function by resonance giving a strong contribution of the zwitterionic structure shown in Figure 2 (A1 and A2). The phenomenon of resonance is responsible for the lower susceptibility of the carbonyl group to nucleophilic attack (by hydroxide anion for instance), leading ultimately to the cleavage of the small ring via the rapid decomposition of a tetrahedral intermediate (Scheme 1). The condition for observing resonance is a co-planar arrangement of the O, C, N and C atoms allowing the delocalization of the nitrogen lone pair electrons onto the oxygen. In the penam family, the fused 5-membered ring induces a default of the so-called nitrogen planarity. Due to the high bicyclic strain, the nitrogen becomes pyramidal and the amide resonance is inhibited (Figure 2 B1). Accordingly, the β-lactam carbonyl behaves as a ketone and is therefore highly sensitive to nucleophilic attack (Scheme 1). In the cephem family, the nitrogen is quite planar and the amide resonance is possible. However, the fused 6-membered ring containing a Δ3 C=C double bond allows the occurrence of another resonance phenomenon involving the nitrogen lone pair electrons and the olefin π electrons, namely the enamine resonance (Figure 2 B2), which significantly weakens the amide resonance. In the carbapenem family, both phenomena (nitrogen pyramidalisation

and enamine resonance) contribute to the high reactivity of the β-lactam carbonyl toward nucleophiles (Figure 2 B3).

The bicyclic skeletons of the penams, cephems, and carbapenems are decorated by side-chains that also play an important role in drug stability. The amino-acyl side-chains anchored at position C_6 (penicillins) or C_7 (cephalosporins) contribute to the fragility by anchimeric assistance to the β-lactam ring cleavage. As shown in Figure 3A, an intramolecular nucleophilic attack of the exocyclic amide oxygen atom onto the β-lactam carbonyl leads to the formation of a 5-membered heterocycle (azalactone) concomitantly with the opening of the 4-membered ring. This reaction requires the particular *syn*-conformation of the side-chain which depends mainly on steric factors. Generally, bulky substituents (oxacillin, piperacillin) increase the drug stability by preventing the *syn*-conformation of the side-chain. The presence of a methoxy group (R' = OCH_3, see Scheme 1) at C_6 (temocillin) or C_7 (cefoxitin), as found in the structure of some antibiotics, requires a special mention. This group behaves as a steric shield and protects the β-lactam carbonyl against nucleophilic attack. This is true for chemical hydrolysis, as well as for enzymatic hydrolysis. As a matter of fact, temocillin features an exceptional stability in water [72] and against most β-lactamases including extended-spectrum β-lactamases from Gram-negative bacteria [73].

Independently of the β-lactam cleavage, cephalosporins can be deactivated by migration of the double bond (prototropic reaction), giving microbiologically inactive Δ2 C=C compounds (Figure 3B). This reaction depends on the electronic effects of the side-chain fixed at the C_3 position. In the cephem and carbapenem families, the instability can be increased by the presence of an electron-withdrawing group on the C_3 or C_2 side-chains, respectively. This substitution favors the enamine resonance and can ultimately lead to the departure of a leaving group Y, once the β-lactam has been opened (Scheme 2B).

Lastly, the S_1-C_5 (penams) or S_1-C_6 (cephems) bond is also fragile and is generally cleaved after the breaking of the β-lactam (O)C-N bond. Oxidation of the sulfur atom (n = 2) giving a sulfone (tazobactam) increases greatly the instability by strong electron-withdrawing effect (Figure 2A).

Table 3 lists the stabilities of the β-lactams used in the clinical studies reviewed in this paper when tested under conditions mimicking their clinical use for continuous infusion and taking a 90% maintenance of the intact molecule as criterion, in accordance with the provisions of both the European and US Pharmacopeias. It is important to note that those conditions are often quite different from those used by manufacturers to assess the stability of their product for compliance with the requirements of the registration authorities, as these most often pertain to dry substances stored in warehouses or pharmacies, not to solutions used for CI.

The key message is that (i) penicllin G, imipenem, and meropenem are quite unstable at 37°C and cannot be maintained for more than a very few hours at 25°C; (ii) ampicillin, cefotaxime and ceftriaxone will withstand storage at temperatures above 25°C for about 6 h only while ceftazidime and cefepime withstand these temperatures for 8-12 h. These molecules, however can be maintained for up to 24 h at temperatures of 25°C or lower; (iii) piperacillin, cefazolin and temocillin will all withstand being maintained at 37°C for 20 h (24htemocillin), and several days at 25°C. Some specific information is given hereunder for specific molecules.

Penicillins

The CI of benzylpenicillin been widely used in outpatient antibiotic treatments [74]. Because of its limited stability, the use of pouches with freezer packs has been proposed [75] as well as for ampicillin ([74]). Conversely, piperacillin (with our without tazobactam) [76;77] and temocillin [38;78] have proven much more stable (up to several days).

Cephalosporins

Ceftriaxone solutions packaged in AutoDose Infusion System bags remain stable for up to 5 days at 23°C ([79]). For ceftazidime, a first study [80] demonstrated stability for 24 h in 0.9 % sodium chloride without protection from light. Others, however, [81]that stability was limited to 8 h if concentrated solutions are kept at 37°C, with lower values in 5 % dextrose compared to 0.9 % sodium chloride ([82]). Ceftazidime stability is considerably enhanced if maintained at room temperature (up to 7 days at 23°C in 0.9 % sodium chloride (AutoDose infusion system bags [79]) or 72 h at 25°C in 5 % dextrose (polyvinylchloride bags[83]). Cefepime as been claimed to be stable for up to 24 h at room temperature [84;85], but we found that clinical formulations quickly develop a strong red-purple color over time [86].

Carbapenems

The stability of imipenem is limited to 3.5 h when maintained at room temperature even in dilute solutions in water [76]. Its stability may, however, be higher in 0.9 % sodium chloride [87] but nevertheless too short for administration by continuous infusion. Meropenem is stable for only 5 h at room temperature [76], but can reach 24 h if maintained in cold pouches at 4°C [88;89]). Doripenem is somewhat more stable [90] but nevertheless not approved for infusion times exceeding 4 h.

Vancomycin

Vancomycin is very stable whether in 5 % glucose, 0.9 % sodium chloride, or water and can be maintained for several days at room temperature [91]. Vancomycin solutions (10 g/L in 5% glucose) were found to be stable during 58 days at 4°C [92], allowing for centralized preparation of ready-to-use infusion bags at the hospital pharmacy for extended periods of time. These preparations can be used over 48h even if exposed to uncontrolled

room temperature and light [93]. Concentrated vancomycin solutions (up to 83 g/L) suffered < 5% degradation when kept for 72 h at up to 37°C [93].

Compatibility

One of the main issues with CI is the compatibility of β-lactams or vancomycin if administered either together with other medications. A first important caveat is that vancomycin and β-lactams are largely incompatible [93] and should never be administered trough the same line. Several studies, indeed, point to major incompatibilities with these antibiotics (see http://www.stabilis.org). Many of these studies, however, have been conducted under conditions that are often quite remote from those used in clinical practice, but ceftazidime and cefepime on the one hand, and vancomycin on the other hand have, however, been tested in the context of continuous infusion [81;86;93]. Concentrating on drugs commonly used in Intensive Care Units, the main compatibilities for these two β-lactams were with macrolides, propofol, phenytoin, midazolam, piritramide, nicardipine, dobutamine, and N-acetyl-cystein, and for vancomycin, moxifloxacin, propofol, valproic acid, phenytoin, theophylline, methylprednisolone, and furosemide. It is highly recommended to test for compatibility all drugs for which no information is available using a protocol that mimic the intended use or to use separate lines.

Pharmacoeconomics

CI may offer pharmacoeconomic advantages over DA by (i) achieving the same therapeutic effect with a lower daily dose (β-lactams), (ii) reducing the number of serum assays necessary for dose adaptation (vancomycin), (iii) by reducing nursing time devoted to preparing and administering these antibiotics.

Reduced antibiotic consumption without loss of efficacy

Several clinical trials have documented the possibility of a similar efficacy with a reduced dosage ([31;40;94-98]). More specifically, the use of CI over DA allowed for a 38 % reduction of costs for ceftazidime in ICU patients suffering from nosocomial pneumonia [99], and of 23 % for piperacillin-tazobactam [34] with equivalent clinical and microbiological outcomes.

Reduced cost of therapeutic drug monitoring

James *et al.* [60] found that the number of samples required for serum drug level determination could be markedly reduced with CI, while Wysocki *et al.* [56] reported reduction in the cost of serum vancomycin determinations per patient of 36 %, with a global saving (for a 10 days treatment) of 23 %. Other similar results were obtained concerning drug acquisition and/or treatment [100-102]).

Reduction of the pharmacy technicians, pharmacists and nursing time

Because it requires only a single nursing activity per day, CI reduces pharmacists, pharmacy technician and nursing time devoted to drug preparation, distribution and administration [31;41;103-106]. Patel *et al.* [107] showed that 93% of TDM assays were performed on routine serum samples during CI compared to 46% for intermittent administration resulting in less venopunctures imposed to patients and a reduction in nursing time. We ourselves observed a reduction of nursing time of about 30 minutes per treatment-day for CI compared to DA of vancomycin.

Health care practitioners' satisfaction with continuous infusion

This is rarely examined and reported as such in the literature, but we had the opportunity to assess it specifically after a hospital-wide switch from DA to CI, trough a qualitative study involving purposely selected groups of health care professionals (Ampe *et al.*, submitted for publication). The satisfaction level, measured on a scale from 0 to 5 was 4.5 for prescribing physicians, 4.3 for nurses and 4.4 for laboratory personnel. The main

and only consistent drawback mentioned was the necessity to maintain a dedicated infusion line in case of co-administration of drugs for which compatibility had not been positively assessed.

Conclusions and perspectives

Most studies presented in this review conclude that CI of β-lactams is superior to DA for pharmacokinetic target attainment (T>MIC), but most clinical studies do not show significant clinical benefit until now. Yet, it becomes also clear that CI will probably be most beneficial in infections with less susceptible pathogens for which a satisfactory target attainment rate is probably be more difficult to reach. It may also be useful for subpopulations of patients, such as those critically ill or immunocompromised. Well designed clinical studies are probably needed in order to draw definite conclusions towards in this context [108]. Other potential advantages such as increased tissue penetration [109;110] and better control of neurotoxicity, and decreased costs could also be usefully further explored. It should, however, be emphasized that carbapenems are not amenable to use by continuous infusion unless the containers are maintained at low temperature or are replaced every 3 to 4 h to minimize degradation.

For vancomycin, the advantages of CI clearly lie beyond considerations about efficacy, and stem mainly from its facilitated use and its easier monitoring. This largely explains the increase in its popularity in hospital setting in Belgium [111] as well as in other European countries. A limit is, however, probably imposed by the concentrations that can safely be reached ([112;113] without triggering nephrotoxicity, and, as consequence, the susceptibility of the target organisms (which, for all practical and PK/PD reasons is probably close to the current S/R breakpoint set by EUCAST [2 mg/L]). This limit, however, will also apply to the BID schedule, since the necessary daily dose will be the same in both situations. Additional advantages could include a faster attainment of serum target

concentrations and less AUC_{24h}-variability that have been demonstrated in several studies and could be important in situations where early adequate serum levels are critical. As for β-lactams, CI of vancomycin also allows to reduce the number of samples necessary for drug monitoring, even though we and others showed that such monitoring remains essential in view of large and still unexplained interpatient and intrapatient variabilities in serum levels [55]. It also offers the possibility of significant cost-reductions.

For both β-lactams and vancomycin, a main practical limitation remains the risk of drug incompatibilities in the absence of a dedicated infusion line, but increasing experience with CI may help to construct the necessary databases on which clinicians could rely in the future. Also, CI should not be considered as a panacea and as potentially replacing or minimizing the necessity of drug monitoring. While this is clear for vancomycin from published evidence, it needs also to be emphasized for β-lactams for which monitoring is more and more advocated [114] in view of the unpredictability of serum levels in critically-ill patients [115]. CI may facilitate its implementation for the same reasons as it helped in improving the process of TDM for vancomycin.

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Table 1. Clinical studies with β-lactams.

antibiotic tested and reference	main pathology	main pathogen(s) [1]	patients [2]	dosage [3] serum concentr. [4]	outcome (% cure CI *vs.* DA) and/or assessment	general conclusion [5]
1.1. Studies comparing continuous infusion and discontinuous administration (controlled studies)						
oxacilline [116]	endocarditis	*MSSA*	Retrospective CI : 78 DA : 28	- CI: 12 g q24h - DA: 2 g q4 h	- Mortality : 8% (6/78) vs. 10% (3/28), (*P* = 0.7) - LOS: 20 versus 25 days (*P* = 0.4) - Microbiological cure: 94% (73/78) versus 79% (22/28), (*P* =0.03)	Superiority for micribiological cure CI is an effective alternative for the treatment of MSSA endocarditis and may improve microbiological cure.
piperacillin/ tazobactam [34]	various severe infections	*P. aeruginosa* *S. aureus* *Enterococcus sp.* *E. coli* *K. pneumoniae*	adults CI: 47 DA: 51	- load: 2 g - infus.: 8-12 g/day - ser. lev.: 13-124 mg/L	- clinical cure: 94 *vs.* 82 % - bacteriological cure: 89 *vs.* 73 % - faster fever normalization	superiority but only for last criterion
piperacillin/ tazobactam [31]	various community and hospital-acquired infections	*C. freundii* Enterobacter *spp*. *K. pneumoniae* *E. faecalis*	hospitalized adults CI: 12 DA: 12	- load: 2 g - infus.: 4-8 g/day - ser. lev.: 39 mg/L	- similar clinical outcomes	equivalence

piperacillin/ tazobactam [32]	complicated intra-abdominal infections	*E. coli* *B. fragilis* Viridans group streptococci *K. pneumoniae* *B. uniformis* *P. aeruginosa*	hospitalized adults CI: 128 DA: 130	- load: 2 g - infus.: 8-12 g/day	- clinical cure: 86.4 *vs.* 88.4 % - bacteriological cure: 83.9 *vs.* 87.9 %	equivalence
piperacillin [33]	sepsis (suspected or documented infection)	*K. pneumoniae* *E. coli* *Enterobacter spp.* *P. aeruginosa* (MIC up to 32 mg/L)	adults CI: 20 DA: 20	- load: 2 g - infus.: 8 g/day - ser. lev.:34-42 mg/L	- mortality rate: 25 *vs.* 30 % - significantly better reduction of APACHE II scores	superiority
piperacillin/ tazobactam [35]	VAP	*P. aeruginosa* *E. coli* *Enterobacter spp.* *S. marcescens* *H. influenzae*	adults CI: 37 DA: 46	- load: 4 g - infus.: 16 g/day	- clinical cure: 89.2 *vs.* 56.5 % (larger differences if organisms with MIC $\geq$ 8 mg/L) - no significantdifference in mortality (21.6 *vs.* 30.4 %)	superiority for infections caused by organisms with elevated MIC
piperacillin/ tazobactam [37]	sepsis (suspected or documented infection)	*Not specified*	ICU patients CI : 8 DA : 8	- load: 4g - infus.: 12/day	- superior free PIP conc. - favorable for pharmacodynamic target attainment	pharmacokinetic superiority favorable pharmacodynamics

piperacillin/ tazobactam [117]	mainly urinary and respiratory tract infections	*Gram (−) bacteria*	Retrospective EXT: 70 DA: 59	EXT: 3/0.375 g q8h; 4h infusion DA: 3/0.375 g to 4/0.5 g q6h; or q8h 30-min infusion	- mortality: 4/70 (5.7%) vs. 5/59 (8.5%)	equivalence
cefazoline [118]	Bone and joint	CoNS: n=9 *Streptococcus* spp: n= 7 Gram-positive anaerobic bacteriae : n=18 Polymicrobial: n=8 Undetermined : n=2	Orthopedic (hospitalized OPAT) retrospective n=100	- CI: 6g q24h (two 12h infusions)	- Two moderate-grade adverse events - median serum cefazolin concentration: 63 µg/ml (range, 13 to 203 µg/ml) and 57 µg/ml (range, 29 to 128 µg/ml) on days 2 to 10 and days 11 to 21, respectively. - median bone cefazolin concentration (n=8): 13.5 µg /g (range, 3.5 to 29 µg /g). - median bone concentration/serum concentration ratio (n=8): 0.25 (range, 0.06 to 0.41). - clinical cure (n=88): 52 cured and 29 probably cured.	The treatment of bone and joint infections with a prolonged continuous intravenous cefazolin infusion was feasible, effective, well-tolerated, safe, and convenient, making it a strong candidate for home therapy.

Cefotaxime [119]	secondary peritonitis.	Enterobacter spp. (MIC range: 0.016 to 0.25 mg/L.)	ICU CI: n=11	o load: 2 g o CI: 4 g/24 h	Total and unbound plasma levels: 24.0+21.5 and 20.3+19.8 mg/L on D2 and 22.1+20.7 and 18.9+19.2 mg/L on D3, respectively. Total and unbound levels of cefotaxime in the peritoneal fluids were 16.2+11.5 and 14.3+10.4 mg/L, respectively. unbound fraction: 81.8+5.9% on D2 and 82.6+7.7% on D3, Unbound fraction at the peritoneal site: 87.0+5.5% on D3. Total and unbound plasma levels of desacetyl-cefotaxime were 9.0+8.1 and 8.4+8.1 mg/L on D2 and 7.6+7.6 and 7.2+7.6 mg/L on D3, respectively. Total and unbound levels of desacetyl-cefotaxime in the peritoneal fluids were 11.9+11.5 and 10.9+10.8 mg/L, respectively.	CI provided a peritoneal concentration >5 times the MIC for the recovered Enterobacteriaceae and the susceptibility breakpoint of cefotaxime for facultative Gram-negative bacilli.

ceftazidime [43]	septicaemic melioidosis	*B. pseudomallei*	adults CI: 10 DA: 11	- load: 12 mg/kg - infus.: 4 mg/kg/h (1 day only) *	survival: 70 *vs.* 18 %	potential superiority but significance limited becasue of high mortality rates in both groups
ceftazidime [41]	cystic fibrosis	*P. aeruginosa*	home therapy children CI: 14 DA: 14	- load: unspecified - infus.: 100 mg/kg/day * -ser. lev.:15.2-50.8 mg/L	no difference in clinical outcome	favorable considering home therapy
ceftazidime [40]	nosocomial pneumonia	*P. aeruginosa* (MIC 4-8 mg/L) *H. influenzae* *S. aureus* (MIC 8-16 mg/L)	ICU patients CI: 17 DA: 18	- load: 1 g - infus.: 3 g/day	- clinical cure or improvement: 94 *vs*. 83 % microbiological cure: 76 *vs.* 80 % - shorter time to fever resolution	equivalence
ceftazidime [42]	VAP	*Gram negative*	ICU patients CI: 56 DA: 65	- load: 1 g - infus.: 4 g/day	- clinical cure: 89.3 *vs.* 52.3 %	superiority

ceftazidime [120]	cystic fibrosis	*P. aeruginosa* *S. aureus* *H. influenzae* (MIC up to >32 mg/L)	adults - cross-over CI followed by DA: 36 DA followed by CI: 34	- load: 60 mg/kg - infus. 200 mg/kg/ day - ser. lev.: 56.2 mg/L	- clinical cure: no difference - toxicity: no difference	equivalence superiority with resistant isolates of *P. aeruginosa*
ceftazidime [121]	Cystic fibrosis	*P . aeruginosa*	Adults Cross over N=56 DA regimen followed by CI regimen	- CI: 100 mg/kg/day - DA: 200 mg/kg/day in 3 doses	- After 2 weeks of antibiotic treatment for both regimens: significant improvements for body weight, leukocyte counts, CRP, FEV1, forced vital capacity, and bacterial load in the airways, with no significant differences between treatment regimens. - Both regimens well tolerated.	continuous or thrice-daily dosing of IV ceftazidime combined with once-daily tobramycin, are equally effective for antipseudomonal therapy in clinically stable patients with CF.
ceftriaxone [46]	sepsis (suspected or documented infection)	*S. aureus* *H. influenza* *E. coli* *M. catarrhalis* *S. pneumoniae*	adults CI: 29 DA: 28	- load: 0.5 g - infus.: 2 g/day	- clinical cure: 45 *vs.* 18 % - bacteriological cure: 62 *vs.* 50 % - larger differences in patients requiring ≥ 4 days treatment	superiority in patients requiring > 4 days of therapy

meropenem [50]	VAP	*P. aeruginosa* *E. coli* *S. marcescens* Enterobacter spp. *K. pneumoniae*	ICU patients CI: 42 DA: 47	- load: 1 g - infus.: 4 g/day	clinical cure: 90.5 *vs.* 59.6 %	superiority
Meropenem [122]	pneumonia	Gram (−) bacteria: 10 Gram (+) bacteria: 10 Others, unknown: 34	Prospective CI: 18 DA: 24	EXT:500 mg q12h 4-h infusion DA: 500 mg q12h 1-h infusion	Mortality: 1/18 (5.6) vs. 9/24 (37.5)	Superiority
Imipenem/cilastine [49]	HAP	Gram (−) bacilli	Prospective RCT CI: 10 DA: 10	CI: 2/2 g DA: 1/1 g q8h in 40-min infusion	1/10 (10%) vs. 2/10 (20%)	Equivalence
meropenem [51]	HAP	A. baumannii	ICU Retrospective IC : 15 DA : 15	EXT: 500 mg q6h 3-h Infusion DA : 1 g q8h	Clinical cure: 15/15 (100%) vs. 15/15 (100%) Mortality: 0/15 (0%) vs. 0/15 (0%)	Equivalence

meropenem [123]	CAP	Gram (−) bacteria: 15 Gram (+) bacteria: 14 Unknown: 21	Geriatric Prospective CI: 25 DA: 25	CI: 1 g/24h DA: 500 mg q12h	Clinical cure: 20/25 (80%) vs. 19/25 (76%) Mortality: 0/25 (0%) vs. 0/25 (0%) Adverse events: 5/25 (20%) vs. 6/25 (24%)	equivalence
imipenem/cilastine or meropenem [124;125]	bacteremia,	A. baumannii, P. aeruginosa, ESBL (+) Enterobacteriaceae	Retrospective CI: 42 DA: 29	IMI/CIL or MER 3-h infusion vs IMI/CIL or MER 30-min infusion	Mortality: 12/42 (28.6) vs. 7/29 (24.1)	equivalence
1.2. Studies evaluating continuous infusion only (non-controlled)						
penicillin G [26]	serious bacterial infections (suspected or documented)	*Streptococci* spp. *Enterococci* spp.	home-based therapy adults 35	- load: no - infus.: 4.8 to 16 g/day - ser. lev.: 0-13.7 mg/L	clinical and bacteriological cures: 80 %	favorable
ampicillin [29]	septicaemia (suspected or documented)	*S. aureus* *E. coli* *K. oxytoca* *K. pneumoniae* *Clostridium spp.* *Bacteroides spp.*	newborn infants 88	- load.: no - infus.: 200 mg/kg/day - ser. lev.: 39 mg/L (30-48)	- 9 deaths	equivalence practical advantages

ampicillin [28]	serious neonatal surgical problems	*S. aureus* *E. coli* *K. pneumoniae*	newborn infants 7	- load.: no - infus.: 200 mg/kg/day - ser. lev.: 28-60 mg/L	- 5 clinical cure - 2 deaths - no toxicity or ototoxicity	uncertain
Ampicillin [126]	septicaemia (suspected or documented)	*S. aureus* *E. cloacae* *K. pneumoniae*	newborn infants 35	- load.: no - infus.: 150-200 mg/kg/day - ser. lev.: 45 mg/L (average)	- 34 clinical cure - 1 death - no toxicity	favorable
oxacillin [30]	burn wound cellulitis	group A β-hemolytic streptococci *S. aureus*	adults 26	- load: no - infus.: 12 g/day	- clinical cure: 73 % -	favorable
ceftazidime [127]	severe post-chemotherapy neutropenia	*not specified*	adults 12	- load: 0.5 g - infus.: 100 mg/kg/day - ser. lev.: > 20 mg/L	- no major side effects - 50 % non responders	unfavorable

ceftazidime [128]	cystic fibrosis	*P. aeruginosa*	home therapy adults 17	- load: 15 mg/kg - infus.: 100 mg/kg/day - ser. lev.: 28.4 mg/L	- clinical improvement: 92 % - development of resistance during treatmentbut return susceptible after 4-6 weeks	favorable
ceftazidime [129]	cancers (lung, breast) with low-risk neutropenic fever	*S. pneumoniae* Coag. (-) *staphyloc.* *E. coli*	adults 135	- load: 1 g - infus.: 2 g/day	- clinical improvement: 95 %	favorable

1.3. Prophylaxis or undefined infection					
cefazolin [47]	coronary artery bypass grafting and cardiopulmonary bypass	adults CI: 73 DA: 64	- load: 2-3 g - infus. 15-20 mg/min during operation time - ser. lev.: 24-51 mg/L (postoperative)	-no related toxicity or adverse events -higher serum and tissue concentrations	favorable

Cefazoline [48]	cardiac surgery	NA	Prospective RCT CI: n=10 DA: n=10	Load.: 2 g - CI: rate 1g/6 h for 18 h - DA: 1 g q6h for 18h	- Free trough serum Css higher and less variable (P<.05 at 15, 18 and 24 hours). - fT> MIC >90% goal reached:9/10 (90%) vs. 3/10 (30%) (P<.05). - higher mean atrial tissue concentration (P<.05).	Administration of cefazolin as loading dose plus continuous infusion has pharmacokinetic and pharmacodynamic advantages relative to intermittent administration. It provides more stable serum levels, lower interpatient variability, and higher myocardial tissue penetration.
cefotaxime [130]	liver transplantation		adults CI: 7 DA: 8	- load: 1 g - infus.: 4 g/day - ser. lev.: 18-26 mg/L	higher serum concentrations	favorable

2.4. Pharmacokinetic/pharmacodynamic studies						
2.4.1. Ampicillin/sulbactam						
[131]	colorectal surgery	*B. fragilis*	adults CI: 8 DA: 8	- load: 2 g - infus.: 12 g/day - ser. lev.: 79 mg/L	no significant effect on antibiotic penetration in tissues	equivalence
2.4.2. Piperacillin/tazobactam						
[132]	VAP	*P. aeruginosa* *S. aureus* (MRSA)	adults CI: 40	- load: 4 g - infus: 12-16 g/day - ser. lev. 25.3-135.3 mg/L (median)	clinical cure: 32/40 microb. cure: 32/40 concentr. in: ELF 12.7-54.9 mg/L (median)	favorable
[133]	HAP UTI Septic shock cellulitis	*P. aeruginosa* *E. coli* *K. Pneumoniae* *Some empiric*	ICU patients CI: 24	- load.: 66 mg/kg - infus.: 200 mg/kg/day - ser level (free) 82 mg/L (average)	75% target conc. attainment after dose adjustment	favorable
2.4.3. Ceftazidime						

[134]	patients requiring ceftazidime treatment	*P. aeruginosa*	ICU patients CI: 10 DA: 8	- load: 12 mg/kg - infus.: 6 g/day - ser. lev.: > 38 mg/L	all patients achieve high serum levels	pharmacokinetic advantage
[110]	severe intra-abdominal infections	*E. coli* *P. aeruginosa* *K. oxytoca* *P. mirabilis*	adults CI: 12 DA: 6	- load: 1 g - infus.: 4.5 g/day - ser. lev.: 47.1 (21.1-92.9)	more favourable concentrations in serum and peritoneal exudate	pharmacokinetic advantage
[135]	neutropenic fever after chemotherapy	*P. aeruginosa*	children CI: 20	- load: 65 mg/kg - infus.: 200 mg/kg/day - ser. lev. ~ 32 mg/L	no toxicity or infectious deaths	pharmacokinetic advantage
[136]	nosocomial pneumonia	*P. aeruginosa* *K. pneumoniae*	ventilated adults CI: 8 DA: 8	- load: 20 mg/kg - infus.: 60 mg/kg/day - ser. lev.: 45.7 mg/L	fT > target concentration (20 mg/L) in all patients	pharmacodynamic advantage

[137]	suspected bacterial infections	*E. aerogenes* *E. coli*	critically ill adults CI: 7	- load: 2 g - infus.: 3 g/day - ser. lev.: 33.5 mg/L	serum concentrations > 4 x the MIC of susceptible pathogens	pharmacodynamic advantage
2.4.4. Temocillin						
[38]	nosocomial pneumonia	non-*Pseudomonas* Gram-negative (MIC up to 16 mg/L)	ICU patients CI: 6 DA: 6	- load: 2 g - infus.: 4 g/day - ser. lev.: 73.5mg/L (total) 29.3 mg/L (free)	stable free serum concentrations above the current breakpoint (16 mg/L)	pharmacokinetic advantage
2.4.5. Cefepime						
[138]	Gram-negative severe pneumonia or bacteremia	not specified	ICU patients CI: 9 DA: 9	- load: not specified - infus.: 4 g/day	no difference in efficacy between CI and DA l longer *f*T > MIC may be associated with more stable bactericidal effect	pharmacodynamic advantage
[139]	Gram-negative infection	*H. influenzae* *Salmonella spp.* *E agglomerans* *K. pneumoniae* *S. typhimurium* *E. cloacae*	adults (cross-over) CI followed by DA: 10 DA followed by CI: 10	- load: 0.5 g - infus.: 4 g/day - ser. lev.: 41.4-49.8 mg/L	C_{ss} > 4 x the MIC of all pathogens	pharmacodynamic advantage

[140]	severe nosocomial pneumonia	not specified (MIC's ≤ 0.5-8 mg/L)	ICU-ventilated adults CI: 20	- load: 2 g - infus.: 4 g/day - ser. lev.: 13.5 mg/L	stable serum levels and penetration into epithelial lining fluid of about 100%	pharmacokinetic optimization serum and epithelial lining fluid
[141]	serious infection (not specified)	*E. coli* *K. pneumoniae* *P. aeruginosa* *A. baumannii*	ICU patients CI: 3 DA: 5	- load: 0.5 g - infus.: 2-6 g/day	bactericidal levels reached for *E. coli* and *K. pneumoniae* > 4 g/day required for *P. aeruginosa* but 6 g/day insufficient for *A. baumannii*	superiority (based on MC simulation)
2.4.6. Imipenem						
[49]	surgery (various indications)	*P. aeruginosa* *K. pneumoniae*	ICU patients CI: 10 DA: 10	- load: 1 g - infus.: 2 g/day - ser. lev.: 8.7 mg/L	no specific adverse effects 1 death	equivalence

2.4.7. Meropenem						
[142]	pneumonia, sepsis and systemic inflammatory response syndrome	*Staphylococcus spp.* (MIC up to 8 mg/L)	ICU patients (cross-over) CI followed by DA: 7 DA followed by CI: 8	- load: 2 g - infus.: 3 g/day - ser. lev.: 11.9 mg/L	no specific adverse effects	equivalence
[143]	pneumonia, sepsis and pancreatitis	*P. aeruginosa*	ICU patients (cross-over) CI followed by DA: 3 DA followed by CI: 3	- load: 0.5 g - infus.: 2 g/day - ser. lev.: 6.5-56.8 mg/L	2 deaths	pharmacokinetic advantage
[109]	nosocomial pneumonia, intra-abdominal sepsis	*E. coli* *K. pneumoniae* *Enterobacter sp.* *S. marcescens* *Citrobacter sp.* *P. aeruginosa* *Acinetobacter sp.* (MIC up to 16 mg/L)	ICU patients CI: 5 DA: 5	- load: 0.5 g - infus.: 3 g/day - ser. lev.: 7 mg/L	- higher concentr. in subcutaneous tissue and plasma	potentially advantageous in less susceptible *P. aeruginosa* and *Acinetobacter sp.*

Notes to Table 1:

[1] main common pathogens only; MIC if reported and above EUCAST breakpoint

[2] CI: continuous infusion; DA: discontinuous administration (usually standard schedule for the antibiotic under study)

[3] for continuous infusion only; load.: loading dose (should normally be reported as mg/kg; if no indication given, the dose shown is assumed to be administered to a normal adult of 70 kg; see also "Practical considerations); infus.: dose used for infusion (should normally be reported as g per 24 h; see "Practical considerations" if reported as mg/kg and per unit of time)

[4] ser. lev.: serum levels in mg/L (at equilibrium and for continuous infusion only unless stated otherwise; most common or mean if several values are reported; range if reported)

[5] based on authors' assessment with independent confirmation by us based on reading of the publication.

Table 2. Clinical studies with vancomycin

Reference	main pathology	main pathogen(s) [1]	patients	dosage [3] serum concentr. [4] AUC_{24h} [5]	outcome (% cure CI vs. DA) and/or assessment	general conclusion [6]
2.1. Studies comparing continuous infusion and discontinuous administration (controlled studies)						
[56]	septicaemia pneumonia	*MRSA*	ICU patients CI: 61 DA: 58	- load: 15 mg/kg - infus.: 30 mg/kg/day - ser. lev.: 20-25 mg/L	- comparable microbiological and clinical efficacy and safety - concentration > 10 mg/L reached faster (p=0.03)	equivalence
[63]	VAP	*MRSA*	ICU patients CI: 16 DA: 53	- load: no - infus.: 2 g/day	- mortality: 25 vs. 54.7 (p=0.03)	superiority
[59]	open heart surgery	*MRSA* Coag. (-) *staphyloc.*	ICU patients CI: 119 DA: 30	- load: 20 mg/kg - infus.: 2 g/day - ser.lev.: 25,0 mg/L	- nephrotoxicity: 36.7 vs. 27.7% in DA (NS)	equivalence

[60]	suspected or documented infections	*Gram-positive*	hospitalized patients CI followed by DA : 5 DA followed by CI: 5	- load: 0.5g - infus.: 2 g/day - ser. lev. 20.2 mg/L	- no difference in PD parameters - no adverse effects observed	equivalence but CI more likely to result in effective bactericidal titers
[57]	documented infections	*MSRA*	ICU patients CI: 13 DA: 13	- load: 15 mg/kg - infus.: 30 mg/kg/day - ser. lev.: 24 mg/L	- equal median duration of fever, bacteremia, mortality rate, and infection related mortality	equivalence
[61]	suspected or documented infections	*not specified*	hospitalized patients CI: 957 DA: 780	- load: 1 g - infus.: 2-6 g/day - ser.lev.: <5 - >40 mg/L	- target concentr. (30-40 mg/L) attainment 81% vs. 20.9% - toxicity <1%	pharmacokinetic advantage higher and more sustained serum levels supporting CI to enhance efficacy

[66]	osteomyelitis	*MRSA* (MIC up to 4 mg/L)	orthopedic patients CI: 23 DA: 21	- load: 20 mg/kg - infus.: 40 mg/kg/day - ser.lev.: 26 mg/L	- higher and less variable serum levels - equal clinical outcome - ADE 5.3% vs.42.9% (p=0.005); ADE leading to treatment discontinuation 8.7% vs. 42.9% (p=0.03)	superiority (pharmacokinetics , safety) alternative for patients requiring prolonged treatment
[67]	osteomyelitis	*MRSA* Coag. (-) *staphyloc.*	orthopedic patients CI: 23 (high dose) DA: 21 (high dose) and 45 (standard dose)	- load: no - infus.: 40 mg/kg/day - ser.lev.: not stated	- less adverse reactions: 4.5% vs.25 % (p=0.007) - equal cure rate at 1 year post treatment	superiority (safety)
[58]	documented infections	*MRSA* Coag. (-) *staphyloc.*	ICU patients CI: 11 DA: 14	- load: 0.5 g - infus.: 2 g/day - ser.lev.: 24.3 mg/L	- no differences in SAPS II scores and length of stay. - significant positive changes in SOFA scores and WBC counts ($p < 0.05$)	equivalence improvement in organ dysfunction without change in overall evolution of the disease

[64]	documented infections (mainly skin and soft tissue and bone and joint infections)	*MRSA* Coag. (-) *staphyloc.* *Enterococcus spp.*	OPAT 167 patients; 40 matched pairs CI: 40 DA: 40	- regimen chosen by the physician - ser lev.: CI: 13.6±6.2 DA: 9.7±5.0	No difference in nephrotoxicity [10.0% vs. 25.0% (p = 0.139)]	equivalence (no difference in nephrotoxicity)
[68]	suspected or documented infections	Not specified	ICU patients retrospective CI: 164 DA : 75	- regimen chosen by the physician DA: 1000-2000 mg adjusted by CI: loading dose: 1000 – 1250 mg CI: 60 mg/h (40 mg/h in case of renal impairment) - ser lev.: CI: median 19.8 (9.8-29.4) mg/L DA trough: median 9.1 mg/L (5.0-15.7 mg/L)	- Less assays per treatment day: 0.38 vs. 0.43 P<0.05 - Less start of RRT during VAN treatment 7/94 [7%]; vs. 12/52 [23%]; P<0.05	Superiority (Less need for RRT during therapy and less TDM assays needed)
[62]	Documented	*MRSA*	OPAT retrospective CI: 188 DA: 56	- Regimen chosen by physician - Ser lev target - CI: 15-25 mg/L - DA: 15-20 mg/L	Clinical failure: 21.28% vs. 30.36% [unadjusted RR: 0.701 (0.432–1.13); P=0.159]	Equivalence (clinical failure)

[144]	Duspected and documented	*Not specified*	Neonates DA: n=15 CI: n=17	- DA: 10 mg/kg/12h adjusted to renal function - DA ser.conc. target: 10-15 mg/L - Load.: 15 mg/kg - CI: 20–60 mg/kg/day according to PMA and creatinine - CI ser. conc. target: 15-25 mg/L	- Ser. conc. within target range 77% (63/82) vs. 46% (23/50) - additional vanopunctures 7% vs. 54% - dose adaptation compromized by missing or incorrect data: 36% vs 0%	CI achieved target concentrations more consistently than intermittent guidelines and resolved the problems associated with monitoring and interpreting vancomycin concentrations.
[65]	Documented	*MRSA*	Adults Cross-over N=12	- load: 15 mg/kg - CI: 30 mg/kg - DA: 15 mg/kg/12 h	- MRSA infections eradicated after 10 days in all patients. - no adverse events observed	Equivalence

2.2. Studies evaluating continuous infusion only (non-controlled) or pharmacokinetic studies

[102]	phrophylaxis	*no*	surgical patients CI: 8 DA: 8	- load: 500 mg - infus.: 30 mg/kg/day - ser.lev. 16 mg/L AUC_{12h} = 178 h^{-1} in blood - AUC_{12h} = 152h^{-1} in pleural fluid	- comparable AUC_{24h} - more sustained concentration in pleural fluid - no difference in clinical efficacy	equivalence
[145]	suspected or documented infections	*MRSA*	hospitalized patients CI: 63	- load: 15 mg/kg - infus.: (g/day) calculated as [0,029*CL(Cr) (mL/min) + 0,94]*target Css*(24/1000)]	- correlation between predicted and observed vancomycin levels (p<0,001)	CI with nomogram may improve vancomycin treatment of MRSA infections
[112]	bone and joint infection	*MRSA*	outpatients CI: 102	- regimen chosen by the physician - ser. lev.: 15,5 mg/L	- cumulative nephrotoxicity: 15.7 % with OR= 21.2 (p= 0.04) for concentration ≥ 28 mg/L	concentrations in excess of 28 mg/L may cause increased nephrotoxicity

[146]	meningitis (50 %) and various infections	*Gram-positive*	ICU patients CI:13	- load: 15 mg/kg - infus.: 50-60 mg/ kg/ day - ser. lev.: 17.8-36.2 mg/L	- clinical and bacteriological cure: 100 % - no diff. in serum pharmacokinetic parameters - improved penetration in CSF for meningitis patients: 48% vs. 18% in other patients ($p<0,05$) - no nephrotoxicity	equivalence
[147]	suspected or documented infections	*Gram-positive*	neonates CI: 24 [A] and 22 [B]	- load: none [A] or 7 mg/kg [B] - infus.: 10-30 mg/kg/day [A] or 10-40 mg/kg/day [B] - ser. lev.: 11 mg/L [A]; 15.4 mg/L [B]	- 56 [A] vs. 88 [B] % of patients reaching serum concentr. target range of 10-30 mg/L ($p<0.01$) - equal toxicity	a loading dose and dose readjustment improve desired drug concentration attainment
[148]	bacteraemia pneumonia	not specified	burn patients CI: 70	- regimen chosen by the physician - ser. lev.:17.1 mg/L	- average CLvan = 7,03 L/h - formula to adapt vancomycin dosage in burn patients	formula useful to assist the clinician in patients with disturbed renal function

[149]	sepsis (suspected or documented)	Coag. (-) *staphyloc.*	premature neonates CI:145	- load: no - infus. 15-30 mg/kg/day - ser. lev.: 13-20 mg/L	- microbiological cure: 93 % - 75% of levels in target range 10-25 mg/L at 48h	equal microbiological efficacy potential pharmacokinetic advantage
[150]	sepsis septic shock (documented)	*MRSA*	ICU patients CI: 25	- regimen chosen by physic ian - ser. lev.: 7.8-57.6 mg/L	- multicompartment model to predict vancomycin serum levels	consistency between model-based prediction and experimental data dose of 3 g/day recommended in order to reach 20 mg/L serum concentr. target
[151]	suspected or documented infections	Coag. (-) *staphyloc.*	neonates and pediatric patients CI: 25	- load: no - infus.: 10-45 mg/kg/day - ser. lev.: 6-64 mg/L	- mean target concentration of 20 – 25 mg/L achieved	daily dose necessary to achieve target showed important individual variations
[152]	post-surgery meningitis	*S. epidermidis* *S. aureus*	surgical patients CI: 8	- load: 50 mg/kg - infus.: 50 mg/kg/day - ser. lev.: 19- 46.1 mg/L	- stable concentr. 4.5-12.7 mg/L in CSF - cure rate: 100% - nephrotoxicity: 12,5%	allows to reach conc.>MIC in CSF ideal serum conc. target: 25-30 mg/L well tolerated given the duration of treatment

[153]	bacteraemia skin and soft tissue	*MRSA*	burn patients CI: 18	- load: no - infus.: 40 mg/kg/day - ser. lev.: 6-32 mg/L	- serum conc. target of 15-20 mg/L achieved in 75% of cases - contra-indicated in case of renal insufficiency	possible pharmacodynamic advantage by prevention of fluctuations in serum concentrations
[154]	severe infections	*MRSA*	ICU patients CI: 20	- load: no - infus.: 2 g/day - ser. lev.: 16.6 to 22.6 mg/L	- clinical cure: 85% - bacteriological cure: 77% - nephrotoxicity: 15% - infection related mortality: 15%	resistance development to fosfomycin and fucidic acid during treatment serum conc. >20 mg/L recommended

[70]	Pneumonia Bacteremia	Gram-positive	ICU patients retrospective CI: 129	- load: - infus.: - ser. lev.: target: 15-25 mg/L	AKI: 38 (29.5%). Risk factors: higher body weight ($p < 0.05$), diabetes ($p < 0.05$) vasopressor need ($p < 0.005$). treatment duration (>10d) ($p = 0.05$) P (AKI) = 1/1+ e-logit with logit = -6.54 + 0.055 × SAPS 3 + 0.067 × weight (kg) - 5.888 × 1 (if vancomycin level < 25 µg/mL) - 3.178 × 1 (if vancomycin level < 30 µg/mL) 25-30 µg/mL vs. <25 µg/mL 24% vs. 8% s; odds ratio 9.75, ($p < 0.0001$). vancomycin concentrations > 30 µg/mL vs. lower 32% vs. 68%; odds ratio 30.69; ($p < 0.0001$). Serum creatinine values at discharge had returned to baseline levels in	AKI is frequently observed during continuous vancomycin infusion particularly when conditions that cause acute or chronic renal dysfunction are present and vancomycin levels above target range are achieved.

[155]	suspected and documented	not specified	neonates n=116 observed for modeling n=58 prospective validation of model	- regimen chosen by the physician - load.: none or 10-15 mg/kg - CI: 15-35 mg/kg/day - ser. Lev.:median 18.8 [5.1-61.5 mg/L]	NONMEM population PK modeling for individualized dosing: Loading dose (mg) = Target concentrations *V Maintenance dose (mg) per 24 h = Target concentration (mg/l) *CL * 24 h V = 0.791 *(current weight (g) /1416)$^{0.898}$ CL = 0.0571 * (current weight (g) /1416)$^{0.513}$ *(birth weight (g) /1010)$^{0.599}$ *[1+0.282*(PNA (days) /17)]*[1/(serum creatinine/42)$^{0.525}$]	Serum levels in the target range (15-25 mg/L) individualized dosing: 70.7% vs 40.4% for current dose regimens.

[156]	Suspected and documented	*Not specified*	Pediatric hemato-oncology retrospective n=160	- regimen chosen by the physician - recomm.: 40 mg/kg/day	Initial dose of 40 mg/kg/day is sufficient for achieving target concentrations (between 15 and 20 mg/L) in children older than 6 years but is insufficient in younger children	Higher VAN doses are needed in children. Authors recommend: - > 6 years: 40-45 mg/kg/day - 2-6 years: 45-50 mg/kg/day - < 2 years: 50-55 mg/kg/day

[157]	Suspected and documented	*Gram-positive*	Intensive care Retrospective N=206	- Regimen chosen by the physician according to local guidelines	nonlinear mixed-effects modeling approach using NONMEM. The final population model for vancomycin was represented by: $TVV=(\theta_1*TBW)$ $TVCL=(\theta_2*CrCl/100)$ where TVV is the typical value of volume of distribution, TBW is total body weight, and TVCL is the typical value of vancomycin clearance. Between-subject variability θi is the value of the parameter for the *i*th subject The population value for clearance of vancomycin was 4.6 liters/h (4.1 to 5.2), and that for volume of distribution was 1.5 liters/kg (1.3 to 1.7)	higher-than-recommended loading and daily doses of vancomycin seem to be necessary to rapidly achieve serum concentrations > 20 mg/L in critically ill patients In spite of an effective loading dose of 35 mg/kg, a daily dose of 35 mg/kg could not keep vancomycin concentrations within target levels if the CrCl was 100 ml/min/1.73 m2. If patients had even higher CrCls, a larger daily dose would have been necessary to maintain desired drug levels over the first 24 h of therapy.

[158]	sepsis	*Not specified*	Intensive care Retrospective N=261	- Load: 15 mg/kg - CI: 30 mg/kg/day based on TBW	- vancomycin concentrations (<20 mg/L) on Day 1: 53% (n=139) on Day 2: 33% (n=87) independently predicted by male sex ($p<0.05$) and high Cl_{Cr} (>120 mL/min/1.73 m^2) ($p<0.001$)	approximately one-half of the septic ICU patients treated with CI had insufficient drug concentrations in the early phase of therapy. A high CLCr was the variable most strongly associated
[159]	Suspected and documented	*Not specified*	Intensive care N=20	- load.: 1g - CI: chosen by the physician - Target css = 25 mg/L	- infusion rate (g/24 h) = [0.0261×CLCr (mL/min) + 1.78]×target Css ×(24/1000).	in ICU patients with normal renal function (CLCr = 120 mL/min), a daily dose of 3000mg CI is needed to achieve Css = 25 mg/L on Day 2.

[160]	Febrile neutropenia (empiric and documented)	*S. epidermidis bacteremia n=2* *Other treatments empiric*	Hematology N=54	- load: 15.5 ± 3.3 mg/kg - CI: 35.4 ± 6.9 mg/kg/d - Css target: >20 mg/L	- Initial Css > 20 mg/L 12% - 32% (21/66) Css >20 mg/mL after dose adjustment. - Only 2 temporarly CrCl increases	monitoring of vancomycin in leukemia patients is necessary • high vancomycin doses are necessary to obtain sufficient levels; • severe renal toxicity is infrequent even for increased doses.
[161]	Empiric and documented	*Not specified*	Pediatric patients N=15	- Conversion DA to CI if subtherapeutic levels - target css: >15 mg/L - CI: 23.8-65.4 mg/kg/day (median, 41 mg/kg/day).	- Mean css = 20.2 mg/L - No nephrotoxicity	Conversion to CI in selected pediatric patients appeared to be safe and well tolerated. Goal plateau Css values were attained in most patients within 24-48 hours

[162]	Suspected and documented	*Not specified*	Intensive care Retrospective N=227	- Load.: <65 kg, 1000 mg; ≥65 kg, 1500 mg - CI: 2000 mg/24 h - Target Css >15 mg/L	- Loading dose correctly applied in 55% of cases - Mean Css: D2: 19.32 mg/L at D2; 21.08 mg/L at D3; - Target level achievement: 70.5% at D2; 84.1% at D3 - Adequate levels at D2 associated with: older age, female sex, higher creatinine concentration, lower body temperature and use of an appropriate loading dose	CI of vancomycin resulted in adequate concentrations in most patients. Some patients may require higher doses, and factors such as kidney function, age and sex, play a role. Note: A weight-based loading dose was superior compared with a non-standardised loading dose.

[113]	Suspected and documented	*Not specified*	Intensive care Retrospective N=207	- Load.:15 mg/kg - CI: 20–30 mg/kg/day based on TBW and adapted to CrCl - Css target: 20-30 g/l.	- 24% (50/207) AKI - Risk factors: severety of illness, lower creatinine clearance at admission, other nephrotoxic agents, longer duration of therapy, higher concentrations of vancomycin during the first 3 days of treatment (Cmean) - Independent factors: (1) early AKI: Cmean (2) late AKI: duration of administration	AKI occured in 25% of patients. Vancomycin concentrations and duration of therapy were the strongest variables associated with the development of early and late AKI respectively.

[163]	Suspected and documented	*Coagulase negative staphylococcus (n=2)* *S. Aureus (n=10)* *MIC: 0.5-3 mg/L*	Intensive care N=22	- Load: 30 mg/kg - CI: 30 mg/kg/day - Target css = 25-30 mg/L	- C24h = 21,3 mg/L (11.6-46.2) - Target attainment at 24h if CrCl < 120 ml/min: 50% (n=14); if CrCl > 120 ml/min: 0% (n=8)	Early TDM and dose adjustement is necessary to rapidly attain target css
[164]	Suspected and documented	*Not stated*	Intensive care N=93	- Load.: 1000 mg (body weight ≤70 kg) or 1500 mg (body weight >70 kg) - CI: 30 mg/kg/day - Target Css = 13.8–20.7 µmol/L	- Patients with ARC (defined as CLCr > 130 mL/min/1.73 m^2) (n=37) had significantly lower Van serum conc. during the first 3 days of treatment (D1, D2, D3) 9.7, 11.7 and 13.8 µmol/L vs. 13.1, 16.6 and 18.6 µmol/L ($p<0.05$)	ARC was strongly associated with subtherapeutic vancomycin serum concentrations on the first 3 days of treatment.

[55]	Suspected and documented	MSSA (n=7), MRSA (n=30), CoNS (n=25), Enterococci (n=7)	Non-ICU N=94	- Load. 15 mg/kg - CI = 2.57 g/24 h adjusted for creatinine clearance - Target css = 25-30 mg/L	- Mean level after loading dose C0h = 27.5 mg/L - Mean C6h = 20 mg/L - 57.4% of patients needed dose increase at 12h - Mean css (>96h) = 27.8 mg/L - Mean free Css = 9.15 ± 6.83 mg/L; - Nephrotoxicity : 10% (2 treatment discontinuations) - Mean steady state AUC 24h = 661 ± 60 mg h/L - AUC 24h/MIC of 667 and 451 as best split values separating failure from success using total and free vancomycin concentrations, respectively	hospital-wide implementation of vancomycin administration by CI is possible but will still require monitoring blood levels because of (i) the difficulties in correctly predicting vancomycin serum concentrations (using presently accepted models based on CCrCl and unanticipated large intrapatient and interpatient variations (ii) the necessity to adjust these levels to the MIC of the causative organism

Notes to Table 2:

[1] main common pathogens only; MIC if reported and above EUCAST breakpoint

[2] CI: continuous infusion; DA: discontinuous administration (usually standard schedule for the antibiotic under study)

[3] for continuous infusion only; load.: loading dose (should normally be reported as mg/kg; if no indication given, the dose shown is assumed to be administered to a normal adult of 70 kg; see also "Practical considerations); infus.: dose used for infusion (should normally be reported as g per 24 h; see "Practical considerations" if reported as mg/kg and per unit of time)

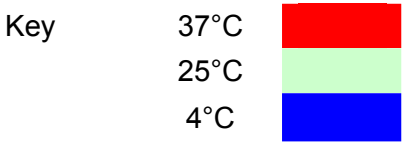
[4] ser. lev.: serum levels in mg/L (at equilibrium and for continuous infusion only unless stated otherwise; most common or mean if several values are reported; range if reported)

[5] if reported by the authors

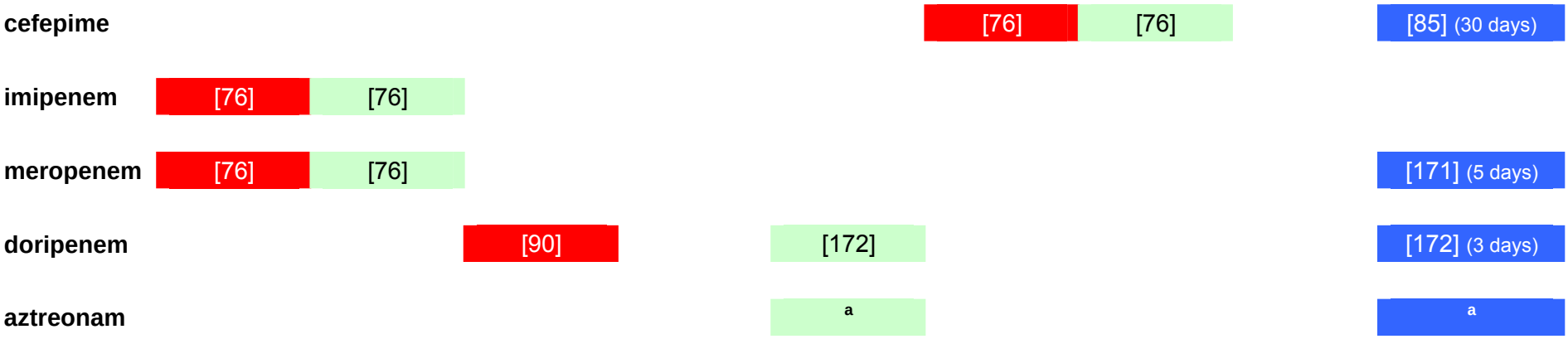
[6] based on authors' assessment with independent confirmation by us based on reading of the publication.

Table 3. Stability of currently used β-lactams in concentrated solutions

Key

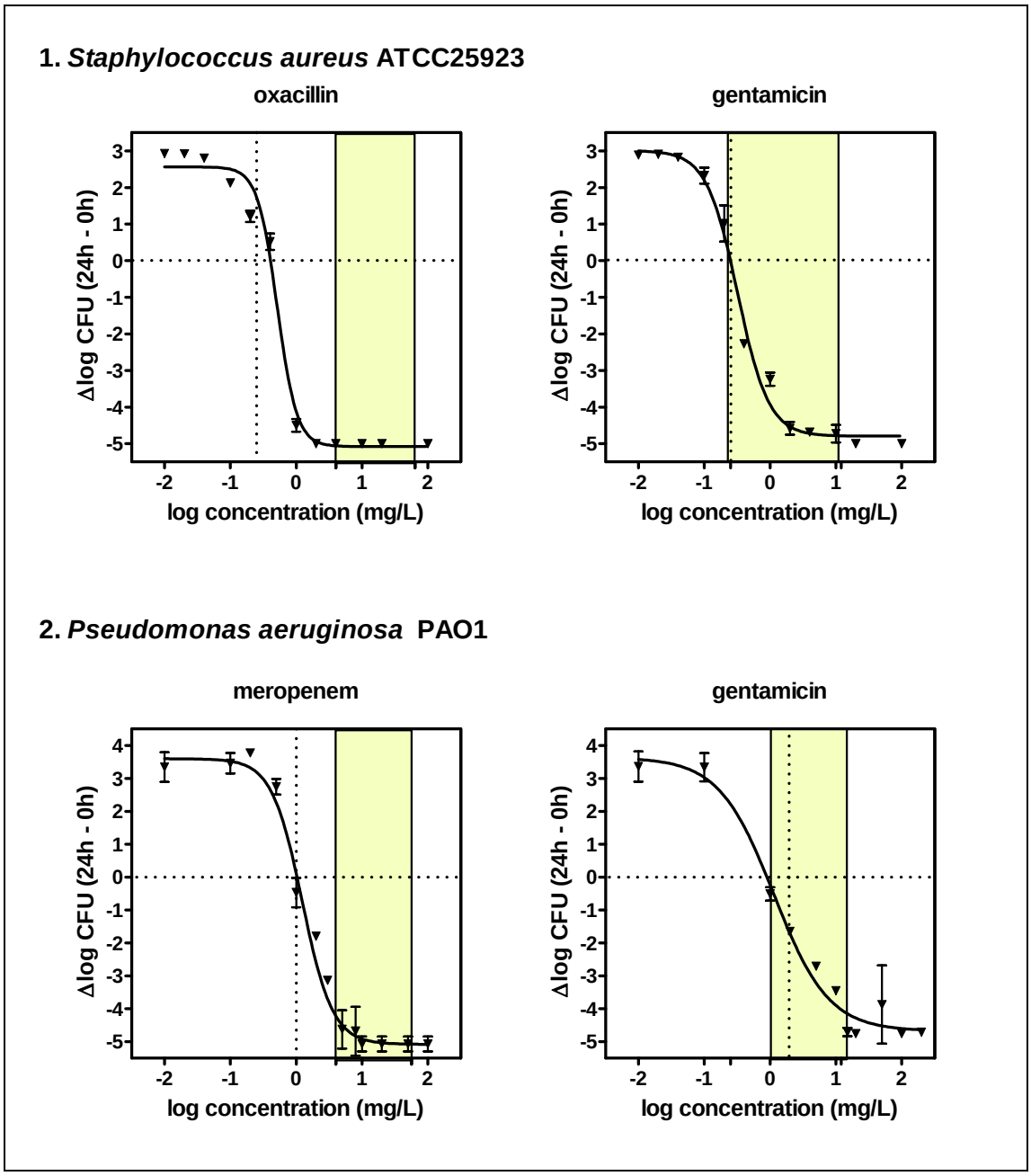


Molecule	time with preservation of 90 % or more of the intact molecule [reference]								
	< 3 h	4-5 h	6 h	8 h	12 h	13 h	20 h	24 h	> 24 h
penicillin G		[75]			[75]				[75]
ampicillin			[165]					[165]	
oxacillin									[166]
piperacillin							[76]		[76]
temocillin								[38]	[38]
cefazolin								[167]	[79] (7 days)
cefotaxime			[168]					[168]	[169](22 days)
ceftriaxone			[170]					[170] (23°C)	[170] (14 days)
ceftazidime				[76]				[76]	[79] (7 days)



[a] Chanteux & Tulkens, unpublished

Figure 1: Concentration-dependence of antibiotics



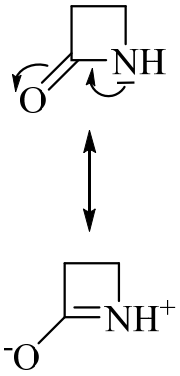
Caption to Figure 1: Concentration-dependence of the activity of two typical β-lactams (left) and an aminpglycoside (right) towards typical Gram-positive (top) and Gram-negative (bottom) organisms (adapted from [173;174]). Bacteria in Muller Hinton broth (cation-adjusted for *P. aeruginosa*) were exposed for 24 h to increasing concentrations of antibiotic (abscissa) spanning from 0.01 to 100 mg/L with the change in the number of viable bacteria from the initial inoculum (typically 10^6 CFU/mL) shown in the ordinate (limit of detection: decrease of 5.2 $\log_{10}$ from this original inoculum. The horizontal dotted line indicate a static effect (no apparent change from the original inoculum). The vertical dotted line shows the MIC of the

corresponding organisms (*S. aureus*: oxacillin: 0.25 mg/L; gentamicin: 0.25 mg/L; *P. aeruginosa*: meropenem: 1 mg/L; gentamicin: 2 mg/L) when tested according to the recommendations of the US Clinical and Laboratory Standards Institute (CLSI). The zone highlighted in yellow correspond to the C_{max}-C_{min} concentration span coomonly observed in humans treated with conventional doses of the corresponding antibiotics ([175;176]; 60 to 4 mg/L for oxacillin or meropenem [assuming a BID schedule]; 15 to 0.25 mg/L for gentamicin [assuming a one-a-day schedule]). The figure illustrates why β-lactams, although being pharmacologically as concentration-dependent as aminoglycosides, will show maximal activity *in vivo* at all clinically-observed concentration, leaving only the time of exposure to become the key determinant for activity (β-lactams kill more slowly than aminoglycosides; not illustrated but see [177]). Conversely, the activity of gentamicin is directly proportional to its concentration over the achievable concentration span.

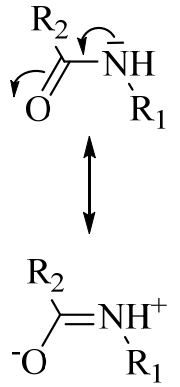
Figure 2: Reasons for instability of β-lactam antibiotics

A: models

A1*: monocyclic β-lactam*

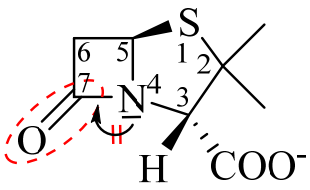


A2*: secondary amide*

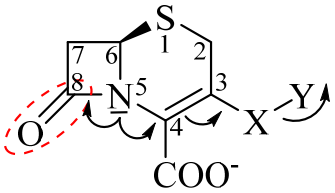


B: β-lactam antibiotics

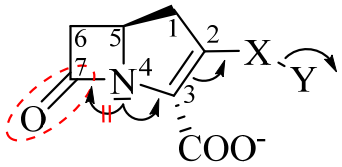
B1*: penam family*



B2*: cephem family*



B3*: carbapenem family*



$X = CH_2$ or heteroatom

Y = leaving group

Caption to Figure 2: Reasons for instability of β-lactam antibiotics

A1 - Monocyclic β-lactams are rather stable because the amide resonance can occur.

A2 - Simple amides are stabilised by resonance.

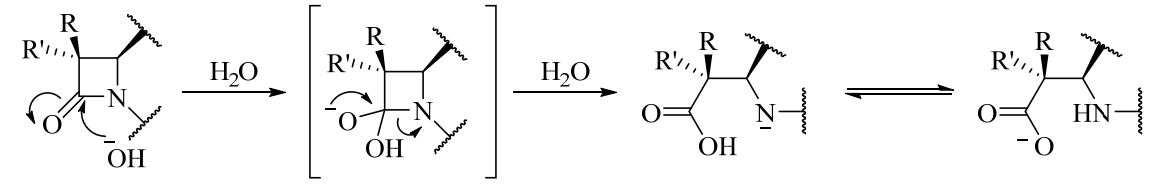
B1 - Penicillins (penams) are unstable because the amide resonance is impaired. Due to the strained bicyclic structure, the nitrogen atom has a pyramidal geometry and its lone pair of electrons is no more conjugated with the carbonyl π electrons.

B2 - Cephalosporins (cephems) are unstable because the amide resonance of the β-lactam ring is weakened by the enamine resonance. The nitrogen lone pair of electrons is delocalised in the fused 6-membered ring.

B3 - Carbapenems (such as imipenem) are highly unstable because they combine the main structural features of penicillins and cephalosporins: strained bicyclic structure preventing the amide resonance and enamine resonance involving the fused 5-membered ring.

Note: In all β-lactam antibiotics, the carbonyl behaves as a ketone, susceptible to nucleophilic attack. This property responsible for chemical instability is also responsible for antibacterial activity.

Scheme 1: Chemical hydrolysis of the β-lactam ring.



nucleophilic attack on the β-lactam carbonyl

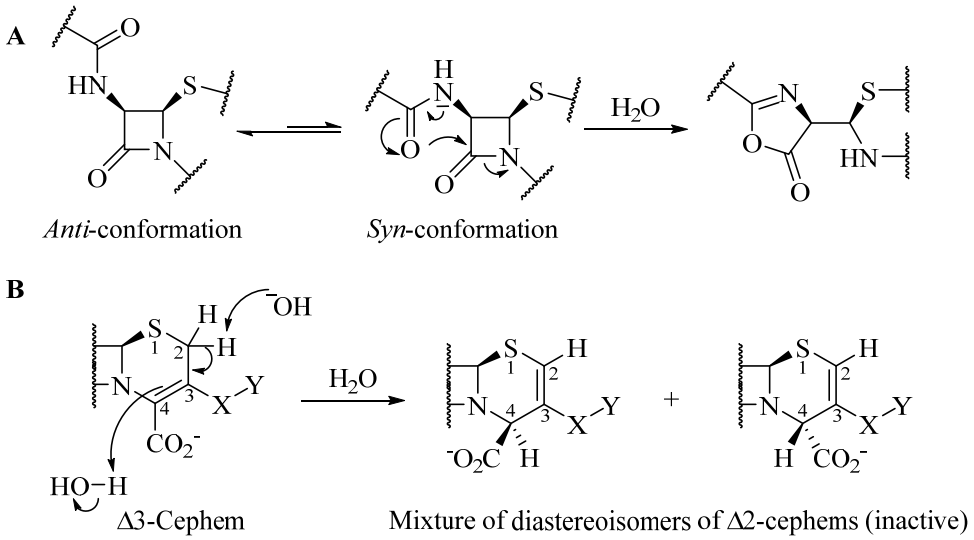
tetrahedral intermediate

ring opening and acid-base equilibrium

Penicillins: R = amide side-chain; R' = H or OCH_3
Cephalosporins: R = amide side-chain; R' = H or OCH_3
Carbapenems: R = H; R' = $CH_3CH(OH)$

R ▬ substituent above the β-lactam plane
R' ┈┈ substituent below the β-lactam plane

Figure 3: Main routes of degradation of β-lactam antibiotics.

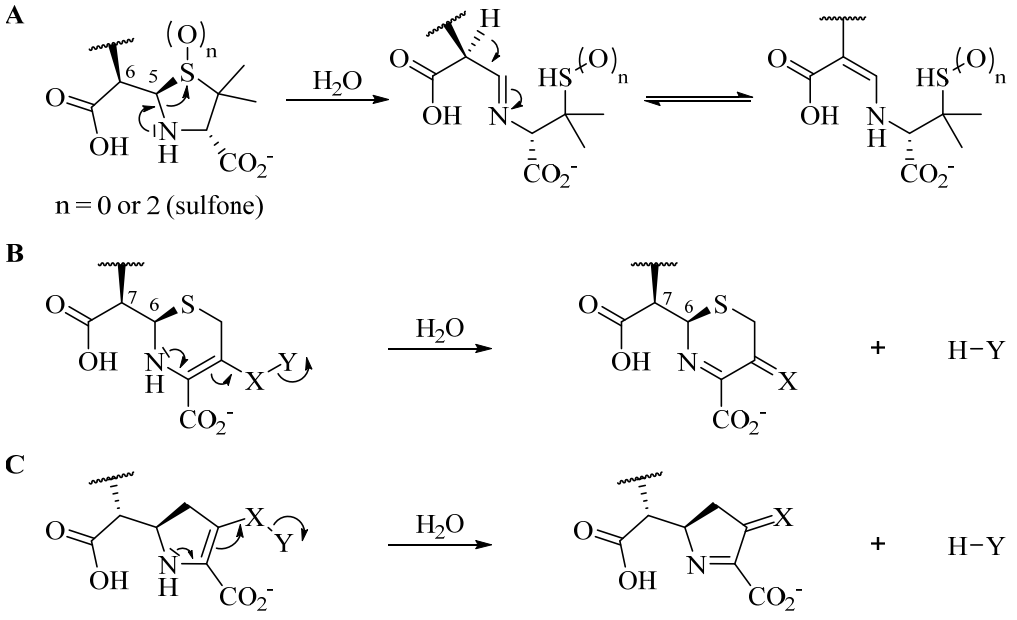


A - In penam and cephem families, the aminoacyl side-chain characterisitic of these classes of antibiotics can contribute to the β-lactam ring opening by anchimeric assistance, *i.e.* an intramolecular nucleophilic attack by the oxygen atom of the amide side-chain, leading to a 5-membered heterocycle (azlactone), precursor of the final hydrolysis product shown in Scheme 1. The *syn*-conformation of the side-chain is required for the occurrence of this reaction. The s*yn*- and *anti*- conformers are in equilibrium, and this equilibrium depends on the particular substituents fixed on the side-chain. This explains the variability of susceptibility to degradation shown for individual molecules in Table 3.

B - In the cephem family, a prototropic reaction, namely the formal migration of one proton C_2-H to the C_4 position accompanied by the double bond migration, renders the molecule microbiologically inactive. The resulting Δ2-cephems exist in the form of two diastereoisomers because the proton can be fixed at position C_4 below or above the plane of the 6-membered cycle. Electron-withdrawing groups at position C_3 favour this mechanism of inactivation. The variability of C_3 side-chain among cephalosporins explains, in part, the differences between individual molecules shown in Table 3 [80].

Mechanisms **A** and **B** can occur simultaneously.

Scheme 2: Evolution of the primary hydrolysis products.



A - In the penam family, the cleavage of the C_5-S_1 bond leads to the 5-membered ring opening. The oxidation of the sulphur atom into sulphone (Tazobactam, n = 2) increases greatly the leaving group ability of the sulphur atom. The mechanism **A** can also occur in the cephem family.

B - In the cephem family, the presence of a potential leaving group Y on the C_3 side-chain allows the formation of a conjugated imine function in the 6-membered ring concomitantly with the loss of HY.

C - In the carbapenem family, the elimination of HY, similarly to the mechanism **B**, is also possible depending on the particular substitutions.

Supplementary Material

Practical recommendations for drug preparation and use

(based on actual publications)

Antibiotic [reference]	**Chemical stability for administration in continuous infusion**	**Clinical use in continuous infusion and *additional recommendations of the authors***
Vancomycin [55;93]	very stable at all concentrations in water or 5% glucose up to > 3 days	• loading dose is essential (20 mg/kg) • infusion must be based on clearance (not on weight) (see practical recommendations at http://www.facm.ucl.ac.be/vancomycin) • monitoring of serum levels remain essential to ensure correct coverage of organisms with elevated MIC (to be checked against EUCAST breakpoints)[a]
β-lactams (this review)	stability is variable and must be examined molecule by molecule (see below)	• loading dose is most easily achieved by administration of the equivalent of the normal initial dose of concentional schedules • infusion: conventional daily dose administered over 24h • monitoring of serum level is desirable especially in case of infection with organisms with elevated MICs (to be checked against EUCAST breakpoints)[a]
Penicillin G sodium [167]	180 mg/ mL in sterile water during 30 days at -20°C, thawed 4 days at 5°C and 12 h at 37°C in portable pump reservoirs	• 12 h at 37°C in portable infusion pump • No more than 6 h at 37°C
Piperacillin sodium [178]	3 and 4 g/ 100 mL in NaCl 0.9 % during 5 days at 23°C protected from light and 21 days at 4°C protected from light respectively	• Ethylene vinyl acetate plastic containers • AutoDose Infusion System bags
Piperacillin/ netilmicin or amikacin [179]	24 h at 29°C after dilution in an L-amino acid solution	• Total Parenteral Nutrition infusion system can be used for newborn infants
Piperacillin/ tazobactam [76;77]	24 h at 37°C and 72 h at 25°C for piperacillin 128 g/ L	• 24 h with infusion pumps at 25 and 37°C
	24 h at 35°C for piperacillin 9, 49.5 and 90 mg/ mL and for tazobactam 1.1, 6.2 and 11.3 mg/ mL	• Elastomeric pump
Piperacillin/ linezolid [180]	3 days at 23°C and 7 days at 4°C for 3 g piperacillin with 200 mg/ 100 mL of linezolid in sterile water	• Infusion containers
Temocillin [38]	24 h at 37°C for 4 g/ 48 mL infusion syringe	

Benzylpenicillin sodium [75]	6-7 days at 3-5°C for 16 megaunits/ 120 mL of NaCl 0.9 %	• No a good candidate for 24 h home iv therapy with standard system • Cold pouch for home iv therapy must be used
Ticarcillin disodium [178]	3 days at 23°C and 21 days at 4°C protected from light for 3 g/ 100 mL in NaCl 0.9 %	• Ethylene vinyl acetate plastic containers -AutoDose Infusion System bags-
Ticarcillin/ clavulanic acid [77]	24 h at 35°C for ticarcillin 12, 70 and 150 mg/ mL and clavulanic acid 0.8, 4.7 and 10 mg/ mL	• Elastomeric pumps
Flucloxacillin/ ceftazidime [181]	24 h at 4°C and room temperature for 2-12 g/ 50 mL and 2-9 g/ 50 mL in NaCl 0.9 %	• Stability and compatibility for continuous infusion at 4°C and room temperature for 24 h
Ampicillin sodium [74]	24 h at 5°C in sterile water or 0.9 % NaCl in infusion-pump pouches for 60 mg/ mL in 0.9 % NaCl or sterile water	• Continuous infusion at 5°C for 24 h only if ampicillin is kept in pouches with portable infusion-pump
Ampicillin/ netilmicin or amikacin [179]	24 h at 29°C after dilution in an L-amino acid solution	• Total Parenteral Nutrition infusion system can be used for newborn infants
Ertapenem sodium [182]	6 days at 4°C (10 mg/ mL in NaCl 0.9 or 0.225 %), 5 days at 4°C (20 mg/ mL in NaCl 0.9 or 0.225 %), 5 days at 4°C (10 mg/ mL in Ringer's solution), 4 days at 4°C (20 mg/ mL in Ringer's solution), 20 h at 25°C (10 mg/ mL in NaCl 0.9 or 0.225 %), 6 h at 25°C (20 mg/ mL in NaCl 0.9 or 0.225 %) and 6 h at 25°C (10 and 20 mg/ mL in Ringer's solution)	• PVC bags • *the long half-life of ertapenem decreases the necessity to use it by continuous infusion if considering PK/PD only*
Imipenem/ cilastatin sodium [76;87]	3.5 h at 25°C for imipenem 8.0 mg/ mL 72 h at 4°C for in sterile water or 0.9 % NaCl (imipenem 2.5 mg/ mL); for 48 h with imipenem 5.0 mg/ mL 9 h at 25°C for in sterile water or 0.9 % NaCl (imipenem 2.5 and 5.0 mg/ mL)	• *Too unstable to be recommended for use by CI*
Meropenem [183]	-In sterile water for injection and in 0.9 % NaCl, at room temperature: 24 h and 10 h for 1 and 20 mg/ mL respectively in PVC bags -In sterile water for injection and in 0.9 % NaCl, at 4°C: 48 h for 1 and 20 mg/ mL respectively in PVC bags -In 0.9 % NaCl for injection,	• PVC bags, commercial easy-to-prepare infusion systems -ADD-Vantage system and Baxter Minibag Plus System • *Maintenance at low temperature is highly recommended unless containers are changed every 4-6 h*

	at room temperature: 24 h and 10 h for 1 and 20 mg/ mL respectively in commercial easy-to-prepare infusion systems -ADD-Vantage system -In 0.9 % NaCl for injection, at 4°C: 48 h for 1 and 20 mg/ mL respectively in commercial easy-to-prepare infusion systems -ADD-Vantage system -In 0.9 % NaCl for injection, at room temperature: 4 h for 2.5 and 20 mg/ mL respectively in Baxter Minibag Plus System -In 0.9 % NaCl for injection, at 4°C: 48 h for 2.5 and 20 mg/ mL respectively in Baxter Minibag Plus System	
[88]	24 h at <5°C for 20 and 30 mg/ mL in NaCl 0.9 %	• Infusion pump with cassette in a cold pouch (replaced every 8 or 12 h)
[89]	24 h at 4°C for 125 and 250 mg/ h infusion rates (equivalent to 3 and 6 g in NaCl 0.9 %)	• Continuous ambulatory drug-delivery infusion pump stored in a cold pouch between 2 freezer packs exchanged at 12 h
[171]	5 days at 5°C for 10 and 20 mg/ mL in NaCl 0.9 % (7 days for 4 mg/ mL)	• PVC bags and elastomeric infusion containers in home therapy • *Maintenance at low temperature is recommended*
[184]	3 h at 32-37°C for 1 g/ 50 mL in normal saline solution	• No administration for > 6 h continuous infusion at room temperature (3 h max. in tropical countries)
Ceftazidime [167]	30 days at -20°C, thawed 4 days at 5°C and 24 h at 37°C in portable pump reservoirs for 36.6 mg/ mL in sterile water	• 24 h at 37°C in portable infusion pump
[185]	8 h at 21-23°C, 96 h at 4°C and 91 days at -20°C for 100 and 200 mg/ mL in sterile water	• Polypropylene plastic syringes
[80]	24 h at 37°C for 1 g/ L in normal saline	• 2 min loading dose and CI of over 24 h in AutoDose Infusion System bags
[79]	1 day at 23°C and 7 days at 4°C protected from light for 2 g/ 100 mL in NaCl 0.9 %	• AutoDose Infusion System bags
Ceftazidime with arginine [186]	-30 days at -20°C, followed by 4 days at 3°C and administered at 30°C over 24 h for 30 mg/ mL in sterile water -10 days at 3°C and administered at 30°C over 24 h for 60 mg/ mL in sterile water	• PVC portable infusion-pump reservoirs and administration less than 24 h when pump reservoir is on the patient's body

[187]	24 h at 22°C, or 7 days at 4°C, then 24 h at 22°C, or 91 days at -20°C, then 24 h at 22°C for 100 mg/ mL in sterile water	• Plastic syringes
Ceftazidime/ aminophylline [188]	24 h at room temperature for 2 and 6 mg/ mL (ceftazidime) in D5W or NaCl 0.9 % and 1 and 2 mg/ mL (aminophylline) in D5W	• Constant-infusion method for 24 h for ceftazidime only • Ceftazidime and aminophylline are chemical incompatible in CI • Ceftazidime was not stable in any admixture containing aminophylline at 24 h; aminophylline remains stable in most cases
Cefepime [84]	24 h at room temperature with light protection for 100 mg/ kg/ 24 h in D5W	• Motorized portable infusion pump with a cold pouch adjacent to the drug reservoir if >29°C
[85]	2 days at 23°C protected from light and 30 days at 4°C for 1 g/ 100 mL in NaCl 0.9% 1 day at 23°C protected from light and 7 days at 4°C for 4 g/ 100 mL in NaCl 0.9 %	• Ethylene vinyl acetate plastic containers -AutoDose Infusion System bags-
[77]	12 h at 35°C for 6, 28 and 50 mg/ mL	• Portable pumps with a cold pack close to the ambulatory drug-delivery device
Cefepime/ metronidazole [189]	-336 h at 4°C (cefepime 1000 and 2000 mg mixed with metronidazole 500 or 1500 mg) -48 h at 23°C (cefepime 1000 and 2000 mg mixed with metronidazole 500 mg) -72 h at 23°C (cefepime 1000 and 2000 mg mixed with metronidazole 1500 mg)	• Use of cefepime and metronidazole in a single minibag or PVC bag
Cefuroxime sodium [186]	-30 days at -20°C, followed by 4 days at 3°C and administered at 30°C over 24 h (30 and 60 mg/ mL in sterile water) -7 days at 3°C and administered at 30°C over 24 h (22.5 and 45 mg/ mL in sterile water)	• PVC portable infusion-pump reservoirs and administration less than 24 h when pump reservoir is on the patient's body
[190]	18-21 days in individual polyolefin bags at -20°C and then light cycle thawing at 4°C for 1.5 g/ 100 mL in dextrose 5 %	• Polyolefin bags
Cefazolin sodium [167]	30 days at -20°C, thawed 4 days at 5°C and 24 h at 37°C in portable pump reservoirs for 73.2 mg/ mL in sterile water	• 24 h at 37°C in portable infusion pump
[79]	7 days at 23°C and 30 days at 4°C protected from light 1 g/ 100 mL in NaCl 0.9 %	• AutoDose Infusion System bags
Cefazolin sodium/ metronidazole [191]	72 h at 8°C for cefazolin sodium 10 mg/ mL and metronidazole 5 mg/ mL	

Ceftriaxone sodium [79]	5 days at 23°C or 30 days at 4°C protected from light for 1 and 2 g/ 100 mL in NaCl 0.9 %	• AutoDose Infusion System bags • *the long half-life of ceftriaxone decreases the necessaity of continuous infusion if considering PK/PD only.*
Cefotaxime/ netilmicin or amikacin [179]	24 h at 29°C in dilution in an L-amino acid solution	• Total Parenteral Nutrition infusion system can be used for newborn infants
Cefotaxime/ metronidazole [192]	72 h at 8°C for cefotaxime sodium 10 mg/ mL and metronidazole 5 mg/ mL	
Cefotaxime/ tinidazole [193]	8 h at 20°C for 1 g of cefotaxime added to 200 mL tinidazole glucose injection solution (tinidazole 0.4 g)	
Cefpirome [76]	23.4 h at 25°C and 7.15 h at 37°C for 32 g/ L	• Not recommended for use in portable infusion pumps carried under clothes for prolonged periods and suitable for infusion from external pumps
Cefotetan disodium [194]	2 days at 25°C, 41 days at 5°C and 60 days at (-10)°C for dilution in dextrose 5 % and NaCl 0.9 %	
Cephamandole nafate [195]	24 h at room temperature without protection from light or 7 days at 4°C for dilution in glucose 5 % or NaCl 0.9 %	• 1 h infusion using PVC infusion bags
Cefamandole nafate/ metronidazole [196]	2 h at 25°C or 6 h at 5°C for 2 % solution of cefamandole in metronidazole injection (0.5 %)	
Aztreonam [197]	24 h at 37°C; 8 days at 5°C or 6 months at -20°C in portable pumps reservoirs for 60 mg/ mL	• Portable pump reservoirs in home programme over 24 h at 37°C
[76]	24 h at 37°C in portable infusion pumps carried under clothing for 100 g/ L	• Portable infusion pump carried under clothing
[77]	72 h at 35°C for 1.1, 6.2 and 11.3 mg/ mL	• Elastomeric pumps
Aztreonam/ ampicillin sodium/ sulbactam sodium [198]	-30 h at room temperature (10 mg/ mL diluted in NaCl 0.9 %) and 94 h at 4°C (10 mg/ mL, 20 mg/ mL, 10 mg/ mL diluted in NaCl 0.9 %)	• PVC minibags
Aztreonam/ vancomycin hydrochloride [199]	7 days at 32°C, 14 days at 23°C, 31 days at 4°C for 4 mg/ mL (aztreonam) and 1 mg/ mL (vancomycin) in dextrose 5 % 7 days at 32°C, 31 days at 23°C and 4°C for 4 mg/ mL (aztreonam) and 1 mg/ mL (vancomycin) in NaCl 0.9 % 3 days at 32°C and 23°C, and 14 days at 4°C for 40 mg/ mL (aztreonam) and 10 mg/ mL (vancomycin) in dextrose 5 %	• PVC containers

	3 days at 32°C and 23°C, and 14 days at 4°C for 40 mg/ mL (aztreonam) and 10 mg/ mL (vancomycin) in NaCl 0.9 %	
Aztreonam/ linezolid [180]	7 days at 23°C or 4°C (2 g aztreonam with 200 mg/ 100 mL of linezolid in sterile water)	• *Infusion containers can be carried under clothes because of drug sufficient stability*

Aims and objectives

The first and original objectives of our work were, trough an **observational study**,

- to critically assess vancomycin administration as routinely performed in our institution [twice daily dosing (BID)].
- to evaluate adherence of health care practitioners to local hospital guidelines for vancomycin TDM (sampling of peak and trough levels).
- to quantitatively measure the deviations from recommended practices.

Based on the analysis of the data obtained during this first part of the study, we decided to perform the following studies using the methods of **qualitative research**:

- analysis of the reasons for non compliance to vancomycin prescription guidelines by medical personnel
- evaluation of the processes underlying the poor performance of routine TDM practice by all involved health care professionals.
- collection of information on health care practitioners' perception about routine TDM practice
- exploration (with all involved personnel) of possible corrective approaches in order to define "best" future interventions aiming at improving vancomycin prescription and its TDM.

Using the results obtained during this second part, our aims have been, through the design and realization of a clinical study:

- to evaluate the feasibility and impact of hospital-wide implementation of continuous infusion coupled to centralized preparation of ready to use infusion bags and a nomogram for dose adaptation in non-ICU patients under the supervision of a clinical pharmacist and an infectious diseases physician.

- to assess toxicity, efficacy, pharmacokinetics and pharmacodynamics of vancomycin administered by continuous infusion in non-ICU patients.
- to assess health care practitioners' perception of and satisfaction towards these interventions.

Having achieved this third part of our study, our final aims were:

- to provide a detailed overview of studies comparing discontinuous administration and continuous (or prolonged) infusion of vancomycin and beta-lactams for **review purposes**.
- to provide **clinical practice guidelines** concerning the use of continuous infusion of vancomycin and beta-lactams considering pharmacokinetics and pharmacodynamics, toxicity, clinical efficacy, drug stability and compatibility, cost and implementation in routine practice.

Introduction to Chapter 2 (qualitative study)

Measurement of serum vancomycin concentrations by therapeutic drug monitoring is widely recommended in routine practice and allows dose readjustment on an individual patient level with the aim of optimizing efficacy and avoiding toxicity.

Recent North American guidelines recommend conventional twice daily dosing (BID) for this antibiotic which was the common practice in our institution. Historically, standard dosing (1g q12h) and associated peak and trough levels of 30-40 mg/L and 5-10 mg/L respectively have been applied for this agent. Because of concerns about the quality of peak levels in routine clinical practice and because of more resistant organisms, recommendations for vancomycin BID have changed to the measurement of trough levels only with higher target values of 15-20 mg/L.

An antibiotic order form had been introduced by the infectious disease management team in our institution and all vancomycin treatments were followed up closely by infectious disease physicians, clinical microbiologists and pharmacists. MICs of causative organisms were determined on a routine basis.

Serious concerns existed about TDM practice as serum concentrations measured and dose adaptations calculated were frequently perceived as unrealistic and untrusty. My role as a pharmacist was to evaluate and if necessary improve TDM practice for vancomycin in collaboration with the existing infectious disease management team.

It was decided to conduct an observational study in order to assess baseline quality of vancomycin administration and TDM and whether their performance was in accordance with local hospital guidelines. As important quality issues were observed according to timing of drug administration and sampling and data communication to the clinical laboratory leading to errors in dose adaptations calculated, a qualitative study was conducted to understand the underlying reasons. It consisted in running focus groups with health care practitioners in order to identify adherence barriers to guidelines and processes underlying their inappropriateness. This study identified insufficient education of health care practitioners and organizational issues related to drug administration and sampling as the main causes for the observed deficiencies.

These two steps make the first part of the paper presented in this chapter.

Because of the negative aspects of these parts it was considered inappropriate to submit them as such to an International Journal. The data were therefore kept for future use. After completion of the study reported in chapter 3 (implementation of continuous infusion), we noted that most health care professionals seemed highly satisfied with the results of the intervention. We therefore decided to add a third step in our study, namely to assess qualitatively and quantitatively how continuous infusion was perceived and implemented in routine practice. We also assessed the impact of continuous infusion on the quality of TDM performance.

This last step has been bundled with the two first ones to submit the paper presented in this chapter.

Submitted

Overcoming Insufficiencies in Therapeutic Drug Monitoring of Vancomycin by Switching from Intermittent Administration to Continuous Infusion: a Combined Observational and Qualitative Study.

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ABSTRACT

Background

Therapeutic Drug Monitoring (TDM) of vancomycin is widely recommended yet its performance in routine practice is rarely assessed.

Methods

Baseline: vancomycin BID (4 months, 46 patients, 132 samples). Intervention: switch to continuous infusion [CI] with centralised drug preparation (1 year, 92 patients, 224 samples). Process indicators: (i) correct sample timing; (ii) implementation of TDM-dosage readjustment recommendations; (iii) prescribed daily dose in accordance to hospital guidelines; (iv) proportion of serum levels values within the recommended ranges. Qualitative studies: focus groups and structured interviews with ward and laboratory personnel to identify difficulties and barriers in TDM performance at baseline and assess satisfaction/dissatisfaction with the intervention.

Results

TDM performance was poor at baseline (BID) with only 53% of peak and 66% of trough samples collected within 30 min from scheduled time, 13% of peak levels and 48% of trough levels within recommended therapeutic ranges [84% too low], 32% implementation of dosage re-adjustment recommendation, and 83% incorrect prescribed daily doses (average: 20% lower). Insufficient knowledge and training of HCPs, and organisational issues were the main reasons for poor adherence and perceived as critical barriers. Implementation of CI was associated with significant improvement ($p<0.0001$) for correct sample timing (97.0%), drug levels within recommended range (66.8%); implementation of dosage re-adjustment recommendations (94.4%) and correct daily doses (86%). Centralised preparation, CI and TDM were perceived by ward personnel as reliable and contributing to the quality of care.

Conclusions

Implementation of CI of vancomycin was effective for improving its TDM performance in routine practice in non-ICU wards.

Introduction

Therapeutic drug monitoring (TDM) of antibiotics is routinely recommended in hospitalized patients.[1-3] While its clinical usefulness has been well documented in settings ensuring a high level of quality for administration and sample timing,[4-7] it has continuously shown major insufficiencies in routine clinical practice.[8-13] This triggered us to assess the quality of routine TDM of vancomycin in a teaching hospital where this drug used to be administred by a conventional twice-daily (BID) mode. We performed an observational study at baseline examining the adherence to guidelines for TDM and its performance, focusing on correct sample timing, implementation of dosing readjustments recommended by the laboratory based on assays of collected samples, correctness of prescribed daily doses according to guidelines, and proportion of serum levels within the recommended ranges. We then applied the methods of qualitative research[14-18] to uncover the human and organizational factors affecting TDM performance. Based on the results of this first study, we decided to implement the use of vancomycin administration by continuous infusion (CI), together with a nomogram for dose adaptation in all non-ICU wards of the hospital. This mode of administration was selected because it is pharmacodynamically equivalent to the conventional BID schedule since vancomycin is primarily a AUC_{24h} /MIC-dependent antibiotic,[19] while presenting several advantages in terms of ease of administration and monitoring[20-24] and the possibility of a controlled centralised preparation procedure.[25] The pharmacokinetic, pharmacodynamic and toxicologic data of this second part of our study have been reported elsewhere,[26] as well as the practical conditions under which this mode of administration can be safely implemented in terms of drug stability and compatibility.[27] The present report focuses on a critical analysis of the reasons why (i) the conventional BID mode of

administration of vancomycin may lead to major performance insufficiencies in routine practice and (ii) how continuous infusion may help to significantly improve the performance of TDM by overcoming a number of practical difficulties and barriers raised by involved ward and laboratory personnel and gaining their support.

Methods

Clinical setting and ethical approval

The study was conducted at a 400-bed tertiary care teaching hospital where Infectious Diseases and Microbiology diagnostic and therapeutic supports were available together with local hospital guidelines for antibiotic use and TDM based on a local adaptation of the Sanford's Guide[28] that was approved by the attending physicians. The study protocol was approved by the Ethical Committee of the CHU-UCL Mont-Godinne (study no. 41/2006).

Observational studies

During 4 months before and 1 year after implementation of CI, one of us (E.A.) identified all patients receiving vancomycin in non-ICU wards (covering >75% of prescriptions of this antibiotic in the hospital). At that time, all patients were receiving vancomycin by short (1h) infusion given every 12h, and monitoring was made based on peak and trough levels (sampling made 2 h after the end of the infusion and immediately before the next administration, respectively) because this double sampling was considered to allow for a more correct calculation of the AUC_{24h} (used for suggestions of dose readjustments) than the commonly recommended "trough level sampling only".[3] Patients with limited survival expectancy (< 3 days), with moderate to severe renal failure, or receiving treatment for less than 72 h were excluded from the study. All data were collected prospectively using a standard record sheet.

In practice, E.A. visited each ward in which vancomycin treatment had been ordered (based on analysis of pharmacy records [vancomycin was a restricted antibiotic requiring special release from the pharmacy]) 15 min before the scheduled

time of administration (based on readings of prescriber's order) and recorded the following data: (i) the actual timing of the peak and trough level sampling; (ii) the timing of administration, (iii) the actual dose administrated, (iv) the actual times of administration and/or sampling entered in the patients' medical chart. Clinical data introduced in the laboratory electronic system for calculating dose regimens based on TDM results were retrieved and compared with the data supplied by the ward to the laboratory and those entered in the patients' medical chart (patient's identification, actual dose, administration schedule, timing of the previous dose, peak and trough samplings). Within 48h of the issuance of the TDM-based recommendations for dosage readjustment, E.A. checked whether these were applied by the ward personnel, and any difference was noted.

Quantitative data pertaining to correctness of the prescribed daily dose, sample timing, proportion of sample values within the therapeutic range, and actual implementation of the TDM-based recommendations for dosage readjustment were compared before and after implementation of CI.

The correctness of vancomycin administration and the pertinence of its TDM ordering was assessed by E.A. (Clinical Pharmacist) and B.D. (Infectious Diseases senior physician), working independently and using predefined criteria corresponding to the approved local guidelines at the time of the study. In case of divergence, reconciliation was made through mutual discussion.

Qualitative studies

Five months after the baseline study (patients treated with vancomycin BID), focus group interviews were organised to collect basic information about the opinions of health care practitioners and laboratory personnel about the performance of TDM and of difficulties and barriers experienced in their practice. Participants (24 from 29

contacted) were purposively sampled according to the number of years of experience with antibiotic use and TDM, to create 4 focus groups balanced to include individuals with different medical and/or scientific backgrounds (see Results for the actual composition of these groups). Participants were asked about their perception and attitude towards TDM service and other points of related interest (in the context of the BID administration of vancomycin), with emphasis on participants' interactions.[29-31] A validated semi-structured topic guide containing questions about the quality of antibiotic use and therapeutic drug monitoring was used with questions about (i) perceived quality, (ii) reasons underlying their adherence or non-adherence to TDM guidelines, and (iii) strategies for improvement if needed. Discussions were led by experienced investigators not involved in the study and not employed by the hospital. Data from field observations were included in the questions asked to the participants to evidence behaviours of which they may have been unaware. Interviews lasted for 2 h. Fields notes were taken by E.A.

One year after implementation of the CI mode of administration of vancomycin, and (i) after the completion of the analysis of the data for pharmacokinetics, pharmacodynamics and toxicity[26] and (ii) after the clinical pharmacist in charge (E.A.) had left the Institution, interviews were conducted with 24 participants (20 of them had participated to the focus groups at baseline; 4 additional participants with comparable medical background and experience to the corresponding baseline participants were included). During these interviews, the respective advantages and drawbacks of CI were discussed and the main points of satisfaction/ dissatisfaction towards the change from BID to CI administration of vancomycin were recorded.

Interviews were audiotaped, and transcribed *verbatim.* Transcripts were analyzed using QSR NVivo® software (QSR International Pty Ltd, Doncaster, Victoria, Australia). E.A. and J.P. independently developed a series of codes for the

first focus group interviews, which showed 87% agreement. For all divergent codes, a consensus was reached after discussion. Emerging themes were discussed with researchers and selected participants in order to validate our analysis and heighten reflexivity. To enhance validity, we constantly looked for data contradicting our findings. All interviews were conducted, recorded, and analysed in the language of the participants and of the investigators (French) to ensure correct interpretation of the participants' declarations. Translation into English for the purpose of this publication was made by E.A. and P.M.T. with the help of a native English colleague with medical education and knowledge of the topic of study.

Statistical analyses

Statistical analyses were performed using Instat version 3.10 (GraphPad software, San Diego, CA) and JMP version 10 (SAS, Cary, NC).

Results

Observational studies

Table 1 shows the patient demographics and vancomycin treatment indications during the first (baseline; BID) and the second (CI) observational studies. While no major differences were observed between the two cohorts in terms of age, there were more documented infections, MRSA colonisations, bloodstream, prosthetic joint and respiratory tract infections, and patients received anticancer chemotherapy in the CI group, due to changes in population case-mix over the two periods.

Table 2 shows a comparison of the process indicators that were recorded during the first (baseline; BID) and the second (CI) periods. Globally, all four processes did poorly score for the BID administration. Of note, deviations from correct time of sampling were almost as important for peak and through levels (see Figure SP1 in the Supplementary Material; in several cases, the observer noted that samples labelled as through but drawn later than scheduled had actually been collected *after* the administration of a new dose of vancomycin). For all processes, scores were significantly higher after implementation of the CI mode of administration.

Qualitative studies

Table 3 shows the distribution and professional background of participants to the qualitative studies. Transcript analysis of the focus groups organised after the first period (baseline; BID) allowed for the construction of the dendrogram (node tree) shown in Figure 1 based on actual records. Branches of the dendrogram represent potential adherence barriers to antibiotic monitoring guidelines identified during a first (pass) analysis without any preconceived idea about their respective importance.

Table 4 shows the main emerging themes (within the 4 conceptual groups of Figure 1) identified during our analysis which could potentially explain why TDM performance was poor and many deviations from guidelines occurred during the baseline period. Of particular significance (based on number of comments, agreement amongst the participants, and analysis of the results of the intervention study) were the comments related the following conceptual groups, namely (i) the socio-cultural and structural elements (inertia of practice, lack of motivation and personal involvement, and organisational problems); (ii) the training and information aspects (mainly insufficient (post-)graduate training in pharmacokinetics; (iii) the low harm-benefit ratio of TDM (too much pain and discomfort imposed to the patient for the amount of information really used for improving therapy). Conversely, comments and discussions concerning the clinical decision making process did not really address the issues related to TDM and were, therefore, not used for our analysis.

Table 5 illustrates how participants expressed (and changed their) opinions about themes related to these 3 key conceptual groups during baseline [BID] and post-intervention [CI] interviews. Firstly, difficulties related to sociocultural and structural elements, including inappropriate techniques, that were considered of paramount importance at baseline (BID) were corrected or largely minimized after intervention (CI) due to clearer definition of responsibilities, easier sample

preparation, and easier sample collection; Secondly, CI was perceived as necessitating less background knowledge in pharmacokinetics, hence facilitating the nursing and patient's surveillance and reducing errors; Thirdly, TDM usefulness (including harm-benefit ratio) was considered as much higher with CI. Two main perceived limitations in the implementation of CI, however, were the necessity to maintain a dedicated infusion line and the need of pumps (uncertain availability and cost). Table 5 also illustrates how TDM performance was perceived by participants as being much improved after intervention.

In a last stage, we ran a survey among prescribing physicians (n=7) concerning (i) their actual use of CI of vancomycin in routine practice in patients with normal renal function; (ii) declared follow-up of TDM dosage readjustment recommendations; (iii) global satisfaction with the hospital-wide implementation of CI and the corresponding TDM (expressed on a scale from 0 to 5 [from lowest to highest level of satisfaction]. Results were very positive with frequency of CI use at 99% (min.: 95; max.: 100), follow-up of TDM dosage readjustment recommendations at 96% (min.: 95; max.: 100) and satisfaction level at 4.5/5 (min.: 4; max.: 5). Global satisfaction was also assessed with nurses (n=10) and laboratory personnel (n=8), revealing a similarly high global satisfaction (scores: 4.3/5 [min.: 3.5; max.: 5] for nurses; 4.4/5 [min.: 4; max.: 5] for laboratory personnel).

Discussion

Poor performance of TDM in routine practice is not an unanticipated finding and our data concerning the BID mode of administration of vancomycin are largely in line with those of other similar recent studies.[12,13,32] The present report, however, significantly adds to the available literature in two respects. First, it combines observational and qualitative approaches, allowing for a proactive exploration of factors underlying the poor performance of TDM at baseline. This multidisciplinary approach has already been successfully applied for quality improvement in other areas of medicine such as pain management[33] or anaesthesia[34]. Second, we were able to analyze the and measure the impact on TDM performance after changing from BID to a CI mode of administration of vancomcyn, and at the same time to assess its acceptance by health care professionals.

Our decision to implement the CI mode of administration of vancomcyin was not only based on pharmacokinetic/pharmacodynamic considerations suggesting its similar efficacy[19] but also on the large body of evidence supporting CI as a mean to obtain stable vancomycin levels at the desired target on a population level.[21] This was actually obtained and further documented in our setting.[26] Furthermore, we also realized that CI coupled with a centralized preparation procedure met many of the concerns of the clinicians concerning the value of vancomycin TDM because it overcame several of the barriers identified as critical for its correct performance when using its BID mode of administration. Thus, this approach was considered as scientifically correct while also and minimizing the necessity of training health care professionals in practical issues of pharmacokinetics related to peak and trough samplings. It was triggered by our finding that the three main reasons (conceptual groups) underlying the poor performance of vancomycin TDM when using the conventional BID schedule were (i) socio-cultural and structural elements (that led

through inertia of practice, lack of motivation and of personal involvement to the use of inadequate techniques), (ii) lack in training and information especially with respect to pharmacokinetics (leading to major insufficiencies in the control of sample timings), and (iii) harm-benefit ratio considerations, with the perception that TDM offering was quite poor in this context. These issues were considered as insurmountable within the limits of our local teaching and coaching capabilities. Most interestingly, failure to implement laboratory recommendations during baseline actually found its origin in the intuitive perception that TDM sampling could not be trusted because of issues related to both uncertainty of actual drug infusion rates and of sample collection timing. Each of these points were specifically addressed and corrected when moving from the BID to the CI mode of administration, which was made easier for nursing (and perceived as more reliable) through the centralised preparation of the drug and its administration by means of infusion pumps.

We cannot, however, exclude the key role of two unavoidable influential effects. The first one is the so-called “Hawthorne effect”[35] (improvement of outcomes when surveillance is in place or an action is launched), which might have influenced in a positive way the results of our observations. Thus, the advantages of the CI may fade away unless close monitoring of the performance of TDM is maintained. A second one may be that the clinical teams were positively influenced by the active presence of the clinical pharmacist, which by it-self, could have resulted in an increased confidence in recommendations for dosage adjustment. However, since the last survey was made after the clinical pharmacist had left the ward, it also means that her influence, if any, was long-lasting.

Lastly, we need to emphasise that CI did not decrease the need of vancomycin monitoring. As explained in our previous publication,[26] targeted serum levels were obtained at the population level but important inter- and intra-patients variations were nevertheless seen. The new message brought by the present report is that not only TDM actual performance with CI was much better but that its acceptance (in terms of efforts for health care professionals and harm-benefit ratio for patients) was markedly improved over the baseline (BID) period.

Our study is limited by the number of patients enrolled and by its performance in a single hospital, which could prevent from generalisation. However and as mentioned above, our observational data concerning the baseline period of our study (BID) are in line with those reported by others in hospitals with a similar general setting. Moreover, several other reports support the usefulness of the CI administration. Our conclusions can therefore be decontextualised (an important point in qualitative research). More specifically, this applies to the identification of organisational and structural issues common to antibiotic usage and guideline implementation[36,37], and aspects related to training and information resources concerning antibiotics,[36,38-40] as well as, more broadly speaking, passive attitude towards learning observed in other medical situations.[41] Thus, we can reasonably conclude that the simplifications in daily ward activities made possible by the use of CI, the lesser need of understanding pharmacokinetics and why accurate sampling times are critical when using the BID mode of administration, and the improved reliability and ease of interpretation of TDM data, all together significantly contributed to the improvements seen. Those may also be expected in other similar hospital settings.

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Transparency declaration

None of the authors have any conflict of interest.

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Table 1: Observational studies: demographic characteristics of patients

characteristic		vancomycin mode of administration			
		discontinuous (BID) [a]		continuous (CI) [b]	
		empiric (n=24)	documented (n=22)	empiric (n= 23)	documented (n= 69)
Age (years)	- mean ± SD	61 ± 13	62 ± 12	62 ± 16	63 ± 13
	- median	62	61	61	62
	- min. - max.	28 - 86	35 - 78	28 - 94	28 - 85
Sex (M/F)		11/13	16/6	19/4	50/19
MRSA colonization		6 (13%) [c]	6 (13%)	8 (35%)	28 (41%)
Diagnostic					
- bacteraemia		0	12 (26%)	1 (4.5%)	29 (42%)
- skin and soft tissue infection		3 (7%)	1 (2%)	4 (17%)	3 (4%)
- bone and joint infection		5 (11%)	2 (4%)	1 (4.5%)	8 (12%)
- prosthetic joint infection		1 (2%)	1 (2%)	5 (22%)	15 (22%)
- abdominal infection		1 (2%)	2 (4%)	0 (0%)	5 (7%)
- respiratory tract infection		1 (2%)	2 (4%)	2 (9%)	8 (12%)
- fever of unknown origin		12 (26%)	0	7 (30%)	0
- other		1 (2%)	2 (4%)	3 (13%)	1 (1%)
Anticancer chemotherapy		5 (11%)	5 (11%)	11(48%)	19 (27%)

[a] daily dose divided in two administrations ordered at 12h interval each and to be infused over a period of 60 min

[b] daily dose ordered for administration by infusion over 24 h (with the help of an infusion pump) with the first administration preceded by a 60 min infusion of a loading dose (see details in ref. [26]).

[c] no. of patients (percentage of patients receiving vancomycin with the corresponding protocol (BID or CI)

Table 2: Comparison of TDM process measures for twice daily (BID; baseline) and continuous infusion (CI; post intervention) modes of administration of vancomycin

Criterium	vancomycin mode of administration		p-value
	BID	continuous infusion	
Sample timing within 30 min. from scheduled time	61.3% [81/132] [a]	97.0% [217/224]	p<0.0001 *
Implementation of TDM dose recommendations	32 % [21/66]	94.4% [205/218]	p<0.0001 *
Prescribed daily dose in accordance with hospital guidelines	17% [95/560]	86% [1395/1622]	p<0.0001 **
% of serum levels in the recommended ranges	33.3% [37/112] [b]	66.8% [159/238]	p<0.0001 *

* Fisher exact test two sided

** Chi-square two sided (because of the large number of observations)

[a] number of total observations (see Table 1 for the number of patients)
[b] most deviations were towards lower than expected values (average: 20 %)

Table 3: Demographic and professional characteristics of participants to the qualitative studies.[a]

Profession	**number**	**junior / senior**	Age > 40 years
Physicians [b]	7	4 / 3	3
Nurses [c]	10	6 / 4	5
Laboratory personnel	8	5 / 3	3

[a] all individuals except 4 participated to both rounds of study (baseline [BID] and post-intervention [CI]; the 4 participants recruited for the second round because of unavailability of the original participants had a matched profession, activity, and experience of TDM;

[b] Medical Doctors specialized in haematology, pulmonology, oncology, general surgery, vascular surgery, internal medicine, or infectious diseases;

[c] working in wards of haematology, pulmonology, oncology, internal medicine, general surgery, vascular surgery, orthopaedic surgery, neurosurgery, or intensive care

Table 4: Emerging themes identified during the analysis of the transcripts of the focus groups and related to perceived as explaining low TDM performance and deviations from local TDM guidelines during the baseline phase (BID).

Conceptual group	Emergent theme [a]
Clinical decision making process	- *diagnostic and prognostic uncertainty* - *perceived severity of the illness* - *patient's frailty* - *patient's comorbidities*
Socio-cultural and structural elements	- *inertia of practice* - *lack of motivation and personal involvement* - insufficient interdisciplinary collaboration [b] - unclear definition of responsibilities [b] - ill-adapted techniques [c]
Training and information	- *insufficient (post-) graduate education* - 'teacher-centred' learning approach - incomplete and/or difficult to apply local guidelines [d] - conflict between local guidelines and external guidelines [d]
harm-benefit ratio of TDM	- *patient too frail* - unnecessary samplings for the information gained [e]

[a] themes corresponding to those noted as such in the dendrogram (node tree) shown in Figure 1 are in italic. See notes for the other themes.

[b] themes arising from points 2.1 and 2.2 of the dendrogram of Figure 1.

[c] additional theme recognized as of critical importance when analyzing the results of the second round interviews (post-intervention; see Table 5).

[d] theme arising from point 4.4 but separated into two distinct items based on further analysis of the transcripts of the focus groups (1st round)

[e] additional theme introduced based on further analysis of the transcripts of the focus groups (1st round)

Table 5. *Verbatim* transcripts from the focus groups (baseline [BID] and interviews (post-intervention [CI]) illustrating key issues related to emergent themes from 3 conceptual groups (socio-cultural and structural elements. training and information and harm-benefit ratio; see Figure 1 and Table 4) considered as critical for the analysis of TDM performance before and after intervention. Comments in italic denote those considered as negative in terms of participants' assessment. Texts between square brackets correspond to authors' adaptation of the transcripts for better understanding of the meaning of the actual declarations. Key: N = nurse; M = Medical Doctor; L = laboratory personnel. Comments in italic are considered as being negative and/or to express criticism of the situation in which TDM is performed.

Baseline (BID)	Post-intervention (CI)
1. Sociocultural and structural elements	
1.1. Inertia of practice, lack of motivation and of personal involvement, unclear definition of responsibilities	
N5: *One does not always do TDM, it all depends on the Junior Officer.*	N8: Doctors simply order to take the samples along with the general sampling for biology in the morning and we just take the samples. it's easy. In the beginning, it's every day. But once the patient's [vancomycin] blood levels are stable, samples are taken less frequently.
N2: *We schedule our blood sampling by ourselves… the doctors do not even know when it happens*	
N7: *It is quite a job to have the order filled out [by the physician]. If, in addition, they also need to get information about timing, [it's even more difficult] …*	
N2: *The administrative assistant writes the order … even though, under normal circumstances, the order must be written by the doctor.*	

M2: *The problem is that it is not our [the physicians'] task to fill out the time [of administration and sampling], because it is the person who is going to give the antibiotic and to perform the blood sampling who must fill out the times…*

L2: *If the dose or the sample timing is missing on the TDM form, we try contacting the ward but we hardly ever are able to contact the person who can get us the right information.*

L5: Samples are almost always collected correctly now. If we measure vancomycin levels that are too high, we contact the Infectious Disease Physicians. If it's really very high levels, we contact the ward physicians to obtain an new sample immediately [which is meaningful now since the blood levels are supposed to be constant] but this hardly ever occurs.

1.2. Ill-adapted techniques

1.2.1. Drug preparation

N6: *We prepare the infusion sets on the ward. We've already had errors in drug preparation. Sometimes we have to re-prepare the dose based on the TDM result.*

N10: We don't have to make the preparation ourselves anymore. We just take the infusion bag and adjust the infusion rate. It's simpler and it takes less time. About 25 min per treatment day I would say.

1.2.2. Frequency of drug administration

N4: *Administration can fall out of regular medication tours for this antibiotic. This is difficult to manage because we often have emergencies to take care with.*

N2: *If a [another] patient calls us we will first go there and the administration will be delayed sometimes for long… .*

N7: I prefer CI , it's easier and in my opinion it's better. You just have to change the infusion set when it's empty. The pump will go into alarm so you don't have to think about it.

M6: We change the dose if needed and it's OK for the next 24h, we don't have to intervene several times a day. Dose adaptation has just become easier.

1.2.3. Control of the infusion rate and availability of access line

N2: *The duration of infusion is the most important problem. We're not able to control the duration of the vancomycin infusion [using the conventional infusion sets]*

N1: *Anyhow, we don't count the drops, we estimate. Once the infusion is installed it will take half an hour, three quarters of an hour or only 15 minutes if it's running faster. We estimate… We cannot stay next to it for half an hour. There is not enough staff to go back and verify halfway whether the perfusion is running correctly and to adjust the infusion rate if necessary.*

No comment was made about availability of access line with the BID mode of administration

N3: CI is easier, more practical and easier to monitor. We know that the infusion rate will be correct at any time.

N3: It's very easy because in case of problems, the pump will go into alarm and we can manage things immediately. We don't have to go back to check every 2 hours whether the perfusion is administrated correctly as we did before.

N2: *Sometimes we have technical problems with the pump and then we try to replace it. It's sometimes difficult to find a spare pump because we also use them for chemotherapy… Sometimes we have to look and wait for a long time.*

N6: *Just the fact that you have to reserve an infusion line for vancomycin. The physicians provide an extra line if necessary. If it's administered together with another drug, it's just the time to put the extra infusion line.*

M4: *The only inconvenience, I guess, is the necessity of a dedicated infusion line for vancomycin. We'll often install an extra line. So multiplication of the number of infusion lines is an inconvenience.*

1.2.4 Sample timing

N3: *We don't have much staff and so if we have to take a sample at 1h30 and another patient calls us at 1h25. If we stay there until 1h50, sampling [for our patient] will be postponed because we cannot leave somebody [else] in a difficult situation.*

N1: We don't have to pay special attention to these sampling times anymore. They can just be scheduled in the "general biology sampling" in the morning, so we just flush the catheter by withdrawing 2 tubes, that's all…

M2: *Nurses are very busy and therefore peak samples are hardly ever performed one hour after the end of the infusion. That's for sure.*

M2: *As the duration of administration is difficult to control, the nurse doesn't know exactly when the infusion is finished. Therefore it's difficult or even impossible to perform a sample exactly one hour after the end of the infusion. It's completely random, I mean.*

N5: For me it's easier by CI because there's only one sample and timing is unimportant. Otherwise we had to perform peak samples and than trough samples two hours later but that strict timing is often not compatible with our workload and so than you often get delay. Now it's easier.

---

2. Training and information

2.1. Insufficient (post-)graduate education

M1: *We learned to do this [TDM] on the job and there is, therefore, a problem of training for medical officers. Speaking for myself, I cannot prescribe vancomycin impeccably… .*

M3: *Personally, I do not know how long after [drug administration] one needs [to wait] for peak level sampling. That's for sure!*

M2: *If nursing does not understand the fundamental importance of rigorous sample timing, the vagueness will only be bigger and it's even dangerous*

N2: We don't have to pay special attention to these samples anymore. They can just be scheduled with all the other samples in the morning. It's become routine practice

M5: I think it works well. It's become routine practice. I feel we cannot go without it anymore.

N1: I prefer CI , it's easier and in my opinion it's better. You just have to change the infusion set when it's empty [and you can sample at any convenient time].

---

3. Harm to benefit ratio of TDM

N1: *Me, when I prick [the skin] 3, 4 consecutive days and the patient is very difficult to prick, and he has had intravenous therapies, and he is covered with haematomas, I wonder why [I do all this]*

N4: We prick patients less. Before we had to perform samplings before and after [each] administration.

N2: *It represents a lot of additional samples for frail patients. Sometimes, I ask myself whether all these samples are necessary.*

M2: *Considering the cost-benefit balance, do we really offer a [good] service ?*

Note: the "cost" alluded to here is the harm caused to the patient, not the financial cost.

M1: We perform just one sampling in the morning for all the scheduled blood analysis. We hardly ever perform additional samples for TDM only anymore. I think about a patient 2 weeks ago. She was haematologically stable and vancomycin levels were also stable for about a week so we could reduce to only 3 blood samples per week.

L3: It's financially less beneficial for us as we perform less TDM and we receive less reimbursement if we only perform one TDM sample in stead of a peak and a trough level.

4. TDM performance: health care practitioners' experience and perception

4.1. Validity of the samples

M2*: I'm convinced that there are pharmacokinetic calculations on which we will base [our next dosing] and which are erroneous because the sample drawing and the timing of the administration have not been made correctly, it is completely random, I mean…*

M7: Before even trough samples were obtained incorrectly. They were no real trough values because they were often just performed together with the other blood sampling without taking care of correct sample timing. Now with continuous infusion, samples are always performed correctly. Samples are usually taken the next morning and we hardly have any problems.

4.2. Follow up of TDM recommendations

M1: *We had an accident last year with vancomycin. This happened with a Junior Medical Officer who followed, verbatim, the recommendations displayed on the computer… "two times 2 g of vancomycin" … and then, renal insufficiency !… [this is] an example, but …*

M5: We always follow TDM dose recommendations issued by the laboratory. They appear on the computer screen next to the TDM result. In case of an overdose, the ID physicians will also contact us.

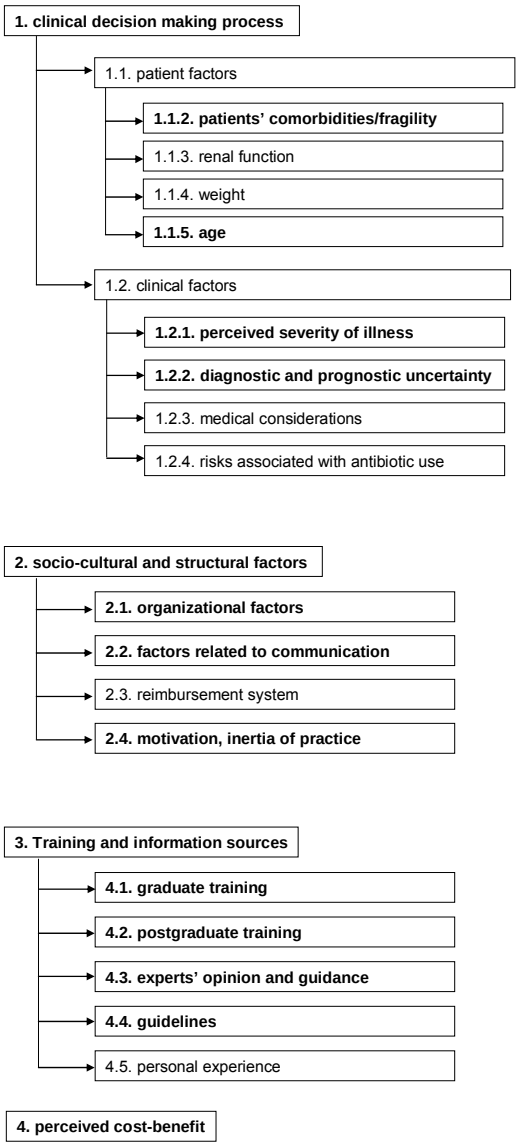
M1: *It is forbidden, in my ward, to follow the therapeutic recommendations of the laboratory, what the lab proposes…*

N2: *We have important fluctuations and blood levels go up and down. We are rarely in a therapeutic range and have to adapt doses all the time.*

M7: We follow dose recommendations. In my opinion treatment follow up is better now and I feel patients are treated correctly. It only happens from time to time during the night shift or with inexperienced staff that they draw a sample by the catheter and forget to flush correctly. But than you get concentrations of 60 mg/L. So you can see this immediately. We than just perform a new sample.

L6: In my opinion it's beneficial for the patients. We see that values are in the target range more quickly.

Figure 1: Dendrogram (node tree) used for the analysis of the transcripts for identification of the emerging themes. This dendrogram was built during a first pass analysis of transcripts in which all emerging themes were noted. Themes with frequent occurrences or of major significance then retained and used to construct Table 4 are shown in bold.

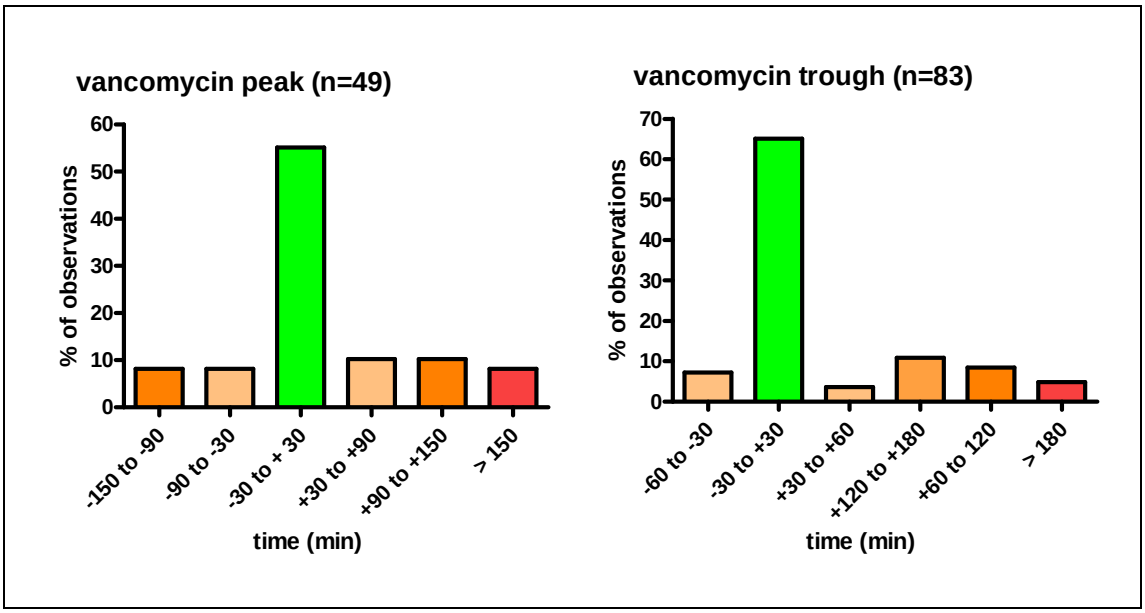


Supplementary Material

Ampe et al.

Overcoming Insufficiencies in Therapeutic Drug Monitoring of Vancomycin by Switching from Intermittent (BID) Administration to Continuous Infusion (CI): a Combined Observational and Qualitative Study.

Figure SP1



Caption to Figure SP1: Observational study (BID): Deviations (in min) from recommended sampling times. Left: timing of peak levels (recommended values: 2 h after the end of the infusion). Right timing of trough levels (recommended values: immediately before the next infusion).

Introduction to chapter 3 (quantitative study)

As explained in chapter 2, we performed a combined observational and qualitative study to evaluate performance of vancomycin therapeutic drug monitoring (TDM) at baseline (BID) in non-ICU patients and to identify processes underlying non-adherence to local hospital guidelines for TDM as well as health care practitioners' perception towards this service. Observational data at baseline were collected during 4 months. This part of the study revealed major insufficiencies in TDM performance including the implementation of the corresponding dose recommendations.

The qualitative approach used triggered us to change the mode of administration of vancomycin from its routine BID schedule to continuous infusion. Our purpose was to evaluate TDM quality during at least a 1 year period and to critically assess the following parameters: (i) correct sample timing; (ii) implementation of TDM-dosage readjustment recommendations; (iii) prescribed daily dose in accordance to hospital guidelines and proportion of serum level values within the recommended range.

We also wished to evaluate the pharmacokinetic, pharmacodynamic and toxicological aspects of this mode of administration. Thus, we examined: (i) whether maintaining stable serum concentrations (set at 25–30 mg/L based on local susceptibility data of Gram-positive target organisms) could be achieved in patients suffering from difficult-to-treat infections (considering both intra- and interpatient variations); (ii) the toxicity and overall efficacy of this mode of administration; and (iii) the correlation between AUC/MIC and clinical outcome in patients for whom vancomycin was the only active agent against a single causative pathogen. We also wished to assess the correlation between free and total concentrations of vancomycin. These various points are addressed in the paper presented in this chapter.

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Implementation of a protocol for administration of vancomycin by continuous infusion: pharmacokinetic, pharmacodynamic and toxicological aspects

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ABSTRACT

Optimising antibiotic administration is critical when dealing with pathogens with reduced susceptibility. Vancomycin activity is dependent on the area under the concentration–time curve over 24 h at steady-state divided by the minimum inhibitory concentration (AUC/MIC), making continuous infusion (CI) or conventional twice daily administration pharmacodynamically equipotent. Because CI facilitates drug administration and serum level monitoring, we have implemented a protocol for CI of vancomycin by: (i) examining whether maintaining stable serum concentrations (set at 25–30 mg/L based on local susceptibility data of Gram-positive target organisms) can be achieved in patients suffering from difficult-to-treat infections; (ii) assessing toxicity ($n = 94$) and overall efficacy ($n = 59$); and (iii) examining the correlation between AUC/MIC and the clinical outcome in patients for whom vancomycin was the only active agent against a single causative pathogen ($n = 20$). Stable serum levels at the expected target were obtained at the population level (loading dose 20 mg/kg; infusion of 2.57 g/24 h adjusted for creatinine clearance) for up to 44 days, but large intrapatient variations required frequent dose re-adjustments (increase in 57% and decrease in 16% of the total population). Recursive partitioning analysis of AUC/MIC ratios versus success or failure suggested threshold values of 667 (total serum level) and 451 (free serum level), corresponding to organisms with a MIC > 1 mg/L. Nephrotoxicity potentially related to vancomycin was observed in 10% of patients, but treatment had to be discontinued in only two of them.

1. Introduction

The pharmacokinetic/pharmacodynamic index governing the antibacterial activity of vancomycin is the area under the concentration–time curve over 24 h at steady-state divided by the minimum inhibitory concentration [1] (AUC/MIC; see [2] for definition), with a value of at least 400 for optimal activity [3]. Thus, vancomycin could be administered by discontinuous infusion as well as by continuous infusion (CI) as far as efficacy is concerned. North American guidelines recommend administering vancomycin as a twice daily or three times daily schedule (doses given in ca. 1 h every 12 h or 8 h apart) and to monitor trough levels [4]. This, however, does not allow accurate determination of the AUC since peak levels, primarily influenced by the volume of distribution (V_d), remain undetermined. In contrast, CI may provide an immediate reading of the AUC value. Actually, CI of vancomycin was shown to allow for a better attainment of target concentrations [5] and to ensure at least equal efficacy, whilst affording equal or decreased toxicity (see [6] for a recent meta-analysis). CI also greatly facilitates the monitoring of vancomycin (since serum levels should not be affected by the time of sampling) and has practical advantages for nursing [5,7,8]. It also allows for a centralised preparation of ready-to-use infusion sets, adapted for administration through volumetric devices, further minimising the risks of dose and timing errors [9]. We report here on the hospital-wide implementation of vancomycin administration for non-intensive care unit (non-ICU) patients under the supervision of a clinical pharmacist and an infectious diseases physician, and we present an analysis of the pharmacokinetics (including the determination of free versus total

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serum levels), the clinical outcomes and the correlations between AUC/MIC and clinical success.

2. Materials and methods

2.1. Overall design, setting, patients and ethical considerations

The investigation was performed over a 13-month period in the non-ICU wards (see caption of Fig. 1) of a 420-bed teaching hospital. Eligible patients were those for whom vancomycin treatment was prescribed for suspected or documented infection according to local guidelines. Excluded patients were those with life expectancy <1 week, baseline serum creatinine >2.3 mg/L or a creatinine clearance <30 mL/min at initiation of treatment, or those who already received vancomycin within 48 h prior to the current infection. All enrolled patients were examined for quality of administration, overall clinical efficacy and side effects, and benefited from dose adaptation based on availability of serum levels (usually once a week). A subset of patients who provided specific informed consent was included for detailed pharmacokinetic analysis with daily follow-up of serum levels and subsequent/eventual dose adaptation. The protocol of the study was approved prior to initiation by the Ethical Committee of the CHU Mont-Godinne (Yvoir, Belgium) and written informed consent was obtained from all patients (or a close relative if the patient was unable to co-operate) for investigations beyond the local standard of care.

2.2. Treatment

Vancomycin (Vancocin®; Lilly, Illkirch, France) 10 g/L in 5% glucose solution for infusion was prepared in the Central Pharmacy and was administered by volumetric infusion pump (Volumed® 7000; Arcomed AG, Regensdorf, Switzerland). Patients received a loading dose of 20 mg/kg (based on actual body weight and an estimated V_d of 0.7 L/kg [10–12]) administered over 1 h for doses <2 g or over 2 h for larger doses. This was immediately followed by CI at a rate K_o (mg/min) calculated according to Eq. (1):

$$K_o = C_{ss} \times 0.65 \times \text{CCrCl} \quad (1)$$

where C_{ss} (mg/L) is the total serum target concentration at steady state, CCrCl is the calculated creatinine clearance (in L/min, based on the Cockroft–Gault formula [13] using total body weight) and 0.65 is a correction factor for prediction of vancomycin clearance from CCrCl [12,14]. Because of the limitations of the Cockroft–Gault formula, CCrCl values >120 mL/min were ignored (38/94 patients) and those patients were dosed as if having a creatinine clearance of 120 mL/min. Our initial serum concentration target value was 27.5 mg/L, corresponding to a daily dose of 2.57 g for an ideal patient (CCrCl = 0.1 L/min; male), and, based on the preparation made, an infusion at 10.7 mL/h (rounded to 11 mL/h for practical purposes). For patients not enrolled in the detailed pharmacokinetic analysis (described in Section 2.5), a first sample was obtained within 8–12 h after initiation of CI and dosing was re-adjusted by increasing or decreasing the speed of the volumetric device by 500 mg increments. A new loading dose was administered if the total vancomycin serum concentration was <15 mg/L. Sampling and dose adjustments were repeated daily using pre-defined criteria (see Supplementary Table SP1) until two consecutive levels in the target range (25–30 mg/L) were obtained, after which samples were taken at least once weekly. Additional details regarding the stability of vancomycin and its compatibility with other antibiotics and other drugs have been published recently [15].

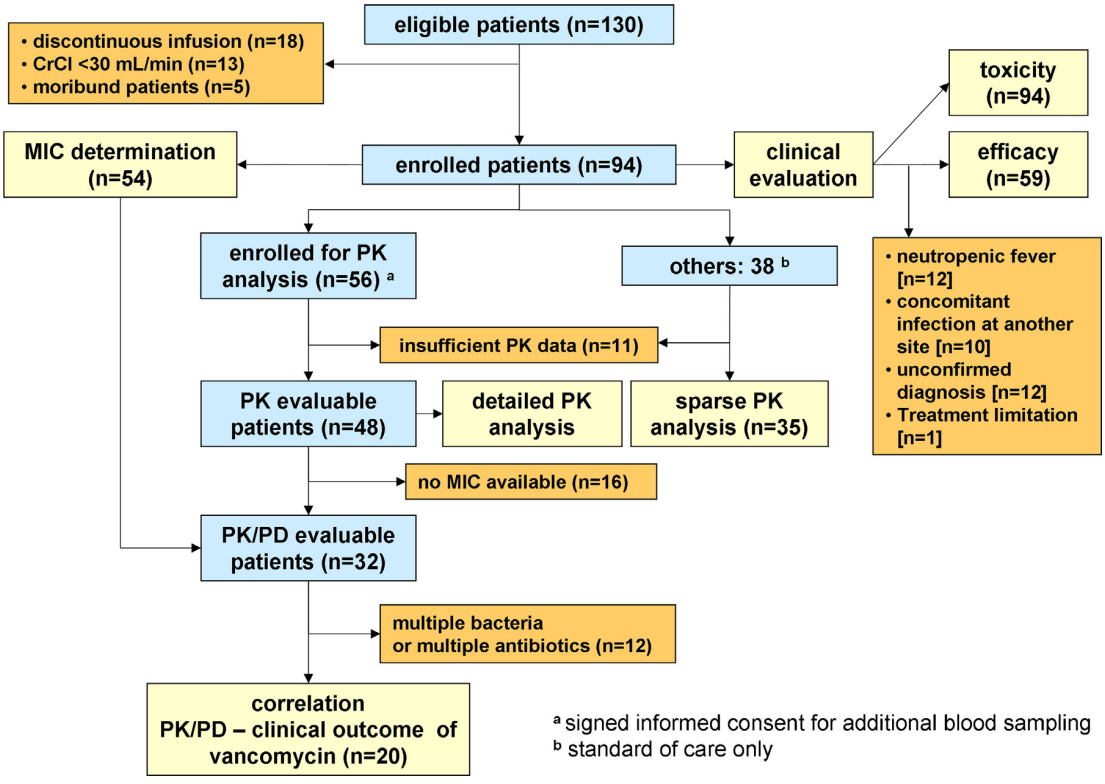

Fig. 1. General outline of the study and number of patients in each group or subgroup. Patients were from the following wards: cardiology (n = 4); cardiovascular surgery (n = 7); general surgery (n = 7); gastroenterology (n = 3); geriatrics (n = 7); haematology (n = 31); internal medicine (n = 8); neurosurgery (n = 2); oncology (n = 6); orthopaedic surgery (n = 10); pneumology (n = 6); and urology (n = 3). CrCl, creatinine clearance; MIC, minimum inhibitory concentration; PK, pharmacokinetics; PD, pharmacodynamics.

2.3. Clinical analysis (efficacy and safety)

Age, sex and weight were recorded before or at initiation of treatment, and the following parameters were recorded on a daily basis: peripheral white blood cell (WBC) count; C-reactive protein (CRP) level; minimum and maximum body temperature; arterial blood pressure; serum creatinine; serum albumin; patient comorbidities (see [16] for classification); consciousness; signs and symptoms of infection; and all concomitant treatments.

Clinical and bacteriological outcomes were assessed both during and at the end of treatment. Clinical cure was defined as the disappearance of all major signs of infection, normalisation of body temperature and marked decrease of CRP. Improvement was defined as substantial positive change of the above criteria. Failure was defined as persistent signs or symptoms of infection (e.g. fever, increased WBC count), appearance of new signs or symptoms of infection, or their worsening after ≥5 days of therapy. Criteria for bacteriological cure were a negative culture from the originally sampled site and absence of signs of persisting infection at this site. Relapses were evaluated over a 6-month period. Assessment of treatment outcomes was retrospectively validated by an external infectious diseases physician not previously involved in the study. As pathologies were diverse, no general rule could be established, but all cases of failure or recurrence were re-examined by three of the investigators (EA, BD and PMT) for confirmation as 'vancomycin failure' based on the best available evidence for each specific patient.

Side effects presumably attributable to vancomycin (based on the drug's official labelling [17]) were recorded, with renal toxicity evaluated until 1 week after the end of treatment [4]. Nephrotoxicity was defined as corresponding to two or more consecutive abnormal serum creatinine levels (increase of 0.5 mg/dL or ≥50% increase from baseline) or a drop in CCrCl of 50% from baseline documented after >3 days of therapy. We prospectively evaluated risk factors for non-vancomycin-induced nephrotoxicity using a list of criteria validated by infectious diseases physicians and clinical pharmacists that included age, pre-existing renal failure, diabetes, concomitant nephrotoxic medication, and medical conditions known to be associated with nephrotoxicity such as sepsis, hepatic impairment, obstructive uropathy and pancreatitis [4].

2.4. Laboratory studies

Samples for microbiology were processed according to standard methods and MICs of Gram-positive pathogens were determined in parallel by microbroth dilution according to Clinical and Laboratory Standards Institute (CLSI) standards [18] and by Etest (bioMérieux, Marcy l'Étoile, France). Total and free vancomycin serum levels were measured by an automated method (Architect®; Abbott Laboratories, Abbott Park, IL) (coefficient of variation ≤2.75%; between-day sample precision, 1.35%) using untreated samples and materials collected after ultrafiltration through Centrifree® centrifugal filter devices (Millipore, Billerica, MA) (20 min, 2000 × *g*, room temperature), respectively, as previously described [19].

2.5. Pharmacokinetics and pharmacodynamics

For patients enrolled for detailed pharmacokinetic analysis, serum samples were obtained on Day 1 at 1, 3 and 6 h after the end of the loading dose and once daily from Day 2 onwards, and the values were used to construct a concentration–time profile for each patient. The AUC for the entire duration of treatment [and expressed as the value for 24 h ($AUC_{24\,h}$)] was determined using GraphPad Prism v.4.3 (GraphPad Software Inc., La Jolla, CA). $AUC_{24\,h}$/MIC values were calculated with MICs arbitrarily set at 0.25 mg/L if reported to be <0.5 mg/L.

2.6. Statistical methods

Statistical analyses were performed using JMP v.9.03 (SAS Software Inc., Cary, NC) and GraphPad Instat v.3.10 (GraphPad Software Inc.). Logistic fit regression and recursive partitioning were used to examine associations between continuous and categorical variables, respectively.

3. Results

3.1. Patient and sample characteristics

Fig. 1 shows the general outline of the study, the number of patients in each group or subgroup, and the reasons for exclusion at each step. In brief: (i) 94 patients were evaluated for toxicity and for quality of administration, 59 for clinical efficacy and 54 for measurement of vancomycin MIC against the putative pathogen; (ii) 48 patients could be evaluated for pharmacokinetics; (iii) pharmacodynamic analysis ($AUC_{24\,h}$/MIC) was performed in a subset of 20 patients with a documented Gram-positive infection and who had been treated with vancomycin as the only anti-Gram-positive antibiotic. Table 1 shows the populations' demographic and major clinical characteristics. The mean duration of treatment was 11.7 ± 8.4 days, with no significant difference between subgroups with respect to all criteria listed.

3.2. Global efficacy and safety

Of the 59 patients who could be evaluated for clinical outcome, 44 (74.6%) were considered as cured, 6 (10.2%) as improved and 9 (15.3%) as failing. Stratifying failures according to the MIC of the putative Gram-positive organism (obtained for 59 patients; see details in Supplementary Table SP2) showed values of 0/3, 3/18, 4/27 (1 was a relapse) and 2/6 for organisms with MICs of 0.25, 0.5, 1 and 2 mg/L, respectively. Relapse (at 6 months) was observed in only three patients (see detailed overview of treatment failures and recurrent infections in Supplementary Table SP3).

Table 2 shows that 13 patients (13.8%) experienced one or more adverse events possibly related to vancomycin treatment, with nephrotoxicity being predominant (10/13; see detailed overview of treatment-emergent toxicity events in Supplementary Table SP4). Seven of those patients had at least one vancomycin serum level >35 mg/L before the onset of toxicity, six had pre-existing mild to moderate renal failure and four had received either vancomycin for >14 days or a large cumulative dose (25 g). However, all those patients also had at least one other risk factor besides vancomycin administration: (i) all had received concomitant nephrotoxic drugs; (ii) eight received diuretics and two suffered from dehydration, making hypovolaemic renal failure not implausible; and (iii) nine were >65 years of age. Of four patients receiving a combination of vancomycin and aminoglycoside, one developed nephrotoxicity after 23 days of treatment. Vancomycin had to be discontinued due to nephrotoxicity in two patients (both presenting several other risk factors for nephrotoxicity, but showing a return of creatinine levels to baseline 1 week after treatment discontinuation).

A third patient developed general erythrodermia and fever after 10 days of treatment that could be ascribed either to vancomycin or to cefepime (both antibiotics were discontinued).

3.3. Pharmacokinetics/pharmacodynamics

Fig. 2A shows the profile of total serum vancomycin concentration over time for all patients with more than three determinations

Table 1
Demographic characteristics of all patients included.

Characteristic	Ratio, mean ± S.D. or prevalence [*n* (%)] in patients evaluated for:				
	Toxicity (*n* = 94)	Efficacy (*n* = 59)	PK (*n* = 48)	PK/PD (*n* = 32)	PK/PD and vancomycin treatment outcome (*n* = 20)
Sex (M/F ratio)[a]	0.75/0.25	0.71/0.29	0.73/0.27	0.74/0.26	0.70/0.30
Age (years)[a]	63.3 ± 13.8	65.1 ± 13.9	62.3 ± 13.2	62.6 ± 14.0	65.6 ± 12.6
CrCl (mL/min)[a]	100.6 ± 42.4	94.4 ± 41.2	105.8 ± 46.7	103.7 ± 41.5	99.0 ± 44.4
Type of infection (*n*)[b]					
Foreign body[c]	21 (22.3)	14 (23.7)	12 (25.0)	10 (31.3)	8 (40.0)
Osteomyelitis	9 (9.6)	8 (13.6)	7 (14.6)	5 (15.6)	5 (25.0)
Septicaemia	31 (33.0)	20 (33.9)	14 (29.2)	11 (34.4)	4 (20.0)
Skin and soft tissue	7 (7.4)	5 (8.5)	4 (8.3)	0 (0.0)	0 (0.0)
Other	26 (27.7)	12 (20.3)	11 (22.9)	6 (18.8)	3 (15.0)
Organism isolated (*n*)[b]					
MSSA	7 (7.4)	4 (6.8)	3 (6.3)	2 (6.3)	2 (10.0)
MRSA	30 (31.9)	19 (32.2)	12 (25.0)	10 (31.3)	7 (35.0)
CoNS	25 (26.6)	15 (25.4)	12 (25.0)	11 (34.4)	8 (40.0)
Enterococci	7 (7.4)	4 (6.8)	4 (8.3)	2 (6.3)	0 (0.0)
Other	25 (26.6)	17 (28.8)	17 (35.4)	7 (21.9)	3 (15.0)
Nephrotoxic medication (%)[b]	58 (61.7)	38 (64.4)	35 (72.9)	24 (75.0)	13 (65.0)
Cytostatic drugs	30 (31.9)	18 (30.5)	15 (31.3)	10 (31.3)	4 (20.0)
Aminoglycosides	4 (4.3)	4 (6.8)	4 (8.3)	2 (6.3)	0 (0.0)
Diuretics	60 (63.8)	37 (62.7)	28 (58.3)	21 (65.6)	12 (60.0)
Treatment duration (days)[a]	11.7 ± 8.4	12.6 ± 7.9	13.9 ± 9.6	15.6 ± 7.6	15.4 ± 7.3

PK, pharmacokinetics; PD, pharmacodynamics; CrCl, creatinine clearance; MSSA, meticillin-susceptible *Staphylococcus aureus*; MRSA, meticillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci.
[a] No significant difference between patients groups [$P < 0.05$, one-way analysis of variance (ANOVA)].
[b] No significant difference between patient groups ($P < 0.05$, χ^2 test).
[c] Patients with at least one prosthesis [cardiovascular, 12.8% (*n* = 12); orthopaedic, 11.7% (*n* = 11); 2 patients had both types of prostheses].

Table 2
Adverse events observed in all enrolled patients (*n* = 94).

Type	Occurrence [*n* (%)]	Treatment discontinuation [*n* (%)]
All[a]	13 (13.8)	3 (3.2)
Nephrotoxicity[b]	10 (10.6)	2 (2.1)
Hypersensitivity reactions[c]	2 (2.1)	0 (0.0)
Leukopenia[d]	1 (1.1)	1 (1.1)

[a] Details of each case are given in Supplementary Table SP4.
[b] Two or more consecutive abnormal serum creatinine levels (increase of 0.5 mg/dL or ≥50% above baseline) or a drop of calculated creatinine clearance ≥50% from baseline after several days of therapy.
[c] Red man syndrome (*n* = 2) and erythrodermia (late in treatment and no hypotension) (*n* = 1); 1 patient had both adverse events.
[d] Decrease of total white blood cell to lowest limit of normal values (1800/mm^3) followed by further decrease of polymorphonuclear neutrophils.

at any time (*n* = 91). The mean concentration reached after administration of the loading dose (time 0 h) matched the targeted level (27.5 mg/L). We examined whether the apparent vancomycin V_d (in L/kg) was influenced by the total body weight using a subset of 53 patients for whom pertinent data were available [serum level at 1 h after loading dose and initiation of the CI, 26.7 ± 5.5 mg/L (range 10.2–40.9 mg/L; interquartile range (IQR) 23.8–29.7 mg/L); weight, 77.7 ± 21.9 kg (range 42.0–155.0 kg; IQR 61–92 kg)]. The mean V_d was 0.82 ± 0.23 L/kg (range 0.48–1.96 L/kg; IQR 0.68–0.89 L/kg) and was essentially unrelated to patient weight (linear regression slope, −0.0026 ± 0.0011; $R^2 = 0.113$). Serum levels, however, fell rapidly to ca. 20 mg/L within 6 h. After increasing the rate of infusion (57.4% of all patients), the mean concentration again reached the targeted value within 96 h and was thereafter maintained at 27.8 ± 5.7 mg/L for the whole duration of treatment. Based on the first stable steady-state level (defined as the first of two successive levels differing by <10%; *n* = 49), we observed a vancomycin clearance of 79.6 ± 26.9 mL/min (range 21.9–132.4 mL/min) and an apparent half-life of 10.0 ± 4.9 h (range 4.2–28.3 h). The correlation between vancomycin clearance and CCrCl was further explored using both linear and non-linear regression. A linear function and a one-phase exponential association fitted the data almost equally well ($R^2 = 0.68$ and 0.72, respectively). The former yielded a slope of 0.47 (95% confidence interval 0.38–0.57) and an intercept (non-renal clearance) at 29.0 ± 5.5 mL/min. The second showed no non-renal clearance (zero intercept), a ratio of vancomycin to creatinine clearance varying from 1.01 to 0.52 in the range of CCrCl values examined (32–237 mL/min) and saturation of vancomycin clearance at 150.3 mL/min (95% confidence interval 111.5–189.0 mL/min). The mean $AUC_{24\,h}$ calculated from data points recorded after 48 h of infusion up to the end of treatment was 661 ± 60 mg h/L (range 441–756 mg h/L; *n* = 32).

Although stable at the whole population level, important variations in serum concentrations (10 mg/L or more) were observed in 40 out of 52 patients for whom more than three successive samples were obtained after 96 h of treatment (Fig. 2B). These variations were not related to age, weight, serum creatinine, serum protein, sex, underlying pathology or hospitalisation in haematology. Conversely, they were positively associated with an increased CCrCl (threshold at >104 mL/min) and negatively associated with the use of diuretics [multivariate modelling prediction expression, $y = 26.81 + (-0.046 \times \text{CCrCl}) \pm 1.65$ where the last term relates to the use (+) or not (−) of diuretics; $P < 0.01$].

Free vancomycin concentrations were measured in samples from a subgroup of 30 patients. Fig. 3 (upper and middle panels) shows that although the correlation between free and total concentrations was satisfactory at the population level ($r^2 = 0.77$), there was a large variation in the free/total concentration ratio between different samples. We looked for a correlation between free concentrations and several potential pertinent clinical factors (including CCrCl and plasma protein levels) but none showed statistical significance. The pattern of free concentration values over time was, however, globally similar to that of total concentrations but with even larger variations (9.15 ± 6.83 mg/L; range 2.0–39.2 mg/L) and a trend towards a sustained increase over time.

The average $AUC_{24\,h}$/MIC ratio in the 20 patients who received vancomycin as single active drug was then correlated with clinical outcome (cure/failure). Recursive partitioning analysis pointed to 667 and 451 as best split values separating failure from success using total and free vancomycin concentrations, respectively, and

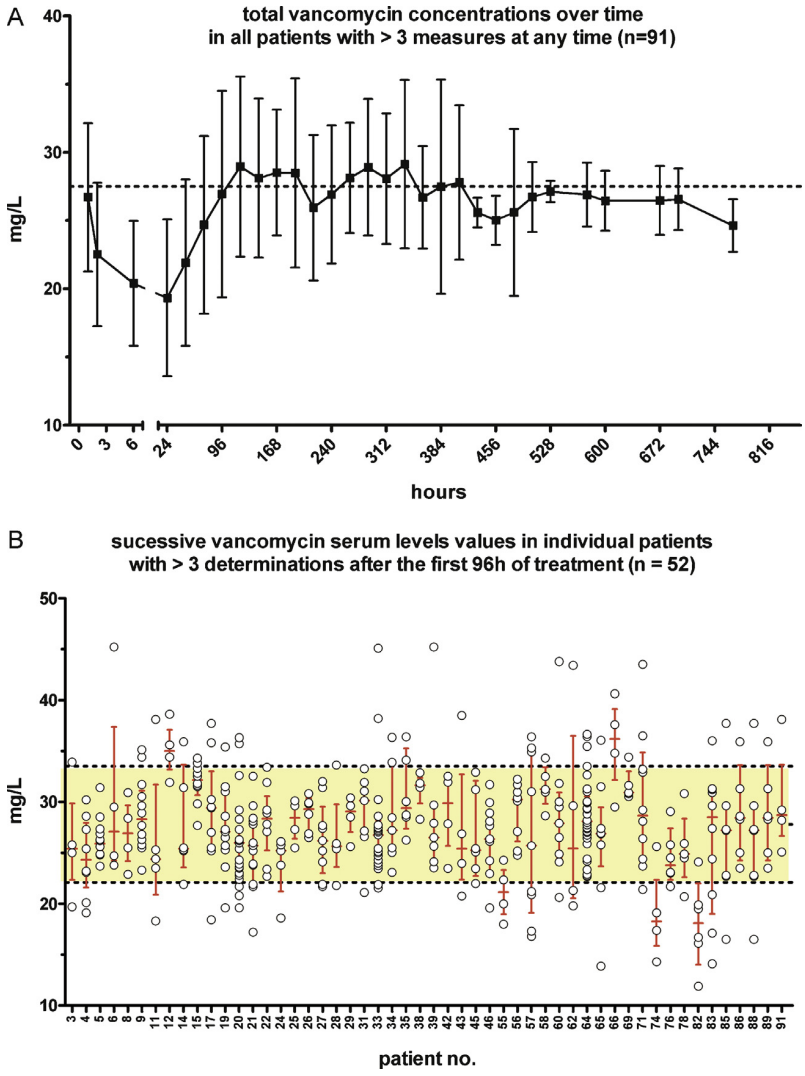

Fig. 2. Total vancomycin serum concentrations. (A) All patients with more than three successive determinations ($n = 91$) over time. Data are presented as concentrations (± S.D.) observed at the corresponding times for the first 6 h of the observation period, and at the closest rounded value (in days) after 24 h. The dotted line shows the targeted serum concentration (27.5 mg/L). Number of patients per data point, 41–80 between 1 h and 168 h; 28–40 between 192 h and 360 h; and 3–7 for longer times. (B) Individual serum levels in individual patients with more than three successive determinations after the first 96 h infusion. Each point represents one value. The red bars show the median and the interquartile range. The highlighted zone shows the mean ± S.D. for all samples. S.D., standard deviation.

MICs determined by microdilution method (Fig. 4; see Supplementary Fig. SP1 for a similar analysis using MICs determined by Etest; although the *P*-value exceeded 0.05 for some of these analyses, the trend was quite obvious).

3.4. Pharmacokinetics/toxicodynamics

Vancomycin serum levels were compared in the 10 patients who developed nephrotoxicity using all values from Day 1 to the time of onset of nephrotoxicity (mean 14.5 days) and in all patients with no evidence of nephrotoxicity and for whom serum levels over a period of 14 successive days were available ($n = 19$). No correlation between increased vancomycin serum level and nephrotoxicity was observed (see Supplementary Fig. SP2).

4. Discussion

Administration of vancomycin by CI has been advocated because of its practical advantages for nursing and serum level monitoring as well as its potential for increased efficacy and decreased toxicity. Contrasting views, however, have been clearly expressed in this context [see, e.g., [20] (systematic review) versus [6] (meta-analysis)]. The present study adds to this large body of knowledge by: (i) showing how CI can be implemented in non-ICU wards of a whole hospital; (ii) providing information on its clinical efficacy and safety; and (iii) presenting information about the ratio of drug exposure (AUC) to the MIC of the offending organism that may separate clinical success versus failure. ICU patients were not included because (i) administration of vancomycin by CI in this population has already been studied by several authors (see [21] for review) and (ii) because using the widely accepted Cockcroft–Gault formula for calculation of creatinine clearance to adjust vancomycin infusion rates is questionable in ICU patients [22].

With respect to pharmacokinetics, our protocol allowed achieving initial serum concentrations close to the target value, indicating that the assumed V_d of 0.7 L/kg was almost correct for most patients. Interestingly enough, no major correction had to be introduced based on actual body weight (within the limits of

weights observed). This does not preclude that other patients, such as those experiencing sepsis, could require higher loading doses [23], which will need to be assessed at the individual level. Conversely, the rapid concentration fall observed when starting the infusion cannot be attributed to an underestimation of the true vancomycin clearance by using the well-accepted ratio of 0.65 to CCrCl [12,14] to guide dosing since its actual ratio was lower if assuming a linear relationship between both clearances. However, this ratio could be higher in patients with low CCrCl if accepting the non-linear model. Possibly also, we simply may have underestimated the true creatinine clearance by using the Cockroft–Gault equation. More sophisticated equations could have been used but these are not validated for medication dosage adjustment. We could also have measured the actual creatinine clearance, but this is not routine practice in non-ICU wards and was therefore considered unsuited in a context of hospital-wide implementation of CI. Actually, the main message is that maintaining the serum level at its targeted value requires careful monitoring-based dosage readjustment. This could be related to higher than anticipated renal clearance, as recently also pointed out by others [23–25], but also to many other factors beyond the clinician's direct control. In our setting, this may have been increased by the decision to disregard CCrCl values >120 mL/min, and a revision of our protocol may be warranted in this context.

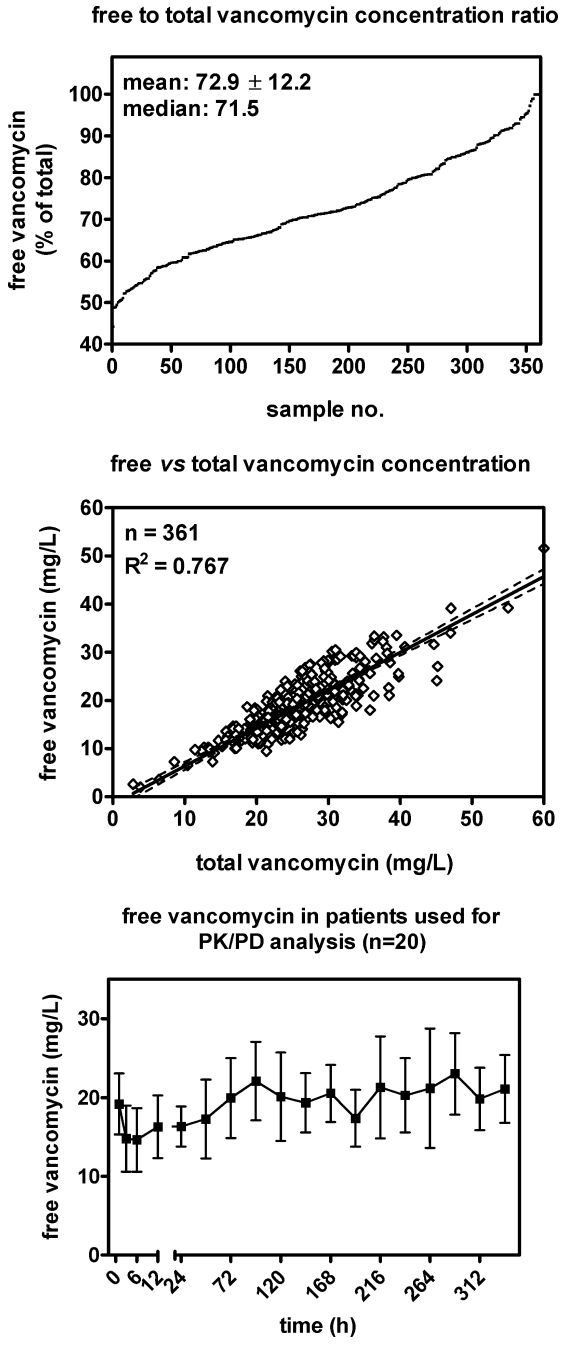

Fig. 3. Free serum vancomycin concentrations. Upper panel: distribution of free fraction of vancomycin in serum samples ($n = 361$). Each point is an individual sample, and samples are ranked by low to high free to total vancomycin concentration ratio. Middle panel: correlation between free and total vancomycin serum levels in the 361 samples shown in the upper panel. The solid line shows the regression line (linear regression) and the dotted lines show the 95% confidence interval band. Lower panel: free vancomycin serum concentrations over time for patients for whom a correlation was made between pharmacokinetic/pharmacodynamic data and clinical outcome ($n = 20$; see Fig. 1). Data are presented as mean (± standard deviation) observed at the corresponding times for the first 12-h observation period and at the closest rounded value (in days) after 24 h.

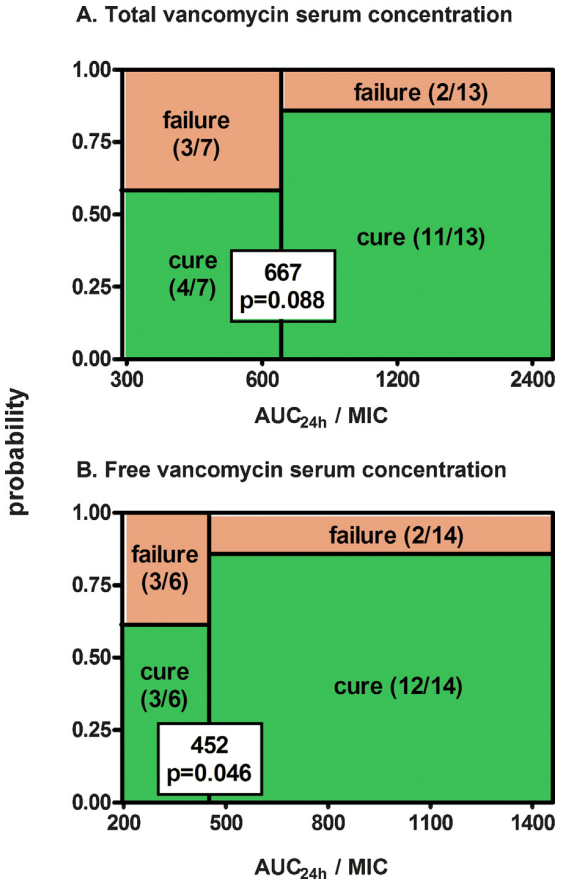

Fig. 4. Pharmacokinetic/pharmacodynamic analysis of clinical outcomes in 20 patients (i) infected by a single Gram-positive organism and having received vancomycin as the only agent active against this organism, and (ii) for whom assignment to antibiotic treatment success or failure could be established. The figure shows the probability of cure or failure as a function of the AUC_{24h}/MIC ratio observed for each individual patient using her/his mean AUC data for the entire duration of treatment and the MIC value (microdilution) of the causative organism. Upper graph, total vancomycin concentration; lower graph, free vancomycin concentration. Data were analysed by recursive partitioning to determine the dichotomous split in AUC_{24h}/MIC distributions that best separates values with low versus high probability of clinical success. Node splitting is based on the LogWorth statistic and the results analysed by χ^2 test (contingency tables). See Supplementary Fig. SP1 for the same analysis using MIC values obtained by Etest. AUC_{24h}, area under the concentration–time curve over 24 h at steady-state; MIC, minimum inhibitory concentration.

We found a direct correlation between the proportion of treatment failures and the MIC of the assumed causative organism when considering the whole group of patients. When limiting the pharmacokinetic/pharmacodynamic analysis to patients for whom vancomycin was the only active agent against the putative causal Gram-positive pathogen, we could confirm that low AUC_{24h}/MIC values were associated with a larger proportion of failures, with a threshold at values higher than that of 400 originally proposed [3]. Thus, considering the serum levels reached, organisms with a MIC ≥ 2 mg/L will obviously prove difficult to be correctly covered, lending further support to the current European Committee on Antimicrobial Susceptibility Testing (EUCAST) vancomycin clinical breakpoints for staphylococci [susceptible (S), ≤2 mg/L; resistant (R), >2 mg/L [26]] and questioning the validity of the corresponding current CLSI breakpoints (S, ≤2 mg/L; R, ≥16 mg/L [18]) as also stressed for patients treated with intermittent dosing [27]. Doses and target serum levels could, however, be decreased for infections caused by organisms with MICs < 1 mg/L, which may offer both toxicological and economical advantages. A study performed in a large cohort of patients receiving intermittent administration has indeed clearly demonstrated a relationship between initial trough levels and the risk of nephrotoxicity (with a threshold value of ca. 10 mg/L but with a clear difference in disfavour of ICU versus non-ICU patients) [28]. With CI, ICU and outpatients appear to be at a higher risk of nephrotoxicity if concentrations exceed 28 mg/L and 30 mg/L, respectively [29,30]. Yet we saw no correlation in our population, questioning the validity of defining any threshold in this context. The weakness of our study, however, is that although a rather high rate of nephrotoxicity was observed, its association with vancomycin remains uncertain as several other causes of renal failure were present. Other toxicities, including thrombophlebitis, were rarely encountered or not seen.

Altogether, our study demonstrates that hospital-wide implementation of vancomycin administration by CI may be a practical and appropriate option for the treatment of patients with severe Gram-positive infections provided that the corresponding MICs remain <2 mg/L. CI, however, will still require monitoring blood levels because of (i) the difficulties in correctly predicting vancomycin serum concentrations (using presently accepted models based on CCrCl) as well as unanticipated large intrapatient and interpatient variations and (ii) the necessity to adjust these levels to the MIC of the causative organism. Whilst vancomycin stability will not cause issues (even under poorly controlled room temperatures as evidenced from many reports), independent lines (or multi-lumen catheters) will need to be used for co-administration of other intravenous medications as vancomycin is reported to be incompatible with many other drugs [17].

Acknowledgment

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Competing interests: None declared.

Ethical approval: The protocol was approved by the Ethical Committee of the hospital in which the study was performed (CHU Mont-Godinne) (internal number EC Mont-Godinne, 48/2007; unique Belgian no. B03920072246).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://www.facm.ucl.ac.be/downloads/IJAA-D12-00806-SM.pdf.

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Supplementary Material

Implementation of a protocol for administration of vancomycin by continuous infusion: pharmacokinetic, pharmacodynamic, and toxicological aspects.

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Contents:

Table SP1: Dose adaptations for deviations of the targeted serum level

Target level: 25-30 mg/L

Actual concentration (measured)	Dose adaptation
0-5 mg/L	• Add a loading dose (20 mg/kg) Increase of the rate of infusion (+ 8 mL/h) [a]
6-10 mg/L	• Add a loading dose (15 mg/kg) • Increase of the rate of infusion (+ 6 mL/h) [a]
11-15 mg/L	• Add a loading dose (10 mg/kg) • Increase of the rate of infusion (+ 4 mL/h) [a]
16-25 mg/L	• Increase of the rate of infusion (+ 2 mL/h) [a]
26-30 mg/L	• No change
31-35 mg/L	• Decrease of the rate of infusion (- 2 mL/h) [a]
> 35 mg/L	• STOP infusion for 6 h • Decrease of the rate of infusion (- 4 mL/h) [a] • Control serum level the next day

[a] standard infusion solution at 10 mg/mL

Table SP2: Organism, MIC (microdilution; Etest®) and clinical outcomes

Data of patients with failures are highlighted in grey.

Patients are ranked by order of increasing MIC (microdilution)

patient no.	organism [a]	MIC (mg/L)		clinical outcome [d]	used in PK/PD analysis [e]
		microdil. [b]	Etest® [c]		
14	*E. faecium*	0.25	0.25	cure	
41	*Streptococcus* spp.	0.25	1	cure	
43	*S. equisimilis*	0.25	0.5	cure	X
3	*S. epidermidis*	1	1.5	cure	
5	*S. hominis*	0.5	1.5	cure	
16	MRSA	0.5	1.5	cure	
18	MSSA	0.5	1.5	cure	
21	MSSA	0.5	0.5	improvement	X
25	MRSA	0.5	1	cure	X
26	MRSA	0.5	1.5	failure	X
27	MRSA	0.5	1.5	failure	X
31	*Corynebacterium* spp.	0.5	0.75	cure	X
32	MSSA	0.5	1.5	cure	
37	MRSA	0.5	1.5	improvement	X
38	CNS	0.5	1.5	cure	X
45	MRSA	0.5	2	cure	
57	MRSA	0.5	1.5	cure	
61	MRSA	0.5	1.5	cure	
13	MRSA	0.5	1.5	unevaluable	
82	MRSA	0.5	1.5	unevaluable	
66	MRSA	0.5	2	cure	
83	MRSA	0.5	2	failure	
23	MSSA	1	1	unevaluable	
6	*S. epidermidis*	1	1	failure [f]	X
2	MSSA	1	1.5	cure	X
50	MSSA	1	1.5	unevaluable	
8	*S. epidermidis*	1	1.5	cure	X
9	MRSA	1	1.5	cure	X
11	MRSA	1	1.5	cure	X
78	*E. faecalis*	1	1.5	relapse	
75	*E. faecium*	1	1.5	unevaluable	
71	MRSA	1	1.5	cure	
8	CNS	1	1.5	improvement	
87	MRSA	1	1.5	cure	
74	MRSA	1	1.5	cure	
15	*S. haemolyticus*	1	2	cure	X
17	MRSA	1	2	cure	X

4	MRSA	1	2	unevaluable	
30	*S. epidermidis*	1	2	cure	
39	*S. epidermidis*	1	2	failure	
81	MRSA	1	2	cure	
12	*S. epidermidis*	1	2	failure	
29	MRSA	1	2	unevaluable	
79	*E. faecium*	1	1.5	unevaluable	
42	CNS	1	3	cure	X
54	MRSA	1	2	failure [f]	X
60	*S. epidermidis*	1	2	cure	
65	*E. faecium*	1	1.5	cure	
76	MRSA	2	2	cure	
1	*E. faecalis*	2	3	failure	
24	*S. haemolyticus*	2	3	improvement	X
34	*S. epidermidis*	2	3	improvement	X
46	*S. epidermidis*	2	2	failure [g]	X
62	MRSA	2	3	cure	

[a] MSSA: methicillin-susceptible *S. aureu*s; MRSA: methicillin-resistant *S. aureus*; CNS: coagulase-negative *staphylococci* .

[b] according to the recommendations of the Clinical Laboratory Standards Institute (Performance Standards of Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement. M100-S22: 1-183. Clinical and Laboratory Standards Institute, Wayne, PA (2012).

[c] bioMérieux SA, Marcy l'Etoile, France

[d] with respect to the causative organism as listed in the Table

[e] patients (i) enrolled in the pharmacokinetic study and for whom sufficient data could be assembled, and (ii) infected by an organism against which vancomycin could be considered as the only active agent (monotherapy)

[f] relapse considered as due to vancomycin lack of efficacy

[g] death possibly due to infection

Table SP3: Detailed overview of treatment failures and recurrent infections

patient no.	Organisms [a] and source [b]	vancomycin MIC (mg/L) microdil. / Etest®	vancomycin treatment duration (days)	clinical outcome
1	CNS (centr. catheter) *E. faecalis (HC 1fl/4)* *C. freundii (HC 1fl/4)* *Enterobacter* spp. *(HC 1fl/4)*	2/3 (*E. faecalis*)	4	Vancomycin treatment for suspected catheter related infection Antibiotic switched to ampicillin + cefepime after 4 days. Death 4 days after switch from gastro-intestinal hemorrhagic shock and sepsis of gastrointestinal origin due to *Enterobacter* spp. and Enterococcus spp. There is evidence that death resulted from a non-infectious cause but the patient was still infected
6	*S. epidermidis (peroperative bone biopsy)*	1/1	10	Conservative treatment of prosthetic device infection at weeks after prosthesis (no removal of prosthetic device) Surgical debridement at day 8 Switch to ciprofloxacin + rifampin at day 10 for the next 6 weeks Recurrence of the collection with removal of prosthesis at day 35
12	*S. epidermidis*, *Enterococcus* spp., *E. coli* (collection samplig)	1/2 (*S. epidermidis*)	14	Vancomycin + cefepime for 2 weeks for retroperitoneal abscess (post nephrectomy) - no drainage Switch to teicoplanin + cefepime for 2 weeks Reappearance of retroperitoneal collection; residual cutaneous fistula with culture positive for *E. faecalis* and CNS (ampicillin susceptible) at the end of antibiotic treatment. Percutanous drainage and initiation of a second treatment with vancomycin and meropenem Thereafter, clinical success after 15 days (no sample available)
26	MRSA (hemoculture)	0.5/1.5	10	Septicemia of unknown origin Persistence of fever and several positive haemocultures until 3 weeks after the end of treatment
27	MRSA (superficial wound culture)	0.5/1.5	20	MRSA surgical wound infection toe despite amputation and postoperative vancomycin treatment Persistence of the infection and new amputation
36	*S. pyogenes (wound culture)*	/	3	Skin and soft tissue infection. Switch to cefazolin after 3 days for 2 weeks CRP increase during treatment and reoccurrence of erysipelas at the end of the antibiotic treatment.

46	CNS (*S. epidermidis* in perioperative cultures)	2/2	28	Wound infection with suspicion of of vascular prosthesis infection. Treatment with vancomycin and ceftazidime, followed by ciprofloxacine and rifampincin No removal of prosthesis (debridement only). Wound necrosis and several perioperative positive cultures after 2 months
54	MRSA (sputum culture)	1/2	7	Respiratory tract (COPD exacerbation). Death (clinical deterioration with fever, dyspnoea and sputum after 6 days of therapy
55	*Helococcus kunzii (bone biopsy)*	/	8	Relapse of chronic osteomyelitis 2 months after surgical debridement and initiation of antibiotic therapy (no prosthesis) vancomycin treatment for 8 days switch to ceftriaxone + rifampicin.after 3 weeks switch to rifampicin + cotrimoxazole for a total duration of 2 months with no sign of infection healing Patient refuses surgical treatment.
78	*E. faecalis* *K. oxytoca* *C. albicans* *(perioperative culture abcess)*	1/1.5 (*E. faecalis*)	10	Abdominal abscess with surgical debridement followed by vancomycin + meropenem + fluconazole Recurrence of abdominal abscess due to *E. faecalis* and MRSA at 3 months
83	MRSA haemocultures (5fl/6)	0.5/2	17	Septic trombophlebitis switch to oral linezolid for 2 weeks Haemoculture at day 20 Confirmation of cervical spondylodiscitis at the end of linezolid therapy Considered as a failure of the antibiotic treatment
86	*S. epidermidis* *E. coli* *(perioperative bone biopsy)*	/	16	Chronic knee prosthesis infection (prothesis not removed; conservative treatment)) first biopsy negative concomitant to treatment with cefuroxime (haemocultures positive for *E. coli*) At day 16, switch to minocyclin for 6 weeks Biopsy positive for *S. epidermidis* and *E. coli* at the end of antibiotic treatment Removal of prosthesis Considered as failure of the suppressive treatment

[1] to protect patients' anonymity, the age and the underlying disease(s) are not reported but the data are available from the authors if deemed important for scientific reasons. Stratification on age showed an equal distribution between <70 and ≥70 years. Prosthesis and diabetes accounted for the most frequent underlying illnesses (4 and 3 cases, respectively).

[a] MSSA: methicillin-susceptible *S. aureu*s; MRSA: methicillin-resistant *S. aureus*; CNS: coagulase-negative staphylococci.

[b] HC: hemoculture (with the number of positive flasks over the total number of samples

Table SP4: Detailed overview of treatment-emergent toxicity events

Patient no.	Age (y)	Infection type	Baseline ClCr (mL/min)	Duration VAN before onset of toxicity (days)	Cumulative VAN dose before onset of toxicity (g)	Highest VAN conc. measured (mg/L)	Risk factors for toxicity - related to vancomycin treatment - other	Type	Description	End of VAN due to toxicity?
12	73	urinary tract infection (renal abscess)	39.2	14	16.0	39.8	age, loop diuretic, enoxaparin, contrast agent, chronic renal insufficiency nephrectomy, renal abscess	renal	Serum creatinine 2.3 at D0. Increase to 2.7at D12 leading to VAN stop. After treatment stop further increase to 5.1 at D+7. dialysis at D+15. Than decrease to 2.8 at D+21 and to 2.2 at D+35.	yes
21	73	sternal osteomyelitis	42.3	31	38.5	34.2	enoxaparin, diabetes, dehydration, age, duration, dose	renal	Serum creatinine 1.2 at D0. Increase to 1.7 at D31, leading to VAN stop. Thereafter increase to 1.8 at D+2 than decrease to 1.1 at D+7.	yes
35	60	catheter sepsis	>120.0	10	34.1	36.4	enoxaparin, dose, diabetes, dehydration, surgery	renal	Serum creatinine 0.8 at D0. Increase to 1.4 at D11 during several days leading to two consecutive dose decreases. Thereafter normalisation to 0.9 at D13.	no
64	73	central nervous system (postsurgical cerebral abscess)	41.0	21	33.6	36.4	loop diuretic, allopurinol, glucose-1-phosphate, age, diabetes, dehydration, duration, dose	renal	Increase of serum creatinine from 1.9 to 3.0 at D30 during 7 days. Stop Van at D35. Thereafter, stabilisation of serum creatinin at 2.6 until D+22.	no
65	66	abdominal (colitis)	103.1	8	24.8	27.5	loop diuretic, enoxaparin, cytarabine, dehydration	renal	Increase of serum creatinine from 0.5 to 1.0 at D8 during 6 days. . Stop VAN at D7. Thereafter normalisation to 0.6 at D+12.	no

66	85	Skin and soft tissue	31.0 .	9	9.4	40.6	loop diuretic, enoxaparin, mild chronic renal insufficiency, dehydration, age	renal	increase of serum creatinine from 1.6 to 2.1 after a 9 day treatment from D+1 until D+18. Thereafter: decrease to 1.7 at D+21.	no
75	76	foreign body (pacemaker)	59.3	7	11.7	47.5	loop diuretic, enoxaparin, age	renal	Increase of serum creatinine from 0.9 to 1.7 after a 7 day treatment from D+2. Thereafter: decrease to 1.4 from D+4 to D+15.	no
86	78	foreign body (orthopaedic)	71.0	3	5.6	34.4	loop diuretic, age, sepsis, dehydration, serum conc.,	renal	Increase serum creatinine from 1.4 to 2.1 at D3 during 3 days leading to dose decrease. Return serum creatinine to 1.4 at D6.	no
93	67	Foreign body infection (pacemaker)	95.0	21	29.5	40.1	aminoglycosides, loop diuretic, duration, dose serum concentration	renal	Increase of serum creatinine from 1.0 to 1.5 from D21 during 6 days. Stop VAN at D23. No serum creatinine determination afterwards.	no
89	84	respiratory tract (exacerbation of COPD)	48.0	9	13.0	36.7	diuretic, dehydration, serum conc.,	renal	Increase serum creatinine from 0.9 to 1.4 at D9. Stop VAN at D10. Rise serum creatinine to 1.8 at D+2. creatinine until D+14. Normalisation to 0.9 AT D+22.	no
85	71	catheter sepsis	73.0	10	28.0	37.7	dose, serum concentration	Hypersen sitivity	Red men at loading dose (1800 mg/2h). General erythrodermia and fever at D10 due to vancomycin or cefepime	no
92	56	foreign body infection (vascular)	66.0	0	1.0	NA	none	red man	Red men at loading dose (1000 mg/1h). Stop after 45 min during 45 min than rest of loading dose administered in 15 min.	no
5	34	foreign body infection (orthopaedic)	109. 6	16	56.0	31.4	enoxaparin, duration, dose	hematolo gic	Decrease of WBC and neutrophils count respectively to 4.8/µL (4-10) and 2.5/µl (2.1-6.3) from D17. Further decrease of neutrophil count to 1.8 at D32.	yes

- To protect patients' anonymity, the reason for admission is not reported but is available from the authors if deemed important for scientific reasons.
- Our analysis did not disclose meaningful association of the reason of admission and the occurrence of a toxic event.

Table SP5: Clinical and bacteriological features of patients with PK/PD analysis

Patients (n=20) with

- detailed pharmacokinetic analysis,
- available MIC value of a Gram-positive organism considered as the cause of the infection, and
- receiving vancomycin as the only anti-Gram-positive antibiotic.

no.	infection type	organism [a]	MIC (mg/L) Etest® / microdil.	treatment duration (days)	clinical outcome
3	catheter sepsis	*S. epidermidis*	1.5/1	9	cure
6	foreign body infection (orthopaedic)	*S. epidermidis*	1/1	10	failure [b]
8	foreign body infection (orthopaedic)	*S. epidermidis*	1.5/1	15	cure
9	foreign body infection (ventriculo-peritoneal drain)	MRSA	1.5/1	28	cure
11	osteomyelitis	MRSA	1.5/1	14	cure
15	catheter sepsis	*S. haemolyticus*	2/1	14	cure
17	osteomyelitis	MRSA	2/1	22	cure (slow improvement over time)
21	osteomyelitis (sternal)	MSSA	0.5/0.5	32	improvement
24	osteomyelitis	S. *haemolyticus*	3/2	14	improvement
25	Central nerve system	MRSA	1.5/0.5	17	cure

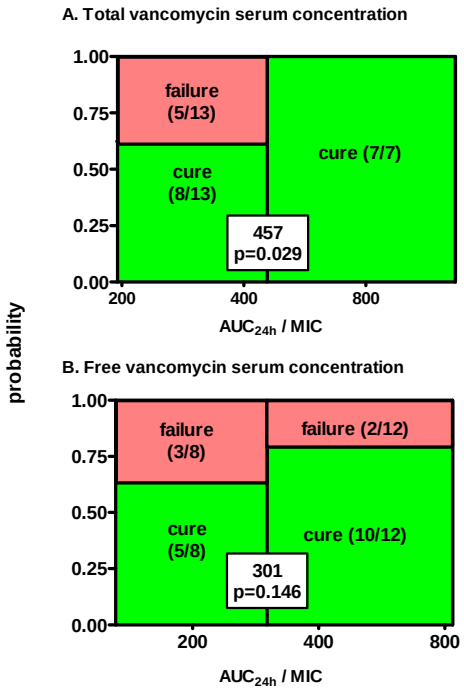
26	bacteraemia of unknown origin	MRSA	1.5/0.5	10	failure (persistence of fever and relapse of infection 3 weeks after the end of treatment)
27	osteomyelitis	MRSA	1.5/0.5	20	failure (MRSA surgical wound infection despite amputation and postoperative vancomycin treatment)
31	bacteraemia of unknown origin	*Corynebacterium* spp.	0.75/0.5	12	cure
34	foreign body infection (orthopaedic)	*S. epidermidis*	3/2	16	improvement
37	respiratory tract	MRSA	1.5/0.5	7	improvement
38	foreign body infection (pacemaker)	CNS	1.5/0.5	10	cure
42	Foreign body infection (pacemaker)	CNS	3/1	9	cure
43	foreign body infection (vascular)	*S. equisimilis*	0.5/0.25	11	cure
46	foreign body infection (vascular)	CNS	2/2	28	failure (relapse of wound infection due to coagulase negative *Staphylococcus* after 2 months)
54	respiratory tract	MRSA	2/1	7	Failure (clinical deterioration; patient died after 6 days of therapy)

- To protect patients' anonymity, the age and the underlying disease(s) are not reported but the data are available from the authors if deemed important for scientific reasons.
- Stratification on age: <70 years: n=11 - ≥70 years: n=9. There was no specific association between underlying disease and cure or failure.

[a] MSSA: methicillin-susceptible *S. aureu*s; MRSA: methicillin-resistant *S. aureus*; CNS: coagulase-negative staphylococci.

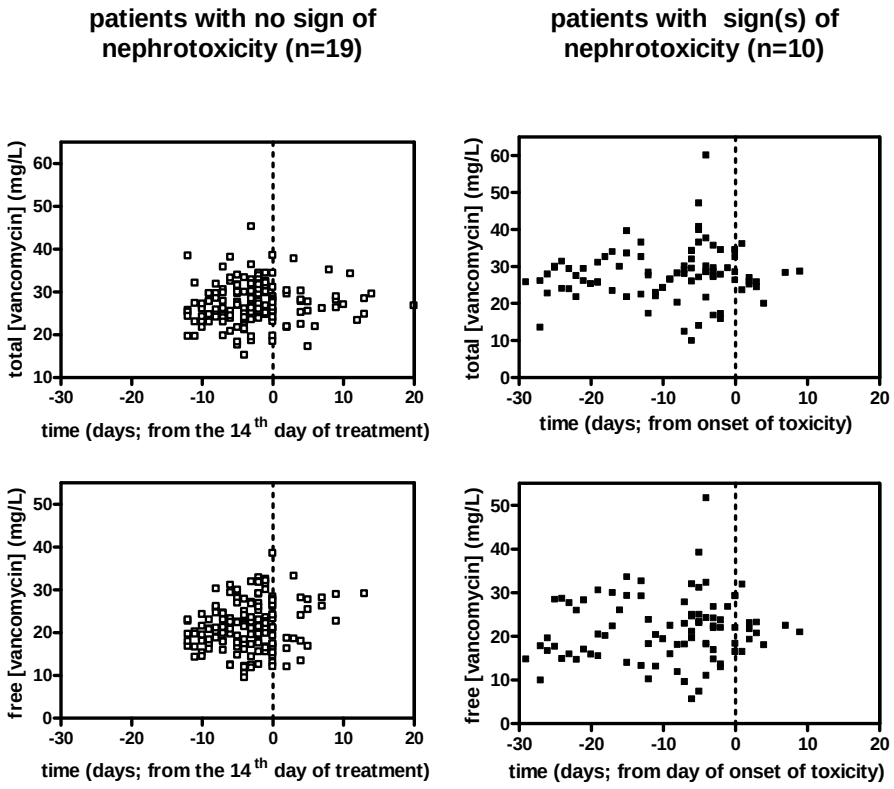
[b] relapse considered as due to vancomycin lack of efficacy

Figure SP1: Success/failures partitioning based on Etest MICs



Caption of Figure SP1: Pharmacokinetic/pharmacodynamic analysis of the clinical outcomes in patients (n = 20) infected by a single Gram-positive organism and having received vancomycin as the only agent active against this organism (monotherapy). The figure shows the probability of cure or failure as a function of the AUC/MIC observed for each individual patient using the mean AUC data of each patient for the entire duration of the treatment (upper graph: total vancomycin concentrations; lower graph: free vancomycin concentration) and the MIC data of the causative organism as determined by Etest® (see Table SP3 for a comparison of individual MIC values as determined in broth). Data were analyzed by recursive partitioning to determine the dichotomous split in AUC/MIC distributions that best separates values with low vs. high probability of clinical success. Node splitting is based on the LogWorth statistics and analyzed by Chi-square test (contingency table).

Figure SP2: Total and free vancomycin serum concentrations in patients without and with signs of nephrotoxicity



Caption to Figure SP2: Total (upper panels) and free (lower panels) vancomycin serum levels in patients without (left panels; n=19) *vs.* patients with signs of nephotoxicity (right panel; n=10). Nephrotoxicity was defined as two or more consecutive abnormal serum creatinine levels (increase of 0.5 mg/dL or ≥50% increase from baseline) or a drop in calculated creatinine clearance of 50% from baseline documented after > 3 days of therapy. For patients with nephrotoxicity, the dotted line refers to the day of the diagnostic, and the data points correspond to the levels measured in these patients before and after that day. For patients without evidence of nephrotoxicity, the dotted line corresponds to the 14th day of treatment with vancomycin and the data points correspond to all available serum levels measured before and after that day.

General discussion, conclusions and perspectives

The observational part of our study shows that the correct performance of TDM of vancomycin, when using its conventional mode of administration (BID) in routine practice, stumbles on numerous major deficiencies even in a hospital setting where guidelines concerning antibiotic monitoring have been issued and approved.

Quality issues were observed according to timing of drug administration and sampling and data communication to the clinical laboratory leading to errors in dose adaptations calculated. The very low scores for almost all TDM parameters and the limited number of serum levels within the therapeutic range are appalling, but have been documented in other similar settings [1-3]).

In a second phase, a qualitative survey was conducted consisting of focus groups with health care practitioners in order to identify adherence barriers to guidelines and processes underlying inappropriateness. This study identified two main causes for the observed deficiencies, namely, organizational issues related to drug administration and sampling and a lack of knowledge or training of health care practitioners which translated into a lack of motivation of individuals and an insufficient interdisciplinary collaboration associated with unclear definition of responsibilities. The lack of clear guidance about which patients would really benefit from monitoring also resulted in a large dilution of efforts ensuing decreased attention to key details (both for physicians and nursing personnel). The two mechanisms identified are of importance in most areas dealing with the quality of medical processes [4-8] but are of particular importance here as TDM performance is critically dependent from the correct execution of successive steps involving a large number of health care professionals.

The major insufficiencies observed at baseline with some underlying factors related to control of drug administration and sampling times that seemed difficult to overcome, together with the fact that many health care practitioners were supportive of CI (which they already used for other drugs) led to the decision to change to the continuous mode of administration. Such an approach may well be appropriate for vancomycin for which a large body of clinical experience is now available [9-11].

We evaluated the feasibility of such an approach at the level of a whole hospital and determined its impact on TDM process measures. Implementation of CI was associated with significant ($p<0.0001$) improvement for correct sample timing, drug levels within recommended range; implementation of dosage re-adjustment recommendations and correct daily doses.

One year after the end of the study, we evaluated actual implementation of CI and health care practitioners' perception and satisfaction towards this approach. This second qualitative survey revealed a positive perception towards CI which was found to be reliable and high mean satisfaction scores of 4/5 (with 5 being the highest score) among health care practitioners. Centralized preparation and TDM during CI were perceived by ward personnel as reliable and contributing to the quality of care. It was also appreciated because it allowed performing TDM on routine clinical samples thereby reducing workload for nursing and limiting the number of samples for patients. Few studies apply qualitative methods for exploring almost purely mathematical problems such as therapeutic drug monitoring issues. However this approach might be useful as it has proven to increase health care practitioners' awareness of TDM issues in our context and thereby might favour acceptation of interventions aiming at improving the situation. CI is now the standard treatment in our institution.

Our findings significantly add to the available literature in two respects. First, the combination of observational and qualitative approaches, allows for a proactive exploration of factors underlying poor performance of TDM at baseline. This approach has already been successfully applied for quality improvement in other areas of medicine [7;8]. Second, we also present the results after changing the mode of administration to CI using the same combined approaches.

Failure to implement laboratory recommendations actually originated from the perception that TDM sampling could not be trusted because of these issues and technical and organizational problems related to both drug administration and sample collection timing. It is noteworthy that however several participants perceived that TDM samples were often taken uselessly, most of them still continued to perform TDM on a routine basis. This could be explained by the fact that they seemed to be only aware of the difficulties they encountered but unaware of problems related to other steps of the TDM process. Several participants expressed during the interviews that the qualitative study had played an

important role by increasing their awareness towards TDM performance and what is really important for its quality.

Our study is limited in terms of number of patients enrolled in the observational part and by its performance in a single hospital, which could prevent from generalization. Yet, our data are in line with those reported by others in hospitals with similar general setting [1-3]. The main emerging conclusions correspond to those of previous qualitative studies addressing the issue of prescribing quality and implementation of complex medical processes, meeting the criterion of decontextualisation of conclusions which is important in qualitative research. More specifically, this applies to the identification of organizational issues and issues related to training and information resources [4-6].

Compared to the intermittent mode of administration (recommended in the current European and American labeling (both stating that vancomycin should preferentially be administered by intermittent 60-min infusions given at 6 or 12 h intervals), CI offers also several practical advantages. It allows indeed for a centralized preparation and ensures an easier mode of administration. Moreover, it also made monitoring and dose adaptation easier and more effective than the previous "peak and through levels" approach originally proposed for routine practice and still used in many hospitals [12], even though those proved very difficult to correctly implement in routine clinical practice [1;2;13;14]. This also appears clearly from the fact that the majority of proposed dose adaptations were accepted, probably because the clinicians perceived the CI of vancomycin and the corresponding TDM safer. The use of a loading dose makes that steady state concentrations can be reached fast during CI allowing dose monitoring and dose adaptation at 12h instead of 36h for intermittent administration [15].

The excellent stability of vancomycin, compared to β-lactams, allows its implementation even in countries or situations where ward temperatures are difficult to control [16]. Attention should, however, been paid to drug incompatibilities which should be individually tested or dedicated and distinct lines used.

Our data revealed that changing the mode of administration to CI coupled with a nomogram and a centralized preparation procedure met many of the issues and allowed to overcome several of the barriers identified as creating major difficulties for correct performance of vancomycin TDM when using its BID mode of administration. Implementation

of CI significantly improved TDM process measures in our context and in light of the universal nature of underlying factors can reasonably been expected to do so in other similar settings.

We also evaluated the clinical and pharmacokinetic aspects of vancomycin continuous infusion (loading dose 20 mg/kg; infusion of 2.57 g/24 h adjusted for creatinine clearance) by: (i) examining whether maintaining stable serum concentrations (set at 25–30 mg/L based on local susceptibility data of Gram-positive target organisms) can be achieved in patients suffering from difficult-to-treat infections; (ii) assessing toxicity and overall efficacy; and (iii) examining the correlation between AUC_{24h}/MIC and clinical outcome in patients for whom vancomycin was the only active agent against a single causative pathogen.

We were able to obtain a first initial serum level close to the target value (based on an assumed volume of distribution of 0.7 L/kg), which is in contrast to a recent report showing that larger loading doses may be needed for patient in critical conditions (where the volume of distribution of vancomycin was estimated to reach about 1.5 L/kg) [17]. However, we observed a first and rapid concentration fall that could be due to a larger clearance of vancomycin than originally proposed by several authors (0.65 x the creatinine clearance) [18;19] but also to a slow redistribution of the drug to peripheral compartments. This could be related to higher than anticipated renal clearance [20], but also to many other factors beyond the clinician's direct control. Because this point may be of critical importance for making practical recommendations, we discuss it in more details hereunder as this was not possible within the limits of our published paper.

> We first wish to underline that our loading dose was probably correct at the population level since it allowed reaching the expected mean serum concentration of 27.5 mg/L at 1 h after the end of the loading dose (which should include the distribution phase of vancomycin). Thus, it seems evident to us is that the decline in concentration seen afterwards and until 24 h, that affected about 57 % of the patients, was due to an insufficient rate of infusion during this period. The initial mean infusion rate was 9 mL/h (2160 mg/24h). After increasing the rate of infusion (the mean increase was of 700 mg/24h), the mean serum levels had returned to their original value. Afterwards, patients needed on an average 3 dose adaptations during the first week of treatment, 2 during the second week and 1 per week from the third week on.
>
> Interestingly enough, and as shown in figure D1, the global concentration time profile observed in patients > 65 years old was similar to that of the overall population. Although age > 65 years was identified as a risk factor for the development of nephrotoxicity during vancomycin treatment in our population, concentrations above the target range were not observed more frequently in this population (> 2 successive

serum vancomycin determinations >35 mg/L at steady state: 7/29 (24.1%) in patients >65 years and 6/24 (25.0%) in patients < 65 years).

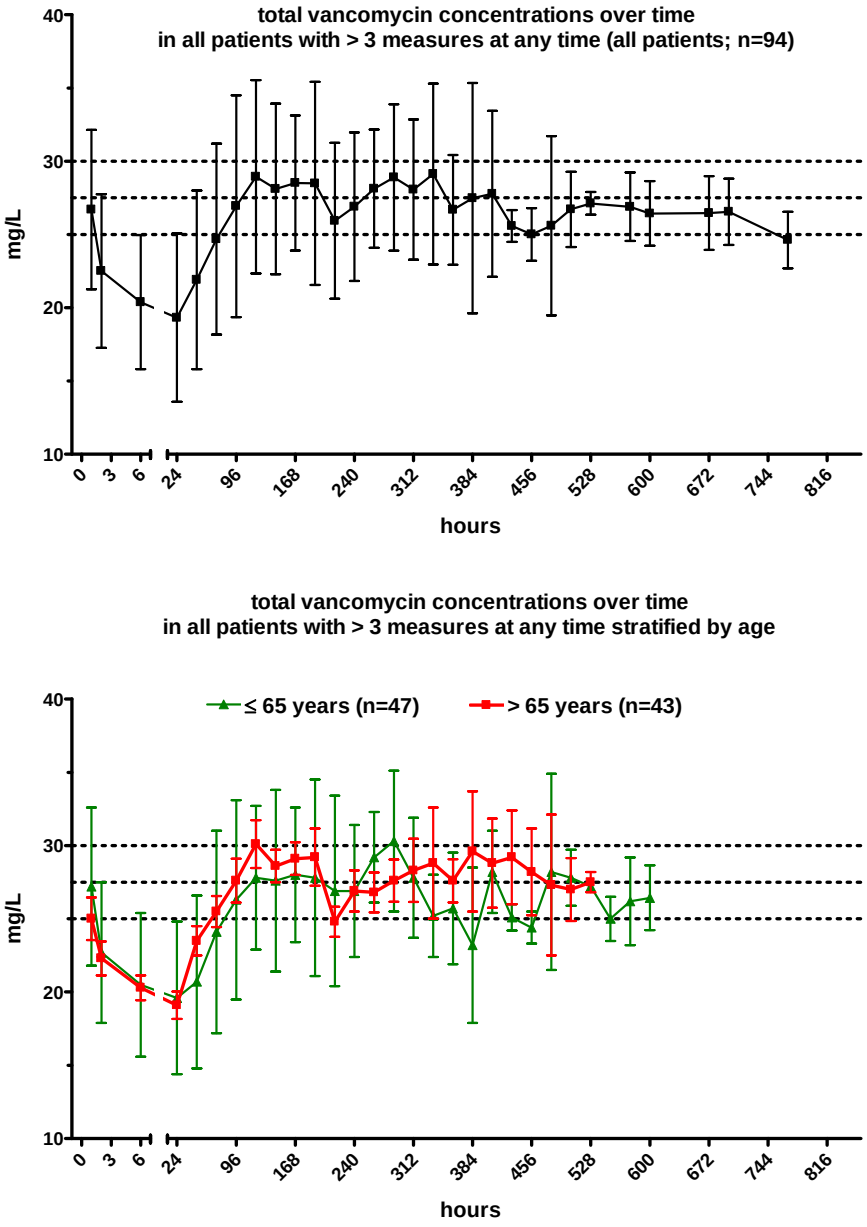


Figure D1: Influence of age on total serum vancomycin over time profile. Upper panel: all patients; middle panel: patients ≤ 65 years; lower panel: patients > 65 years. The number of patients correspond to those for which data was available at day 1 (24h). The number declines over time to 2 or 3 (last data points; no value is shown if corresponding to only 1 patient). Values are shown ± SD. Statistical analysis of the differences between groups at identical time points during the first 120 h (unpaired t-test two-tailed): no significant difference.

Based on these results, we would recommend daily monitoring at the initiation of treatment, which can be decreased to twice weekly monitoring during the second week and once weekly monitoring thereafter in patients with normal and stable renal function, irrespective to age.

Increased surveillance of vancomycin serum concentrations should be recommended in elderly patients or patients with pre-existing renal failure due to the increased risk of developing nephrotoxicity during treatment leading to subsequent increase in serum vancomycin levels or in patients with rapidly changing renal function in order to adapt treatment accordingly.

Based on the above observations, an initial infusion rate of on average 20 % higher (11 mL/h corresponding to 2640 mg/24h) could be proposed in all patients.

It can be argued that patients with increased calculated creatinine clearance have been underdosed and that those are responsible for the fall of concentration observed during the first 24 h of infusion. We therefore calculated and present in Figure D2 the serum levels for patients with a calculated creatinine clearance < 120 mL/min *vs.* those with a higher calculated creatinine clearance. No obvious difference was seen, and both groups showed a clear decline in serum concentrations during the first 24 h.

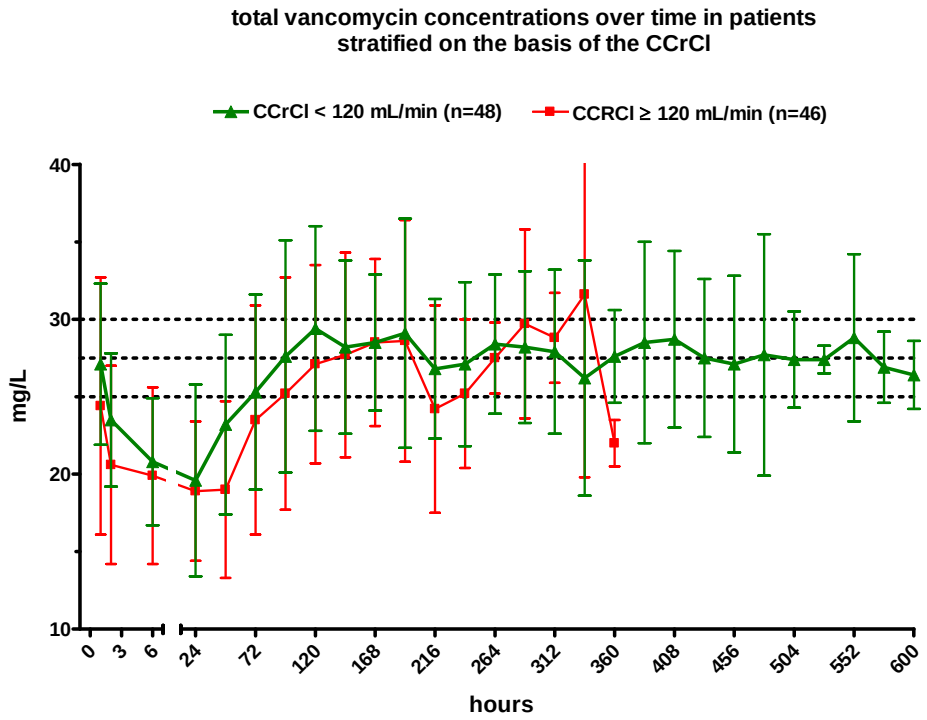


Figure D2: Influence of calculated creatinine clearance on total serum vancomycin over time. The number of patients correspond to those for which data was available at day 1 (24h). The number declines over time to 2 (last data points shown). Statistical analysis of the differences between groups at identical time points during the first 120h (unpaired t-test two-tailed): no significant difference.

This clearly shows that the too low initial rate of infusion affects all patients, irrespective of their renal function. We may suggest that this reflects an

underestimation of the true clearance of vancomycin. We used the accepted ratio of 0.65 to that of creatinine clearance [18] but this ratio was calculated on a limited numbre of patients. It may, therefore, need revision. Note, however, that patients with an increased calculated creatinine clearance have globally slightly lower initial serum concentrations. Additional correction for those patients may, therefore, be warranted.

In all but five of the patients needing dose increase, the infusion rate was increased beyond the maintenance dose and again decreased afterwards. Such a scenario is very likely in the context of daily monitoring of vancomycin serum levels and subsequent dose adaptation. In the absence of a loading dose, steady state is indeed considered to be reached after about 6 halve-lives, which, for vancomycin, would correspond to approximately 36 h. In this context, it must be noted that too frequent monitoring may actually lead to overcorrection of the dosage, since values may be obtained at a time at which equilibrium is not yet reached. This may lead to unanticipated overshooting that will require subsequent important dose decrease. These, in turn, may well lead to subtherapeutic concentrations. The same may happen in patients who really need a dose increase. Systematic administration of a second loading dose at 24 h to compensate for the difference between the concentration measured and the target concentration of 27.5 mg/L could be considered as this would allow to reach target levels in a timely manner and to re-evaluate steady state drug concentrations at 48 h.

The large variability in drug concentrations observed was probably due to intra- and interindividual variability in distribution volume and creatinine clearance. Simple factors such as insufficient control of drug administration or drug instability could be excluded as administration was made with the help of validated infusion pumps throughout and we checked for vancomycin stability in our setting. Interestingly enough, these was also a major variability in the free drug concentrations, as is now shown in Figure D2 (upper panel). We noted also a large variation of the percentage of free fraction (spanning from about 50 to almost 100 %). We also have examined whether values were constant for individual patients. The lower panel of Figure D2 shows that there was actually an important variability in the free fraction in individual patients. These results are not in line with what is usually reported in textbooks about the average protein binding of vancomycin (55%) and suggests that calculation of the free drug concentration based on the total serum concentration measured may lead to inaccurate conclusions.

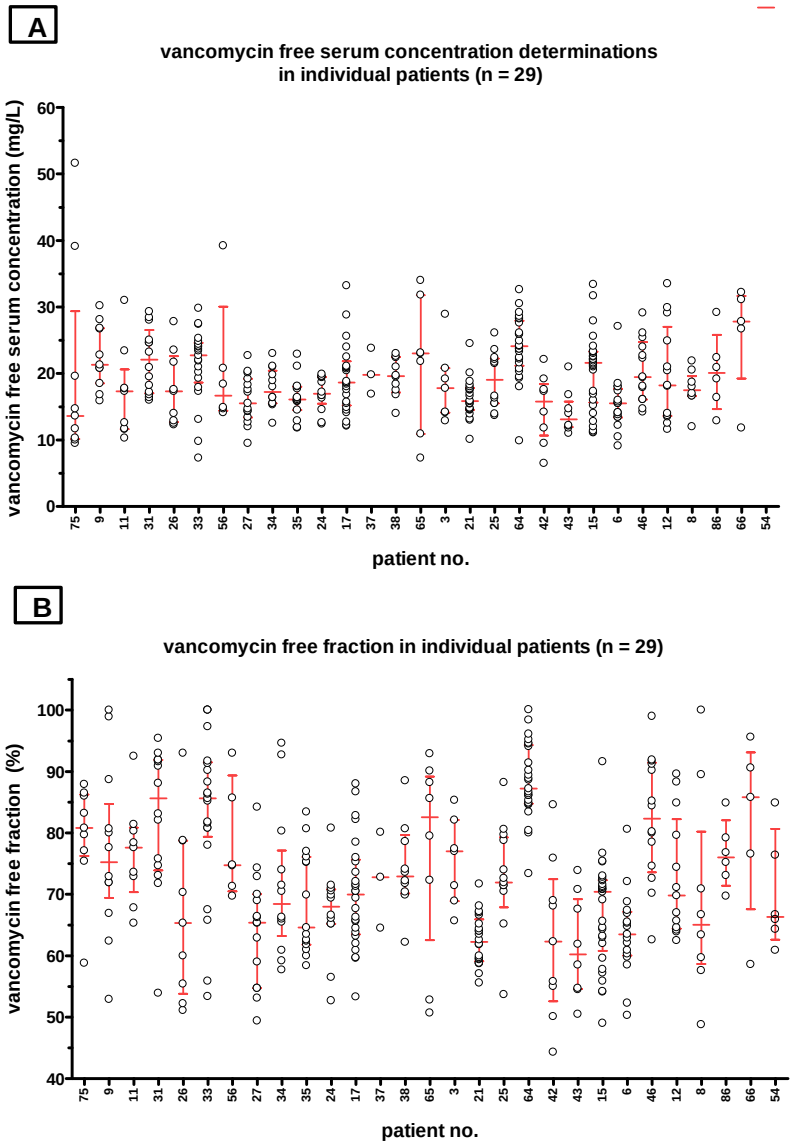


Figure D3: Upper panel: Individual free vancomycin serum levels in patients with more than three successive determinations after the first 96 h of infusion. Lower panel: Individual free fraction of vancomycin in the same patients. Each point represents one value. The red bars show the median and the interquartile range.

A series of analytical pitfalls have been described concerning the methodology for determination of the free fraction of antibiotics [21] that need to be considered here. Binding of drugs to the ultrafiltration device has been described but seems unlikely in this context as this would lead to lower free serum levels and thus to lower free fraction whereas the observed free fraction of vancomycin was somewhat higher than theoretically expected. A recent study found understimation and higher variability in vancomycin protein binding for clinical laboratory measurement compared to HPLC [22]. However this seems unlikely to be

the case in our context as the analytical method used (Architect®; Abbott Laboratories, Abbott Park, IL) had a coefficient of variation ≤2.75% and a between-day sample precision of 1.35% and, in our own experience, showed good correlation with standard HPLC methods [23]. Differences in pH or electrolyte concentrations of sera are known to influence protein binding but were not considered as no sample treatment was performed and therefore possible differences would only reflect the true clinical situation. Finally, storage of serum samples at 80°C followed by thawing at 25°C might have influenced the degree of protein binding but these effects were not analyzed.

Conversely, high inter-patient variability can be explained by the fact that our study population was heterogeneous, since it was hospital wide and, therefore, included patients with very different pharmacokinetic profiles and pathologies. But this is the daily reality the clinician is confronted to and makes our study more realistic than many other studies using narrowly defined populations.

High intra-individual variation can also be explained by changes in distribution volume and renal clearance over time which may be circadian or related to the changing disease status of the infected patient. Here again, those are clinical realities that need to be taken into account and may not be addressed by strict guidelines. It also heralds the limit of studies aiming at defining patients in terms of mean population and most likely deviations, as individual situations may modify the pharmacokinetic parameters much beyond what most available models can safely predict. Thus, it would reinforce our conclusion that monitoring remains essential even if only for detecting and correcting for unanticipated and unexplained deviations from the predicted values, and for checking that the actual correction measures were effective.

There is however room for improvement of our protocol. First, the decision to disregard CCrCl values >120 mL/min might have worsened the inter-patient variability, since there is evidence that a number of patients with severe infections may actually be excreting the drug faster than estimated on the basis of our truncated calculations. We also may need to enlarge our population before definitive recommendations can be made concerning the loading dose. Lastly, a larger infusion rate than what we originally proposed may be essential during the first hours of treatment. In this context, a recent publication suggested that a infusion dose of 3 g/daily may actually be necessary to obtain a target concentration of 25 mg/L [24]. In this context, it has been argued that therapeutic drug monitoring is not

required in patients with normal renal function [24]. However, in our study, maintaining the serum level at its targeted value required careful monitoring-based dosage readjustment even for patients with apparently normal renal function (up to 57% increase and 16 % decrease at the level of the population). Interestingly, no correlation between vancomycin serum levels and the patients' weight has been observed, but this reassuring conclusion is probably of limited value due to the limited number of patients with extremely low or high weights included.

Taken globally, however, we wish also to mention that the number of variables that need to be taken into account to correctly predict the serum levels make such predictions quite difficult in routine practice because of lack of data. Predictions are also difficult due to the variable impact these parameters may have when moving from one patient to another. At the end of the day, it may seem more reasonable to guide dosages based on measured levels than on complex algorithms and predictions.

Moving now to pharmacodynamics and toxicodynamics, we set our target level at a high value (25-30 mg/L) in order to cover organisms with decreased susceptibilities. We indeed observed MICs > 2 mg/L, but only when using Etest® determinations, which incidentally confirms that this method tends to measure higher MICs of Gram-positive organisms for this antibiotic compared to broth microdilution [25-27]. Previous studies showed that clinical failures (related to lack of antibiotic efficacy) may become more frequent when the MIC of the offending organisms exceeds 2 mg/L [28]. Such high sustained vancomycin levels may represent a risk for renal toxicity. We observed nephrotoxicity in 10% of patients however treatment had to be discontinued in only two of them. This rate of nephrotoxicity is actually in line with a previous study that set the target attainment limit at 28 mg/L but not as high as other reports observing up to 25% nephrotoxicity for patients with similar drug concentrations [29;30]. Of note, however, many patients presented other risk factors for the development of nephrotoxicity making the relationship between vancomycin levels and nephrotoxicity uncertain. Possibly, the interventions of the clinical pharmacist and infectious disease physicians could have prevented the persistence of higher, potentially toxic serum levels and may have minimized this risk. However, no correlation could be made between the development/occurrence of renal toxicity and vancomycin serum levels, thus questioning the validity of any threshold in this context.

The global rate of clinical cure or improvement we observed in this study was high and similar to that of other studies examining continuous infusion [15]. We found a direct correlation between the proportion of treatment failures and the MIC of the assumed causative organism when considering the whole group of patients. When limiting the pharmacokinetic/pharmacodynamic analysis to patients for whom vancomycin was the only active agent against the putative causal Gram-positive pathogen, we could confirm that low $AUC_{24\ h}$/MIC values were associated with a larger proportion of failures, with a threshold at values higher than that of 400 originally proposed [28].

The present study adds to the large body of knowledge on CI of vancomycin by: (i) showing how it can be implemented in non-ICU wards of a whole hospital; (ii) providing information on its clinical efficacy and safety; and (iii) presenting information about the ratio of drug exposure (AUC) to the MIC of the offending organism that may separate clinical success versus failure. Its use in ICU patients has been described elsewhere [15;17;31].

We suggest that a AUC_{24h}/MIC ratio even higher than proposed from an analyses made with discontinuous administration may be necessary to optimize clinical success. This may be due to the fact that our study not only included infections due to MRSA but also to other Gram-positive organisms such as coagulase-negative *Staphylococci* and *Enterococci*. Studies including one type of organism only must be encouraged in this context, but will probably need to be multicentric to assemble enough patients in a reasonable period of time, which would also introduce unwanted sources of variations. It must also be noted that inadequate surgical debridement of the infection site might have contributed to treatment failure in some cases and can be considered a confounding factor in the analysis of the clinical efficacy of vancomycin in our study.

By and large, however, and considering the serum levels reached, Gram-positive organisms with a MIC ≥ 2 mg/L will obviously prove difficult to be correctly covered by vancomycin given by CI, and, *a fortiori*, by discontinuous administration. This lends further support to the current vancomycin clinical breakpoints set for *Staphylococcus* spp by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [susceptible (S), ≤2 mg/L; resistant (R), >2 mg/L] and questioning the validity of the corresponding current CLSI breakpoints (S, ≤2 mg/L; R, ≥16 mg/L). In any case, there is clearly a need for methods allowing fast obtainment of serum concentrations in order to allow optimized and timely dose adaptation in pharmacokinetically critical situations or faced to difficult to treat infections or

infections due to less susceptible organisms. For organisms having vancomycin MICs >2-4mg/ml other antibiotics or other strategies are urgently needed.

We also report data on the free fraction, where even higher intra-patient and inter-patient variability was observed, and, most importantly, no constant correlation with total levels could be demonstrated. Our study confirms a previous report from our laboratory based on a more limited number of samples [23], and shows that it is, therefore, impossible to obtain a reliable estimate of the free fraction based on the total fraction measured at an individual sample level. We could not, however, establish which of the two values (total or free concentration) was best correlated with activity or toxicity. The hot debate about whether it is only the free fraction that needs to be considered for predicting antibiotic effects on prokaryotic or eukaryotic targets remains therefore open as far as our results are concerned.

Our study has several limitations that need to be underlined.

Firstly, TDM samples were still sometimes performed via the infusion line of vancomycin by less experiences personnel. However, since the vancomycin concentration in the infusion bag is 10 mg/mL, which is about 500-fold larger than the targeted serum levels, such a mistake is immediately picked up by the laboratory and a new sample asked. Secondly, the necessity of a dedicated infusion line for vancomycin was mentioned but this problem was solved by the standard application of an extra infusion line in patients for whom the drug was prescribed. A third problem encountered in daily practice was the occasional difficulties in obtaining additional infusion pumps from other wards but, this never leading to treatment discontinuation.

Second, more sophisticated methods for estimating the true creatinine clearance could have been used and could have helped in better fine-tuning dose adjustments. However, this approach was perceived as unrealistic in a context of hospital wide implementation.

Third, and in the general context of clinical trials, the absence of a control group treated by discontinuous infusion did not allow confronting our data on safety and efficacy. With respect to quality of TDM, we only could have "pre"- and "post"-intervention groups. Although prospective, randomized trials in which control and intervention groups are enrolled

during the same and defined period are obviously preferable, this could not be done for both ethical and practical reasons. Most health care professionals, indeed, perceived TDM as applied to the BID administration as being unreliable and too difficult to implement correctly, even before we started our observational studies. When this part of our work was completed, the insufficiencies of TDM were so blatant (and known within the Institution) that it was felt impossible not to react with a constructive proposal, namely switching to an improved mode of administration such as the continuous infusion. Future prospective and randomized trials will, therefore, need to be performed in Institutions where the BID mode of administration is still applied and accepted as the standard of care by health care practitioners.

Fourth, and in the context of toxicological evaluation, we potentially missed a number of patients presenting red man syndrome because patients receiving less than 72h of vancomycin treatment were systematically excluded from our analysis.

Fifth, and in the context of pharmacodynamic evaluation, the low number of patients, especially with organisms with high MIC's, made the recursive partitioning analysis intrinsically weak. Future studies should, therefore, further evaluate hospital-wide implementation of CI on a larger number of patients. They should try to uncover the factors that contribute to the large variability of vancomycin concentrations in individual patients in order to further improve dosing strategies and obtain more stable drug concentrations. Other aspects, such as pharmacoeconomic advantages, should also be examined.

Lastly, we showed that CI of vancomycin can be implemented hospital-wide, however the heterogeneity in our study population might have prevented from uncovering the factors explaining inter- and intra-patient variability in drug concentrations observed. Further research therefore should focus on in depth pharmacokinetic analysis in well defined patient populations such as orthopaedic patients with osteomyelitis, hematologic patients with documented infections, patients infected with more resistant organisms with MICs between 2-8 mg/L or patients with hyperclearance, or morbidly obese patients.

A more critical limitation may affect our conclusions, namely the proposal to direct therapy based on an AUC_{24h}/MIC ratio of at least 400 (or even higher if using our own data). The definition of this target range applied during our study was based on the available data from well designed animal studies pointing at an AUC_{24h}/MIC ratio of 400 necessary for

optimal clinical success (see the review of Craig [32]) together with limited but quite compelling human data from one clinical study pointing at the same AUC/MIC ratio in patients with lower respiratory tract infections [28] . Both this study and our own study have been performed on a limited number of patients and should be confirmed by well designed prospective trials including specific types of infection and organisms with decreased susceptibility (but still susceptible to vancomycin) before definite conclusions can be drawn according to the target AUC_{24h}/MIC ratio for this agent. In the meantime, however, a target of AUC_{24h}/MIC ratio of 400 in the empirical setting, assuming an MIC of 1 mg/L, seems reasonable at first glance (this was the MIC of the majority of organisms targeted during our study), which means a stable serum level of approx. 17 mg/L. However, we also had strains with higher MICs (up to 2 mg/L), which would, therefore, mean that higher serum concentrations (up to 34 mg/L) may be required. Our target concentration of 25 to 30 mg/L may therefore appear, retrospectively, as acceptable, especially since it does not markedly exceed the toxic concentration (28 mg/L, according to [29]). Of course, once susceptibility data are available, serum concentrations may be decreased to avoid unnecessary exposure to the drug. Conversely, we will not recommend to increase the serum level above 30 mg/L, and this heralds a limitation in the use of vancomycin for organisms with an MIC ≥ 2 mg/L. Patients with infections caused by such organisms may, therefore, be eligible for treatment with alternate antibiotics, such as linezolid, telavancin, tigecycline, or ceftaroline [33;34], but with the caveat that each of those drugs carry their own limitations. We would not recommend daptomycin without careful susceptibility testing based on the observation that strains with increased MICs for vancomycin often also show a decreased susceptibility to daptomycin [35].

It may be asked whether there would not be also room for improving the conventional (BID) mode of administration of vancomycin. This may be all the more critical since this mode of administration is still widely used and even recommended in the recent guidelines of the Infectious Diseases Society of America (where it is plainly said that continuous infusion should not be recommended [36]). Our view is that many important limitations concerning routine performance of TDM during BID administration of vancomycin have been identified in our setting, several of which have also been reported elsewhere. Current guidelines on vancomycin TDM recommend only trough sampling because reliable peak samples are difficult to obtain in routine practice (there is also non-written comments that recommending through levels only stems from unjustified extension of aminoglycoside TDM recommendations to vancomycin). Our study shows that important deviations also occur for

trough samples, compromising the validity of these samples. Furthermore single trough levels do not allow for good estimation of the AUC which is the parameter driving efficacy for vancomycin. The major barriers to correct sample timing identified during our qualitative study were insufficient knowledge and awareness of health care practitioners concerning pharmacokinetics and the importance of correct sample timing. Combined with ill-adapted administration techniques and organizational issues, this did not allow sampling according to the hospital guidelines. Thus, optimizing the BID mode of administration would require considerable effort from the ward personnel. Overcoming all these issues, and running the necessary educational activities seemed to all stakeholders a difficult and endless task due to frequent changes in staff, especially in the context of a teaching hospital. Clinical pharmacists providing pharmacokinetic services have proven major improvements in this context in the US [37;38] but those are not routinely available in the European context. Random sampling with correct registration of the actual sample timing has been proposed as a means to ensure correct registration for the pharmacokinetic calculations needed with TDM when using the BID mode of administration. Our observational study revealed that such information, however, was only transmitted correctly to the clinical laboratory in 55 % of cases. Computerized prescribing coupled with registration of the patient and the sample including sample timing directly into the hospital informatics system seems a good solution providing such infrastructure is available. However, several samples will still need to be performed to allow for correct estimation of the AUC during BID administration of vancomycin.

Actually, available evidence of studies comparing vancomycin BID to CI does not allow drawing definite conclusions to which administration technique should be preferred in clinical practice. We can even go on to suggest that there is no published and clear evidence for BID to be superior to CI (see our analysis presented in the chapter 1 of this Thesis). In this context, it would be worth conducting a large clinical trial comparing feasibility, pharmacokinetics, pharmacodynamics, clinical outcome and tolerability of an optimized BID towards administration of the same daily dose of vancomycin by CI.

Altogether, our study demonstrates that hospital-wide implementation of vancomycin administration by CI may be a practical and appropriate option for the treatment of patients with severe Gram-positive infections provided that the corresponding MICs remain <2 mg/L. CI, however, will still require monitoring blood levels because of (i) the difficulties in correctly predicting vancomycin serum concentrations (using presently accepted models based on

CCrCl) as well as unanticipated large intrapatient and interpatient variations and (ii) the necessity to adjust these levels to the MIC of the causative organism. Whilst vancomycin stability will not cause issues (even under poorly controlled room temperatures as evidenced from many reports), independent lines (or multi-lumen catheters) will need to be used for co-administration of other intravenous medications in order to avoid drug incompatibilities. Finally, our approach could be applied in the future to other AUC_{24h}- or "time above MIC"-dependent anti-infective drugs such as, for antibiotics, clindamycin, macrolides, novel tetracyclines (tigecycline, e.g.), novel glycopeptides with short to medium half-lives (telavancin,e.g.) or linezolid (for which some data are already available [39;40]), or, for antifungals such as triazoles and flucytosine.

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Additional Material

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Correlation between free and total vancomycin serum concentrations in patients treated for Gram-positive infections

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ABSTRACT

Routine therapeutic drug monitoring (TDM) reports only total vancomycin (VAN) concentrations, although protein binding varies and it is generally accepted that only free VAN is active. The aims of this study were to examine the correlation between free and total VAN concentrations in order to estimate whether free VAN levels can be predicted based on its total concentration. A high-performance liquid chromatography (HPLC) method was set up and validated (against routine laboratory immunoassays) for measurement of free [ultrafiltration (Centrifree®); cut-off 30 kDa] and total [solid-phase extraction (Oasis® MCX cartridge)] VAN in serum. Samples ($n = 65$) from patients ($n = 15$) treated by continuous infusion were analysed. There was a wide variation in free to total VAN ratios [range 12–100%; mean 63.6 ± 25.8%, with 59 values falling outside the 95% confidence interval (57.3–69.9%); median 70.2%]. The correlation between free and total VAN was poor ($R^2 = 0.55$). Artefacts such as pH variation of sera could be excluded. Both intrapatient and interpatient variabilities were large and no correlation could be made with patients' clinical conditions. Total VAN concentration is not predictive of free VAN concentration, suggesting that actual determination of free VAN might be recommended as an improved method of TDM.

1. Introduction

Despite the recent introduction of new antistaphylococcal drugs, vancomycin (VAN) remains widely used to treat infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and other β-lactam-resistant Gram-positive cocci [1–3]. However, the potential rise in minimum inhibitory concentrations (MICs) of VAN in target organisms [4,5] makes it increasingly critical to adjust its dosage in order to ensure adequate concentrations in blood and other infected areas as well as to avoid undue toxicity [6–8]. Moreover, only the total fraction of VAN is routinely measured and taken into consideration for dosage adjustment in clinics [7], even though it is known that, as for most antibiotics [9], it is probably the free fraction of VAN that is critical both for diffusion into infected areas [10,11] and for binding to its bacterial target [12,13]. In recent recommendations [7] it was stated that free drug levels could be predicted based on an average binding value of ca. 50%. An original study concluded that there was a satisfactory correlation between free and total VAN concentrations in patients' serum, with a mean value for the free fraction of 41.9 ± 14.1% [14], apparently justifying this approach. Yet other studies have pointed out an important variability in VAN protein binding not only between animals and man but also between volunteers and patients and between patients [15–18]. Because the importance of optimising VAN therapy as effectively as possible has been advocated by many authors in difficult-to-treat patients for the reasons stated above (see, e.g., [7,19–22]), we decided to re-examine to what extent free and total drug concentrations are correlated. To this effect, we used samples from a population of patients receiving VAN in our institutions for suspected or documented Gram-positive infection and for whom therapeutic drug monitoring (TDM) was routinely performed under close supervision by a clinical pharmacist. A preliminary account of the findings has appeared previously [23].

2. Materials and methods

2.1. Materials

VAN and cefuroxime (CXM) (used as internal standard) were obtained from GlaxoSmithKline S.A. (Genval, Belgium) as the commercial products Vancocin® 500 and Zinacef®, respectively, registered for clinical usage in Belgium and complying with the

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provisions of the European Pharmacopoeia (>90% purity). All products used for high-performance liquid chromatography (HPLC) analysis were of HPLC grade and were obtained as follows: acetonitrile and methanol from BioSolve® (Westford Chemical Corporation, Westford, MA); sodium acetate anhydrous from Acros Organics (Thermo Fisher Scientific Inc., Waltham, MA); glacial acetic acid, orthophosphoric acid 85% and hydrochloric acid fuming 37% from E. Merck AG (Darmstadt, Germany); and pure formic acid from Riedel-de Haën (Honeywell Specialty Chemicals Seelze GmbH, Seelze, Germany). Oasis® MCX solid-phase extraction cartridges [average pore size 80 Å; average particle size 30 μm; surface functionality (sulfonic acid substituents $-SO_3H$) 1.0 meq/g; sorbent mass 1 cc] and analytical columns [Atlantis® dC18 (150 mm × 4.6 mm) and Symmetry Shield® RP18 (150 mm × 4.6 mm)] were from Waters Corp. (Milford, MA), and ultrafiltration devices (Centrifree®; cut-off 30 kDa) were from Millipore Corp. (Billerica, MA).

2.2. Sera

Commercial human serum (from AB donors) used for setting up the methods was purchased from Lonza Ltd. (Basel, Switzerland). Clinical samples were from hospitalised patients undergoing treatment with VAN at two of our university hospitals (Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium, and Cliniques Universitaires Saint-Luc, Brussels, Belgium) in general internal medicine, intensive care, orthopedy and haematology wards and for whom TDM was ordered by the attending physician as part of their normal care. Material used for the present study was obtained as leftovers from samples after transfer and use by the clinical laboratories of the participating institutions and was maintained at −20 °C until analysis.

2.3. Sample preparation and HPLC assay of free and total vancomycin

An HPLC assay was used to ensure maximal accuracy and also because none of the routine laboratory methods for VAN determination are validated for assay of the free drug. The following methods were devised, based partly on a method describing the extraction of total VAN from serum [24] and the behaviour of CXM chosen as internal standard [25]. For total VAN, thawed samples were subjected to solid-phase extraction by passage through Oasis® MCX cartridges conditioned with 1 mL of methanol followed by 1 mL of water. Samples (500 μL) were mixed with 500 μL of water, 30 μL of orthophosphoric acid 85% and 10 μL of CXM (1 g/L). Following low-speed centrifugation, 1 mL was loaded on the cartridge and completely drawn through under light vacuum (typically 2 mmHg). After washing with 1 mL of 0.1 N HCl and twice with 100 μL of methanol, VAN and CXM were desorbed with 1 mL of methanol containing 5% ammoniac and the eluate was immediately neutralised with 36 μL of HCl 37%. Following evaporation under airflow at room temperature, the residue was reconstituted in 250 μL of 70 mM sodium acetate buffer (pH 5.0) for HPLC analysis (buffer mobile phase). The latter was performed on an Atlantis® dC18 column using stepwise gradient elution at a flow rate of 1 mL/min unless otherwise stated with the buffer mobile phase and the elution phase (acetonitrile/methanol/0.1% formic acid 63:27:10 v/v/v) being varied from 95–5 (2 min), 70–30 (3 min), 60–40 (21 min; 0.5 mL/min) and 5–95 (2 min). Detection was made at 280 nm using a diode array detector with analysis of the absorption spectrum (200–400 nm) for positive identification of VAN and CXM. The concentration of VAN was calculated by integration of the peak area ratio between VAN and CXM, based on standard calibration curves. For free VAN, 500 μL of sample was subjected to ultrafiltration using Centrifree® tubes by centrifugation at 2000 × *g* (3153 rpm) for 30 min at 4 °C (5810R Eppendorf centrifuge; Eppendorf AG, Hamburg, Germany). The filtrate (200 μL) was mixed with 2 μL of CXM (0.5 g/L) and used as such for HPLC analysis. The latter was performed with a Symmetry Shield® RP18 using a mobile phase made of 70 mM sodium acetate buffer (pH 5.0) and acetonitrile/methanol (70:30 v/v) mixed to form a stepwise gradient exactly as for total VAN except that the 60–40 step was run for 16 min only and at 1 mL/min.

All analyses were carried out with a Waters 2690 Separations Module, equipped with two pumps, a degassing line and a thermostated autosampler, connected with a Waters 996 photodiode array detector and operated with the Millenium32® software (Waters Corp.). Baselines were visually inspected and were manually adapted when necessary. The typical intraday coefficients of variation for total VAN were 6.8% at 4.4 mg/L, 0.2% at 15.7 mg/L and 0.2% at 26.8 mg/L, and for free VAN were 12.5% at 2.7 mg/L, 2.3% at 9.9 mg/L and 2.5% at 15.1 mg/L.

2.4. Comparison with routine laboratory methods

Samples were analysed independently by two established laboratory methods: a particle-enhanced turbidimetric inhibition immunoassay (PETINIA) performed with a Dimension® Xpand® Plus instrument (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany), which was used for both free (after ultrafiltration) and total VAN measurements; and a fluorescence polarisation immunoassay (FPIA) performed with an Abbott AxSYM Instrument (Abbott Diagnostics, Abbott Park, IL) for total VAN measurements.

2.5. Patients and clinical data

Patients were from two teaching hospitals and were treated for suspected or proven Gram-positive infection by an organism susceptible to VAN and for whom the use of β-lactams was considered inappropriate. Pertinent clinical, microbiological and biological data were obtained by retrospective analysis of the corresponding medical files. All patients included in the modelling analysis were from a single institution (Cliniques Universitaires UCL de Mont-Godinne) and received VAN by continuous infusion for documented Gram-positive infection. No patient received haemodialysis or haemofiltration during the treatment period.

2.6. Ethical considerations

The present study was part of a larger study aiming at evaluating the impact of the supervision of TDM by a clinical pharmacist and was approved by the ad-hoc ethical committee of the leading clinical centre for this study (Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium).

2.7. Statistics

Descriptive statistics and linear regression analyses were made using GraphPad Prism® software (GraphPad Software, San Diego, CA). Modelling was performed using JMP 7.0® (SAS Institute Inc., Cary, NC).

3. Results

3.1. Validation of the assay methods

Commercial serum samples were spiked with known amounts of VAN to set up the methods and to determine the recovery of the antibiotic. Fig. 1 shows two typical chromatograms obtained from the serum of a patient treated with VAN and analysed for free

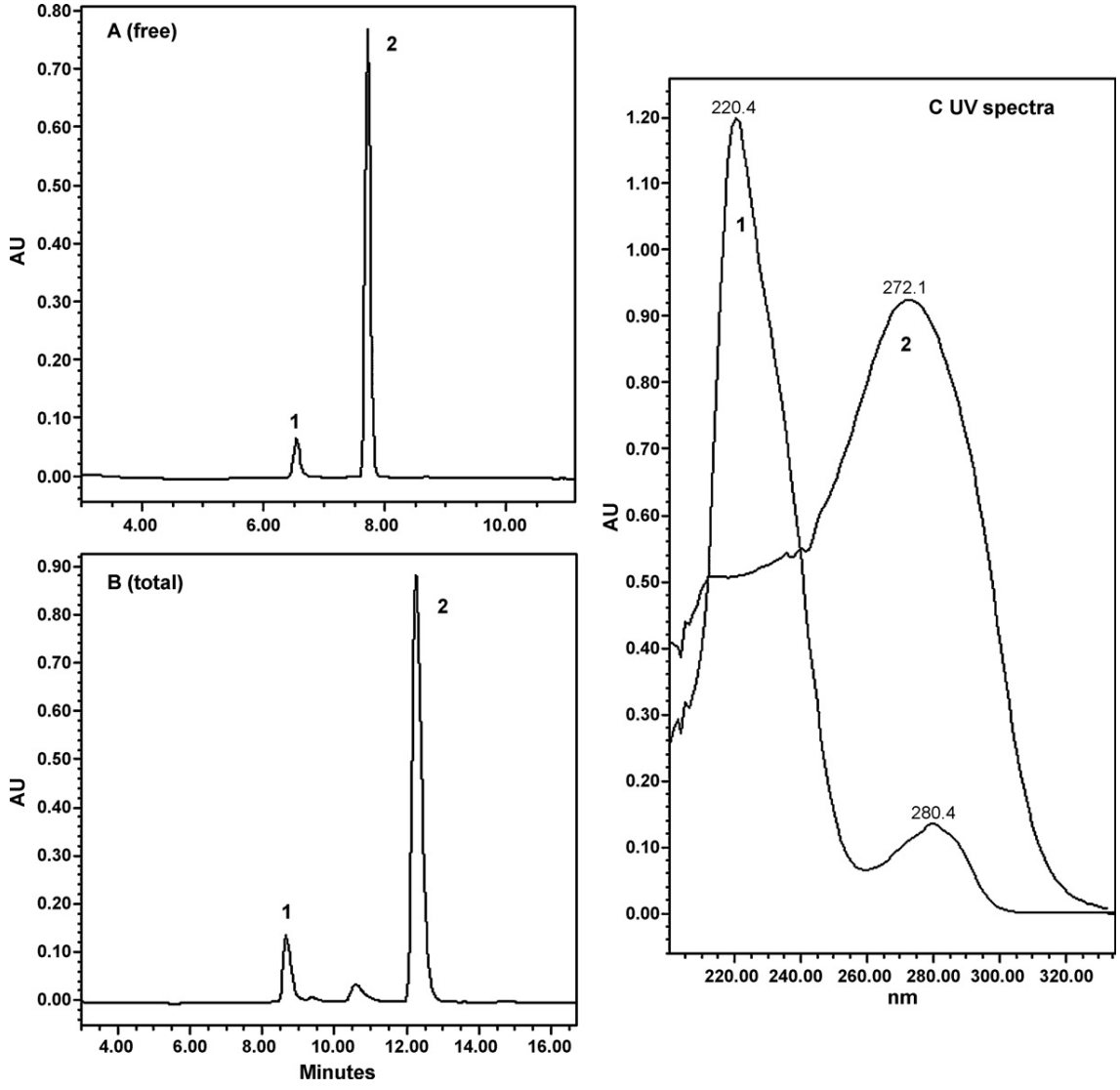

Fig. 1. Typical chromatograms of (A) free and (B) total vancomycin from a clinical sample. **1**, vancomycin; **2**, cefuroxime (internal standard). (C) Identification by ultraviolet spectra of vancomycin (**1**) and cefuroxime (**2**).

(Fig. 1A) and total (Fig. 1B) VAN content, together with the identification of VAN and CXM based on their absorption spectra (Fig. 1C). The method allowed for unambiguous detection of VAN with a retention time of ca. 6.5 min (free) and 8.5 min (total), respectively, and well separated from the internal standard (CXM) in both situations with a limit of quantification of 1.6 mg/L (total) and 0.3 mg/L (free), a linearity of the response up to 300 mg/L (free and total), intraday variation coefficients of ≤8.3% (total) and ≤14.8% (free) and interday variation coefficients of ≤9.6% (free) and ≤15.4% (free) for three concentrations (7.5, 25 and 45 mg/L). VAN recoveries (free and total) tested at three concentrations (10, 20 and 40 mg/L) were between 98.2% (lowest) and 103.9% (highest) of the nominal value. No or little disturbing interferences were noted for most of the samples analysed.

Fig. 2 shows the correlation between the HPLC method and the clinical laboratory method (PETINIA) for both free and total VAN using clinical samples selected for a drug content spanning the entire meaningful clinical range (3–35 mg/L). The correlation between the two methods was satisfactory ($R^2 > 0.95$), but with slopes around 0.8 and a slight divergence of zero values (up to 1.9 mg/L). As a further validation, total VAN concentrations were compared between HPLC and another clinical method (FPIA), with a correlation coefficient (R^2) of 0.83, a slope of 0.82 and a deviation of the origin at 2.2 mg/L.

A potential influence of pH on the extent of protein binding of VAN was examined as follows. First, the pH of all samples was measured and it was observed that it could vary between 7.4 and 8.1. The values of free fraction observed for eight clinical samples with pH values spanning this range were then compared, but no correlation between binding and pH was seen. In parallel, samples from one batch of commercial VAN-free serum were spiked with VAN at 10, 20 or 30 mg/L, adjusted to pH 7.1, 7.4 and 8.1, and then processed for measurement of free and total VAN. The mean value of free VAN was 40.7 ± 4.4% for all samples ($n = 25$) with no significant effect of pH or concentration taken individually [$P \geq 0.2$, one-way analysis of variance (ANOVA)] or globally ($P \geq 0.2$, one-way ANOVA).

3.2. Determination of free/total vancomycin concentration ratios in clinical samples

First, the free and total VAN concentrations were measured using the HPLC method in 65 samples obtained from 15 patients

treated with VAN in a single institution and receiving the drug by continuous infusion (with a total concentration target set at 27 mg/L) for 1–43 days (mean 19 ± 10 days). The results of this analysis are presented in Fig. 3 as (i) the percentage of free VAN with respect to total VAN (upper part) and (ii) the correlation between the free and total concentrations of VAN in each individual sample. There was a clear variation of the total concentration despite the mode of administration used (continuous infusion), which will be analysed elsewhere. Within the context of the present paper, the main observations are that: (i) the mean value for percentage of free VAN was close to 65%, which is higher than usually considered [7]; (ii) there was a considerable spread of the individual values, which increased almost continuously from as low as 12% to 100% (samples with values >100% are within the error margin of the assay); and (iii) only a weak correlation could be established between the free and total concentrations for each of the samples, with the majority of the data falling outside of the 95% confidence interval. Similar conclusions could be reached if the values obtained by HPLC for both free and total concentrations were corrected for discrepancy between HPLC and PETINIA determinations using the equations shown in Fig. 2.

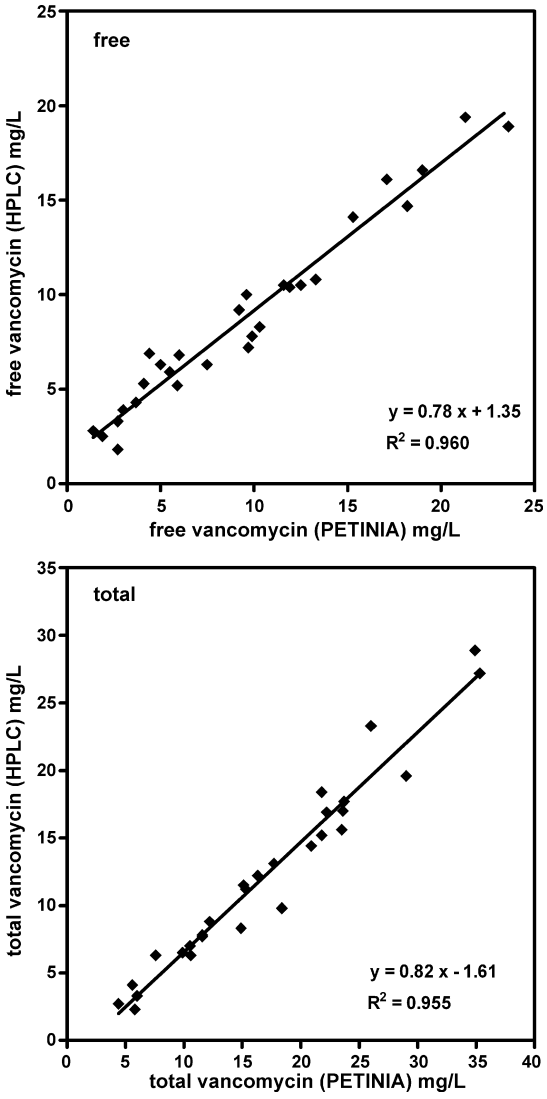

Fig. 2. Correlation between the vancomycin serum concentration (upper panel, free; lower panel, total) as determined by high-performance liquid chromatography (HPLC) (ordinate) and by the routine clinical laboratory assay [particle-enhanced turbidimetric inhibition immunoassay (PETINIA)] (abscissa).

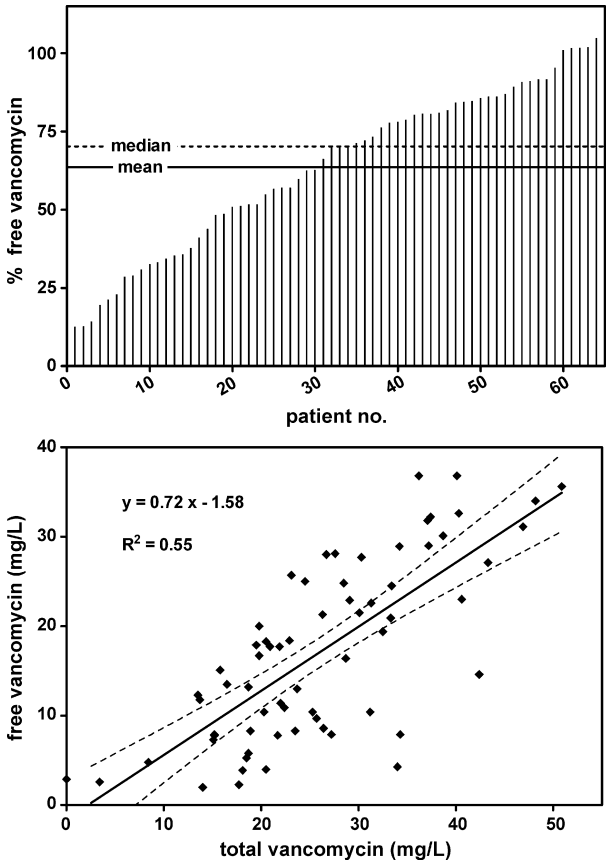

Fig. 3. Free and total vancomycin concentration in 65 samples from 15 patients receiving vancomycin by continuous infusion. Upper panel: % of free vancomycin in individual samples ranked by increasing value with mean (solid line) and median (dotted line). Lower panel: correlation between free and total vancomycin concentrations for each individual sample with 95% confidence interval (dotted lines).

Two approaches were used to try to gain insight into this apparent lack of correlation between free and total VAN concentrations. In the first approach, we examined whether binding was influenced by the actual total concentration of VAN, disclosing potential saturation. No significant correlation between the free/bound percentage ratio and the total concentration could be demonstrated (regression equation $y = 0.29x + 56$; $R^2 = 0.012$; $P = 0.37$). In the second approach, samples were stratified (i) by patients (for whom at least four independent samples could be assayed) and (ii) by medical environment and underlying pathology [intensive care (trauma and severe sepsis), haematology (post-chemotherapy fever) and orthopedy (trauma)]. Fig. 4 shows that (i) the intrapatient variation in percent protein binding was very large (28.6–87%; mean 50.1%), however, interpatient variability was even larger ($P < 0.01$, two-way ANOVA) and (ii) the medical environment and corresponding main underlying pathology was without apparent effect. In a second step, a logistical regression model was applied using patients' available clinical data (gender, age, main diagnostic, co-morbidities, co-administration of other antibiotics, administration of immunosuppressors, total protein levels, creatinine level, white blood cell counts and C-reactive protein level) to try to relate the free fraction level to one or several of these parameters, but without success ($P > 0.05$ for all conditions univariate or multivariate). Of note, the patient population analysed did not include burns patients, patients with insufficient protein diet or patients suffering from nephrotic

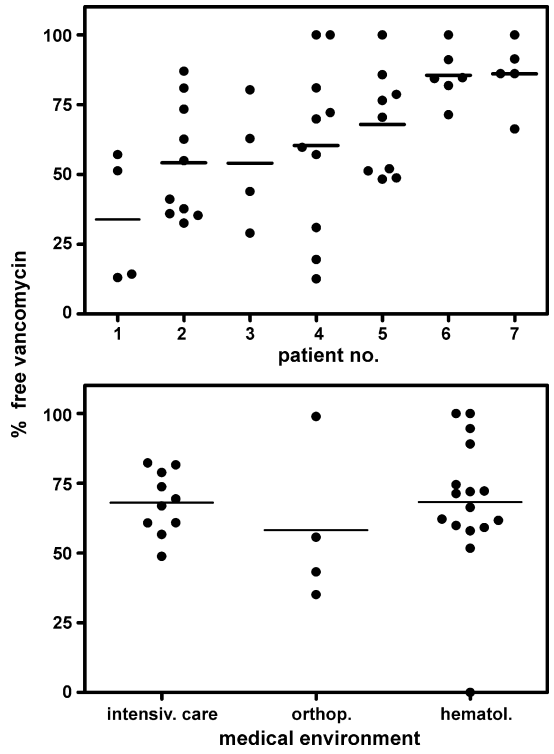

Fig. 4. Variation of free vancomycin fraction: individual data and mean (horizontal bar). Upper panel: stratification of samples by individual patients for whom four or more samples were available. Lower panel: stratification of samples by hospitalisation ward (with different main underlying pathology) using one single sample by patient obtained during treatment {the difference between the three groups is not significant [$P = 0.68$ by one-way analysis of variance (ANOVA); $P = 0.37$ by Kruskal–Wallis test (non-parametric ANOVA)]}.

syndrome, severe hepatic dysfunction or other clinical situation in which serum protein content could have been qualitatively grossly abnormal.

4. Discussion

The present study shows that the free fraction of VAN can vary considerably in samples obtained from patients treated with this drug, irrespective of their main medical situation, not only between patients but also for an individual patient during treatment. Previous studies have already found a large variation in VAN protein binding, with ranges from 7.9% to 71% [14], 23% to 59% [18] and 3.7% to 47% [26]. The present study extends over these observations by showing that (i) this variability can be even larger than suspected and (ii) the free fraction is only poorly related to the total drug concentration, making predictions very hazardous. This is in apparent contrast to the conclusion of a previous study [14] where free and total VAN concentrations were claimed to be correlated. This study analysed a similar number of samples ($n = 62$) from patients ($n = 12$) also suffering from infection. Close analysis of the raw data of this study, however, shows a coefficient of determination (R^2) of 0.67, which was improved to 0.90 (and presented as such in the abstract) by use of orthogonal regression and suppression of one sample with a high protein binding value. We did not apply such corrections here because the main point of this study was not so much about getting population information but to examine how the total VAN concentration of a given sample could safely and reliably predict the corresponding free drug concentration. Also, most samples used by Ackerman et al. [14] were apparently drawn over a short period of time, whereas ours were obtained over the whole duration of treatment, giving more chance for patient and treatment factors to exert a disturbing effect and thereby being more representative of the true clinical situation. Finally, in contrast to the study of Ackerman et al., we did not exclude patients on the basis of age, sepsis, hypotension or trauma, which are common situations encountered in VAN-treated patients.

Variability of the free to total VAN concentration ratios, and the ensuing lack of predictability of the true free level from total level determinations, has been ascribed to lack of control of pH during separation of the unbound and bound drug [27]. This artefact could be ruled out here as our validation study did not evidence a variation of binding due to pH (within the range of values observed in our clinical samples) at clinically meaningful VAN concentrations. The serum protein binding characteristics of VAN have been studied in detail and found to be predominantly related to albumin and immunoglobulin A (IgA) serum content [28,29]. In our study, no correlation could be made with total serum protein content. IgA could not be specifically assayed as the study was retrospective and non-interventional, but no patient had evidence of myeloma or other gross pathology involving IgA.

The significance of the present data, together with the observation made by others regarding the variability in the free fraction, with respect to the activity of VAN needs to be underlined. Indeed, several studies indicate that a critical threshold of drug exposure [pharmacodynamically expressed as the 24-h area under the concentration–time curve divided by the MIC (AUC_{24h}/MIC) [30] or, in recent guidelines, as minimal trough levels in the case of discontinuous administration [7]] must be met to ensure clinical success in staphylococcal infections. Because it is the free VAN concentration that probably matters most in this context (see discussion in [7,31]), reporting total levels may be insufficient and even misleading. The same could also apply to the use of TDM values for prevention of nephrotoxicity (see [32] for an example with continuous infusion), since it may develop via a tubular secretion mechanism [33] that ought to be primarily related to the free rather than the total drug concentration. More systematic assay of free VAN concentration could, therefore, be of interest to improve our knowledge of VAN pharmacodynamics/pharmacokinetics and help in better assessing which parameter and which serum concentration values are associated with successes and failures or with toxicity. Conversely, it could be argued that the variability in the therapeutic and toxicological responses and the often claimed difficulties in linking the results of TDM with clinical outcomes [34] may find its origin in the unpredictability of free VAN levels from total levels as described here.

Acknowledgments

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Competing interests: None declared.

Ethical approval: Ethical approval awarded by the Commission d'éthique médicale (COM 050) of the Cliniques Universitaires UCL de Mont-Godinne, with no. 48/2007 (local) and B03920072246 (unique Belgian no.) communicated on 25 July 2007.

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Stability and compatibility of vancomycin for administration by continuous infusion

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Background: Vancomycin is increasingly used by continuous infusion, but few specific data are available about stability under practical conditions of preparation and use, and compatibility with other intravenous drugs commonly used in the routine hospital setting.

Methods: Vancomycin stability [defined as recovery ≥93% of the original content (validated HPLC assay)] was examined throughout the whole process of centralized preparation, storage and use in the ward by infusion for up to 48 h, with allowances for deviations from recommended practice [exposure to high temperature; use of concentrated solutions (up to 83 g/L)]. Compatibility was assessed by mimicking co-administration in a single line via Y-shaped connectors with contact of 1 h at 25°C, followed by visual inspection (professional viewer), detection of particulate matter (particle analyser) and HPLC assay of vancomycin.

Results: Vancomycin was stable during the whole process and also during 72 h exposure of concentrated solutions at temperatures up to 37°C. Major incompatibilities were seen with β-lactams (temocillin, piperacillin/tazobactam, ceftazidime, imipenem, cefepime and flucloxacillin) and moxifloxacin, but not with ciprofloxacin, aminoglycosides and macrolides. Propofol, valproic acid, phenytoin, theophylline, methylprednisolone and furosemide were also incompatible, whereas ketamine, sufentanil, midazolam, morphine, piritramide, nicardipine, urapidil, dopamine, dobutamine and adrenaline were compatible. No effect or incompatibility with *N*-acetylcysteine or amino acid solutions was detected.

Conclusions: Centralized preparation of vancomycin and its use by continuous infusion in wards is safe concerning stability, but careful attention must be paid to incompatibilities. Several drugs (including all β-lactams) require distinct intravenous lines or appropriate procedures to avoid undue contact.

Keywords: European Pharmacopoeia, β-lactams, propofol, valproic acid, phenytoin, theophylline, methylprednisolone, furosemide

Introduction

Vancomycin is increasingly used by continuous infusion because of facilitated monitoring (sampling time is not critical after the first loading dose, making interpretation of blood levels and pharmacokinetic calculations easier), potential decreased toxicity, easier nursing and the possibility of centralized preparation of ready-to-use solutions.[1–4] To safely implement this mode of administration in a routine hospital setting it is, however, essential to ensure that vancomycin remains stable over the whole process and that incompatibilities with other medications co-administered by the intravenous route are avoided. Vancomycin has been repeatedly reported to be stable in various media for several days (see Nornoo and Elwell,[5] LaPlante *et al.*[6] and Dotson *et al.*[7]), but few studies have been performed in the actual conditions of its clinical use, including potentially accidental exposure to high temperatures. Concerning compatibility, vancomycin is notorious for being incompatible with several β-lactams,[8–10] but few studies have examined other antibiotics or other commonly used drugs that are administered by the intravenous route in routine clinical practice.

In preparation for the implementation of continuous infusion of vancomycin in all non-intensive care unit wards of a 400 bed hospital, we initiated a study in which: (i) the stability of the drug

under the actual conditions of its use in patients (from its preparation in the Central Pharmacy to the end of the infusion) and after exposure to high temperatures was measured; and (ii) its compatibility with other drugs was tested *in vitro* using conditions mimicking their use in patients.

Materials and methods

Stability studies

These studies reproduced exactly the projected conditions of use of vancomycin by continuous infusion in our hospital. Hence, vancomycin (Vancocin®; Lilly, Illkirch, France) solutions (10 g/L in 5% glucose) were prepared in 250 mL VIAFLO® polyolefin bags (coextruded layers of polyethylene, polyamide, polypropylene; Baxter s.a., Lessines, Belgium) and stored at 4°C (for a maximum of 58 days; tested previously for stability[11]) until transferred to the ward where they were maintained in a domestic refrigerator (~4°C) until about 15 min before use. Patients were infused at a rate of 11 mL/h if they had normal renal function (lower and higher rates were used in case of decreased or increased calculated CL_{CR}). The infusion was made with the bag exposed to uncontrolled room temperature and normal light for typically 24 h, but for up to 48 h for patients requiring low infusion rates. At the end of the infusion, the amount of fluid remaining in the bags was collected and assayed for vancomycin content. In parallel, samples of concentrated solution of vancomycin (up to 83 g/L) were incubated at increasing temperatures up to 50°C and for up to 72 h to mimic situations that might cause an accelerated degradation such as: (i) the administration of vancomycin from motor-operated syringes (commonly used in several clinical set-ups and requiring the use of concentrated solutions); or (ii) accidental exposure to high temperatures during storage, transport and use.

Compatibility studies

For this study, drugs recommended for administration by the intravenous route were selected for: (i) their common association with vancomycin in clinical practice (antibiotics and antifungals); (ii) their common use in a hospital setting; and/or (iii) their known potential for incompatibility gained from an analysis of current databases.[12,13] We used a protocol similar to that used by us for the study of the compatibility of β-lactam antibiotics with other drugs that mimic the conditions of their use when co-administered through the same line from two distinct containers via a Y connector.[14,15] In brief, a solution of vancomycin at a concentration corresponding to its nominal concentration used in continuous infusion (10 g/L) was mixed with an equal volume of each of the tested drugs prepared at a concentration corresponding to its most common clinical use (taking into account the recommended concentration and time of infusion, as per the corresponding drug label; see Table 1). The mixtures were then kept at 37°C for 1 h to mimic what could happen if the infusion flow was stopped for that period. The solutions, transferred to glass vials, were then examined with the naked eye for signs of physical incompatibility (e.g. precipitation, flocculation) or colour change using an Allen LV28 Liquid Viewer (PW Allen & Co. Ltd, Tewkesbury, UK) operated with two polarizing filters and compared with a pure solution of vancomycin and distilled water. Solutions were thereafter tested for the presence of non-visible particles by passing them through a particle analyser [Sub Micron Particle Analyser COULTER N 4 MD (Coulter Corp., Miami, FL, USA)] with a threshold set at twice the value of a pure solution of vancomycin. Chemical compatibility was assessed by determining the vancomycin content in comparison with an untreated sample.

Vancomycin assay and criteria for stability

We used a validated HPLC method with UV detection (diode array analysis for confirmation of the absorption spectrum) as described in detail in a previous publication[16] (but without the serum extraction procedure steps) and using pure, untreated vancomycin (vancomycin hydrochloride hydrate; Sigma-Aldrich, St Louis, MO, USA) as an external standard. Stability was defined as <7% disappearance of the signal in a treated sample compared with an untreated control, in compliance with the provisions of the seventh Edition of the European Pharmacopoeia (online version) concerning the acceptable limit of content of vancomycin preparations (93%).[17]

Ethical approval

The protocol of this study (with respect to drug administration to patients) was approved by the Ethics Committee of the hospital in which the study was performed (CHU Mont-Godinne; internal number EC Mont-Godinne: 48/2007; unique Belgian number: B03920072246).

Results

The concentration of vancomycin in the remaining fluid of the infusion sets after up to 48 h was 10.1 g/L ($n=20$; range: 9.6–10.3 g/L) compared with the initial nominal concentration of 10 g/L, thus complying with the provisions of the European Pharmacopoeia (>93%). Concentrated vancomycin solutions (up to 83 g/L) suffered <5% degradation when kept for 72 h at up to 37°C. Only samples exposed to 50°C showed >7% degradation.

Table 1 shows the results of the compatibility studies. For anti-infectives, four out of the five β-lactams with activity against Gram-negative bacteria tested (temocillin, piperacillin/tazobactam, ceftazidime, imipenem) were incompatible. Cefepime was physically and chemically compatible when mimicking its administration by continuous infusion (but its degradation was >10% after 24 h at 25°C and after 14 h at 30°C and <10 h at 37°C) and chemically incompatible when mimicking its thrice-daily administration. Flucloxacillin was also incompatible. Conversely, all three aminoglycosides tested (amikacin, tobramycin and gentamicin) were compatible. Among the fluoroquinolones, ciprofloxacin was compatible, but moxifloxacin was chemically incompatible. Macrolides (erythromycin and clarithromycin) and fluconazole were compatible.

For other drugs commonly used in hospitalized patients, sedatives (ketamine, sufentanil, midazolam, morphine and piritramide), antihypertensives (nicardipine and urapidil) and vasopressive drugs (dopamine, dobutamine and adrenaline) were all compatible. In contrast, propofol (mostly used as a hypnotic, but also for procedural sedation), valproic acid and phenytoin (anticonvulsants), theophylline (bronchodilator), methylprednisolone (glucocorticoid) and furosemide (diuretic) were all physically incompatible. In contrast to what had been observed with β-lactams,[14,15] *N*-acetyl-cysteine (used as an antioxidant in cases of paracetamol intoxication) did not cause alteration of vancomycin and nor did amino acid solutions (used for parenteral nutrition).

Discussion

This study is the first, to our knowledge, to systematically assess the stability and compatibility of vancomycin in conditions directly pertinent to its use by continuous infusion in hospitalized patients, with solutions kept at room temperature without replacement for up to 48 h and with attention paid to other drugs that could be co-administered through the same infusion

Table 1. Compatibility of vancomycin with other drugs under conditions mimicking their co-administration through the same infusion line; items shown in bold correspond to conditions of incompatibility[a]

Drug	Dose (mg)[b]	Volume per administration (mL)	Time of infusion (h)	Drug:vancomycin weight ratio[c]	Results[d]
Anti-infectives					
temocillin	**2000**	**20**	**0.33**	**12.63**	**i (phys)**
piperacillin/tazobactam	**4000**	**20**	**0.33**		**i (phys)**
ceftazidime	**6000**	**48**	**24**		**i (phys)**
imipenem	**1000**	**40**	**0.5**		**i (phys)**
	1000	**200**	**0.5**		**i (phys)**
cefepime	4000	48	24		c[e]
	2000	**10**	**0.33**		**i (chem)**
flucloxacillin	**1000**	**4**	**0.33**	**6.31**	**i (phys)**
amikacin[f]	1500	100	0.25	25.25	c
tobramycin[f]	600	100	0.25	10.1	c
gentamicin[f]	600	100	0.25	10.1	c
ciprofloxacin	400	200	1		c
moxifloxacin	**400**	**250**	**1**		**i (chem)**
erythromycin	100	20	0.33		c
clarithromycin	500	10	0.33	6.31	c
fluconazole	200	100	0.5		c
Sedatives/anticonvulsants/analgesics					
ketamine	480	48	24		c
sufentanil	0.12	24	24	2.1×10^{-5}	c
midazolam	600	120	24	0.11	c
morphine	5	5	1	0.02	c
piritramide	10	5	1	0.04	c
propofol	**300**	**300**	**24**		**i (phys)**[g]
valproic acid	**1200**	**12**	**24**	**0.21**	**i (phys)**
phenytoin	**750**	**15**	**0.25**	**12**	**i (phys)**
Bronchodilators					
theophylline	**200**	**10**	**0.33**	**2.39**	**i (phys)**
Antihypertensives, vasodilators and drugs acting on the sympathetic nervous system					
nicardipine	120	120	24	0.02	c
urapidil	2400	480	24	0.42	c
isosorbide dinitrate	6	30	1	0.02	c
furosemide	**960**	**96**	**24**	**0.17**	**i (phys)**
dopamine	0.4	1	0.016	0.1	c
dobutamine	0.84	0.84	0.016	0.21	c
adrenaline	0.5	10	0.33	0.0063	c
Hormones					
insulin	60 IU	0.6	3	0.08 IU/mg	c
methylprednisolone	**500**	**10**	**0.5**	**4.0**	**i (phys)**
Miscellaneous					
N-acetyl-cysteine	10000	100	24	1.74	c
amino acid solution[h]	18000	1000	24	3.16	c

[a]See Servais and Tulkens[14] for a general description of the methods.
[b]Calculated (when appropriate) for a 70 kg male subject.
[c]In final infusate.
[d]Key: c, chemically and physically compatible; i, incompatible; phys, physically incompatible (precipitate, flocculation and/or presence of particles as evidenced by passing solutions through a particle analyser); chem, chemically incompatible—less than 93% recovery (>7% loss of antibiotic compared with nominal content).
[e]Physically and chemically compatible, but degradation of cefepime limits its stability to 24 h at 25°C, 14 h at 30°C and <10 h at 37°C (see Baririan *et al.*[15]).
[f]Assuming a once-daily schedule (30 min infusion of the total daily dose).
[g]Trapping in emulsion.
[h]VAMIN® (standard amino acid solution for parenteral nutrition; 18 g of amino acid nitrogen/L).

line. The experimental set-up included conditions that could be accidentally encountered, such as exposure to high temperatures and prolonged contact of drugs in the infusion set in cases of flow arrest. While this may lead to overestimation of risk, it also heralds conditions that clinicians may need to carefully assess when dealing with specific situations and a patient's therapeutic needs. This is particularly important for incompatibilities with the anti-Gram-negative β-lactams (all classes). These antibiotics are indeed commonly associated with vancomycin in empirical therapies of severe infections. Incompatibility of vancomycin with ceftazidime,[18] cefpirome,[19] cefotaxime[9] and ceftriaxone[8] has already been described, but not studied in the context of continuous infusion of vancomycin. Although incompatibilities with β-lactams are often described as concentration dependent (as seen for cefepime here and reported for aztreonam[20]), only very diluted solutions (down to 1 g/L) appear safe in this context, making these drugs quite difficult to use in practice. Thus, β-lactams should be considered as incompatible with vancomycin for all practical purposes, and their administration, if therapeutically needed, must imply specific measures such as the use of independent lines or multiple-way catheters, or the temporary suspension of the vancomycin infusion. Alternative anti-Gram-negative antibiotics such as aminoglycosides or ciprofloxacin may also offer a viable solution.

Globally speaking, the other incompatibilities detected are scattered among pharmacological classes without evidence of a specific relation to structure or biophysical properties. However, the number of drugs tested is limited. The main message is, therefore, that clinicians will need to request specific compatibility tests for all other drugs not mentioned here that they intend to use for specific patients. In this context, efforts coordinating various sources of information such as those appearing in monographs[13] or developed for online use (http ://www.stabilis.org) represent a useful development. It will, nevertheless, remain essential for practitioners to determine whether the conditions of testing actually apply to their projected use of the drug and, if not, to undertake the appropriate studies.

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Transparency declarations

None to declare.

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