Journal of Infection and Public Health (2015) 8, 355—363

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Observational clinical study on the effects of different dosing regimens on vancomycin target levels in critically ill patients: Continuous versus intermittent application

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Received 18 October 2014; received in revised form 13 January 2015; accepted 23 January 2015

KEYWORDS
Vancomycin;
Intensive care unit;
Infection;
Therapeutic drug monitoring

Summary Different dosing regimens for vancomycin are in clinical use: intermittent infusion and continuous administration. The intention of using these different dosing regimens is to reduce toxicity, to achieve target levels faster and to avoid treatment failure. The aim of this phase IV study was to compare safety and effectiveness in both administration regimens. The study was conducted in 2010 and 2011 in three postoperative intensive care units (ICUs) in a tertiary care university hospital in Berlin, Germany. Adult patients with vancomycin therapy and therapeutic drug monitoring were included. Out of 675 patients screened, 125 received vancomycin therapy, 39% with intermittent and 61% with continuous administration. Patients with continuous administration achieved target serum levels significantly

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http://dx.doi.org/10.1016/j.jiph.2015.01.011
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earlier (median day 3 versus 4, $p = 0.022$) and showed fewer sub-therapeutic serum levels (41% versus 11%, $p < 0.001$). ICU mortality rate, duration of ICU stay and duration of ventilation did not differ between groups. Acute renal failure during the ICU stay occurred in 35% of patients with intermittent infusion versus 26% of patients with continuous application ($p = 0.324$). In conclusion, continuous administration of vancomycin allowed more rapid achievement of targeted drug levels with fewer sub-therapeutic vancomycin levels observed. This might indicate that patients with more severe infections or higher variability in renal function could benefit from this form of administration.
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Introduction

The glycopeptide vancomycin was introduced into the anti-infective armamentarium in the 1950s, before modern pharmacodynamic and pharmacokinetic methods were established to guide dosing practices [1,2]. More than 50 years of routine usage and research followed and the agent has been well characterized. Recommendations have changed over time, and higher vancomycin trough serum levels are desired, especially in severe infection, depending on the pathogen identified. Although widely debated, there are recommendations that trough levels of between 15 and 20 mg/L should be achieved to prevent development of resistance and to achieve sufficient serum tissue levels [3]. Nevertheless, it remains a clinical challenge to merge all available patient-based data, e.g., location of infection, weight, glomerular filtration rate, co-morbidities and co-medication, into suitable dosing guidelines and thereby use this information to achieve appropriate trough serum levels [4]. Recently, the frequency of therapeutic drug monitoring (TDM) and appropriate vancomycin utilization were verified in a prospective trial evaluating the clinical and educational value of additional intensive care unit (ICU) chart reviews by clinical pharmacists [5]. In contrast, nomograms have been analyzed with the intention to improve dosing patterns, but they failed to help in achieving sufficient vancomycin serum levels [6]. Similarly, using dosing recommendations provided by the current vancomycin product information has been demonstrated to be even worse for obtaining target serum levels [7]. Consequently, TDM is recommended to guide vancomycin therapy [3], and data from a recent clinical trial showed that repeated measurements increase the safety of target serum levels in a subset of medical ICU patients [8].

Vancomycin interacts with cell wall synthesis in gram-positive bacteria, and there has been controversy regarding the optimal pharmacological description [9]. Some authors have reported time-dependent bacterial killing properties, and others have favored concentration-dependent models for vancomycin. Two dosing regimens are repeatedly discussed with the intention of optimizing vancomycin serum levels and subsequent patient outcome. Intermittent administration regimens may be beneficial with regard to possible post-antibiotic effects described in several experimental settings, without being definitively proven in clinical studies [10—12]. Continuous infusion may achieve target plasma levels faster. This dosing regimen was described to achieve more stability in the area under the serum concentration—time curves (AUC) combined with the possibility to measure serum levels earlier [12—14]. Clinical data comparing both dosing regimens are limited and there remains uncertainty regarding optimal dosing strategies in ICU patients. In this context, this study was performed to evaluate the effectiveness and safety of the two different dosing regimens for vancomycin for empirical anti-infective treatment in surgical ICU patients.

Materials and methods

Study design and setting

This trial represents a phase IV study, including surgical patients treated in three ICUs at Charité university hospital, a tertiary medical care center in Berlin, Germany. The study is based on a secondary analysis of prospectively obtained data from a larger interventional clinical trial on antibiotic stewardship from 2010 and 2011, conducted to improve guideline adherence in critically ill patients [15].

Patients, data collection and measurement

Adult patients were screened for study inclusion by having an ICU stay of at least 36 h. Inclusion criteria

for the study population were the administration of intravenous vancomycin during the ICU stay at more than one dose and therapeutic drug monitoring performed, excluding patients with oral vancomycin therapy or single shot antibiotic therapy in the context of a previous surgery.

All study wards used standards for vancomycin therapy, providing detailed information regarding both administration methods (Table 1). To assess overall implementation rates as a surrogate for the applicability of given recommendations, all therapy days were analyzed consecutively for each patient. Days were defined as adherent to recommendations when (A) measured vancomycin serum levels were within predefined limits and (B) vancomycin dosing was promptly adapted depending on measured serum levels according to the drug monitoring recommendations. Adherence to the recommendations was expressed as rate of adherent days in relation to all days with vancomycin for every consecutive patient. Acute renal failure was defined using RIFLE criteria for injury, failure or loss [16]. Duration of ventilation was compared for patients with any mechanical ventilation via endotracheal intubation or tracheotomy as the time of active ventilator support.

The primary study aim was to evaluate vancomycin serum levels after induction of systemic intravenous vancomycin therapy, depending on the administration regimen chosen. Secondary study aims were to describe differences in the clinical courses associated with both application strategies.

Therapeutic drug monitoring (TDM) for vancomycin

For all study wards, therapeutic and diagnostic recommendations regarding anti-infective therapy are implemented based on a computerized decision-support system called ABx [15,17,18]. This program also provides detailed information for dosing and therapeutic drug monitoring (TDM) for vancomycin (see Table 1). Information provided was consented in interdisciplinary rounds based on national and international guidelines for vancomycin administration [3]. The attending ICU physicians in charge made the decision of which specific dosing regimen was applied—intermittent or continuous vancomycin administration—independently from this observational study project.

Serological vancomycin testing was performed for routine TDM in every patient with vancomycin therapy, using standard competitive homogenous enzyme immunoassays in our central laboratory. For patients with intermittent vancomycin administration, determination of the first trough level is recommended at least before the 4th administration, compared with continuous administration, for which the first drug monitoring is recommended 24—36 h after initiation. Serum vancomycin thresholds have recently been widely debated [3] and levels of 15—20 mg/L were suggested to achieve higher vancomycin levels at the sites of severe infections. As higher thresholds have also been associated with higher nephrotoxicity [19] in patients with less severe infections, a more careful dosing strategy has been suggested [3,20]. For the purposes of this study and in concordance with the guidelines [3,20], a serum level of at least 10 mg/L was used as the target, assuming that this is the minimally effective dose on infection sites, and the maximum dose was 20 mg/L, to provide a toxicity margin [3].

Statistical analysis and ethic review

Results are expressed in proportions, with the medians and 25—75% quartiles or arithmetic means and standard deviations given as appropriate. Depending on the scale levels and distributions, tests for statistical significance were performed with the two-tailed Student's *T*-, Wilcoxon—Mann—Whitney- or Fisher exact-tests. A p-value of <0.05 was considered to be significant. Analyses of time courses were visualized using cumulative incidence curves and the generalized Wilcoxon test was used to analyze the statistical significances of effects. Calculations were conducted with PASW, Version 19 (SPSS Inc., USA).

The clinical study was approved by the local Ethics Review Board and the data safety authorities. Due to the observational nature of the evaluation, the Ethics Review Board waived the need for informed consent.

Results

Patient characteristics and administration regimen

A cohort of 675 consecutively admitted ICU patients were screened. One hundred twenty-five patients received intravenous vancomycin, comprising the study population. Out of these, 49 (39%) were treated with intermittent infusion, versus 76 (61%) with continuous application. Both treatment groups did not differ in terms of gender, age or co-morbidities. Furthermore, scoring systems showed comparable values for surrogate values indicating the severity of disease at admission. During their ICU stays, patients in the group with intermittent

Table 1 Recommendations for therapeutic drug monitoring for vancomycin therapy based on a computerized decision-support system implemented on the study wards [17,18].

1. **Dosing regimens for initial vancomycin therapy:**
   1.1. Intermittent administration
   In adults: 500 mg vancomycin every 6 h given over 1 h or 1 g every 12 h, given over 1 h. For empirical therapy, a full loading dose is recommended independent from renal function.

   1.2 Continuous administration
   Using continuous vancomycin administration, targeted drug levels are more easily attained. Vancomycin should be administered continuously by the central line only, as it may irritate vein surfaces.
   Initiation of therapy with 1 g vancomycin as an infusion given over 1 h, followed by
   • in patients with normal renal function, 2 g vancomycin continuously infused during 24 h [e.g., 1 g of vancomycin in 50 mL of solution with a rate of 4.2 mL/h in a perfusion pump];
   • in patients with impaired renal function and creatinine clearances of <50 mL/min, 1 g vancomycin continuously over 24 h [e.g., 1 g of vancomycin in 50 mL of solution with a rate of 2.1 mL/h in a perfusion pump];
   • in patients with impaired renal function and creatinine clearances of <20 mL/min, 500 mg vancomycin continuously during 24 h [e.g., 1 g of vancomycin in 50 mL of solution with a rate of 1 mL/h in a perfusion pump]

2. **TDM for initial vancomycin therapy:**
   2.1. Intermittent administration
   Trough level measurement is superior to peak level monitoring for therapeutic drug monitoring of vancomycin. The first trough level should be measured just before the 4th administration of intermittent vancomycin infusion. After obtaining blood for laboratory testing, administration of vancomycin should be continued until results of the TDM are available. Doses should be adapted when the TDM results suggest higher or lower trough levels than targeted.
   Targeted trough levels: 10—15 mg/L; for severe infection: 15—20 mg/L.

   2.2 Continuous administration
   TDM should be initiated after 24—36 h of continuous vancomycin administration. Doses should be adapted when TDM results suggest higher or lower trough levels than targeted. If sufficient therapeutic drug levels are detected, further routine TDM should be initiated every week of therapy.
   Targeted levels: 15—20 mg/L.
   In case of changes in renal function or co-medication with nephrotoxic drugs, more frequent TDM is recommended.

vancomycin infusion developed urogenital- and central venous catheter-related infections, as well as infections of soft tissues, significantly more often than the group with continuous administration. The duration of vancomycin therapy was significantly longer in the continuous-infusion vancomycin population. All basic characteristics are displayed in Table 2.

Vancomycin therapy adherence

The overall mean implementation rate of vancomycin therapy recommendations was 69% (95% CI 65—73%). Comparing both dosing regimens for the intermittent vancomycin infusion population, a median of 67% of all administration days (25—75% quartiles 50—88) were found to be adherent with the given recommendations versus 71% (25—75% quartiles 57—89) in the group with continuous application ($p = 0.244$).

Vancomycin serum levels and time course of vancomycin therapy targets

The time courses of vancomycin levels in both populations are displayed in Fig. 1. The first vancomycin measurement was performed on ICU day 3 ± 5 in the group with intermittent infusion, versus day 2 ± 2 in the group with continuous application ($p = 0.007$). Comparing all TDM values, at least a single sub-therapeutic trough level (<10 mg/L) was observed in 75.5% of patients in the intermittent group, compared with 30.3% in the continuous group ($p < 0.001$). In contrast, at least a single supra-therapeutic level (>20 mg/L) was found in 44.9% of patients in the intermittent group and in 63.2% in the continuous group ($p = 0.065$).

One main therapeutic goal for the initial administration of vancomycin is to achieve sufficient serum levels in the first hours of therapy. Therefore, we analyzed the duration until serum levels reached the reference levels of 10—20 mg/L

Table 2 Patient characteristics and therapies. Binary variables are given in percentages (%); continuous variables are given in medians (with 25—75% quartiles) or means (with ±standard deviations).

	Intermittent vancomycin group *N* = 49	Continuous vancomycin group *N* = 76	Significance level
Gender *N* (% females)	15 (31%)	31 (41%)	ns
Weight (kg)	80 (70—90)	70 (60—90)	ns
Age (years)	67 (48—75)	60 (50—70)	ns
Co-morbidities (%)			
Cardiac	67%	61%	ns
Pulmonary	41%	30%	ns
Vascular	35%	38%	ns
Hepatic	18%	15%	ns
Renal	41%	32%	ns
Metabolic	47%	36%	ns
Neurological	29%	20%	ns
Immunosuppression	18%	17%	ns
Infections (%)[a]			
Pneumonia	78%	72%	ns
Endocarditis	12%	8%	ns
Urogenital	25%	11%	0.047
ZNS	12%	22%	ns
Abdomen	18%	15%	ns
Catheter-related	49%	24%	0.006
Bones and joints	12%	5%	ns
Soft tissues	31%	9%	0.003
Unknown focus	7%	2%	ns
SAPS II on admission	51 (40—69)	47 (35—61)	ns
SOFA on admission	9 (5—13)	7 (3—11)	ns
TISS-28 on admission	37 (28—50)	40 (31—46)	ns
APACHE on admission	25 (19—33)	24 (17—28)	ns
Duration of vancomycin therapy	5 (3—8)	7 (4—11)	0.009
Proportion of drug serum levels *below* reference TDM in mean ± SD[b]	41 ± 37%	11 ± 23%	<0.001
Proportion of drug serum levels *above* reference TDM[b]	19 ± 28%	36 ± 37%	0.010

[a] Infections during ICU stays; more than one focus possible per patient.
[b] Reference TDM for intermittent application: 10—20 mg/L; for continuous application: 15—20 mg/L. Number of TDM results below 10 mg/L or above 20 mg/L is divided by total number of TDM measurements. SD, standard deviation.

vancomycin. The resulting cumulative incidence curves are displayed in Fig. 2, showing faster achievement of reference levels for the continuous administration method. Patients with continuous administration achieved target serum levels significantly earlier, on median day 3 (25—75% quartiles: 2—7) versus day 4 (25—75% quartiles: 3—8) in the intermittent group ($p = 0.022$).

Clinical course of patients

In total, 38 (78%) of the patients with intermittent vancomycin infusion survived, whereas 61 (80%) of the patients with continuous administration survived ($p = 0.822$).

Acute renal failure during the ICU stay was detected in 35% of the patients with intermittent infusion versus 26% in the group with continuous application ($p = 0.324$).

Median ICU stay was 16 days (25—75% quartiles: 8—35) in the intermittent group versus 20 days (25—75% quartiles: 11—27) in the continuous group ($p = 0.729$). The duration of ventilation also did not show differences, with 256 h (25—75% quartiles: 31—748) in the intermittent group versus 365 h (25—75% quartiles: 99—569) in the continuous population ($p = 0.424$).

Discussion

The most important finding of this study is that, with continuous administration of vancomycin, reference serum levels are achieved earlier compared

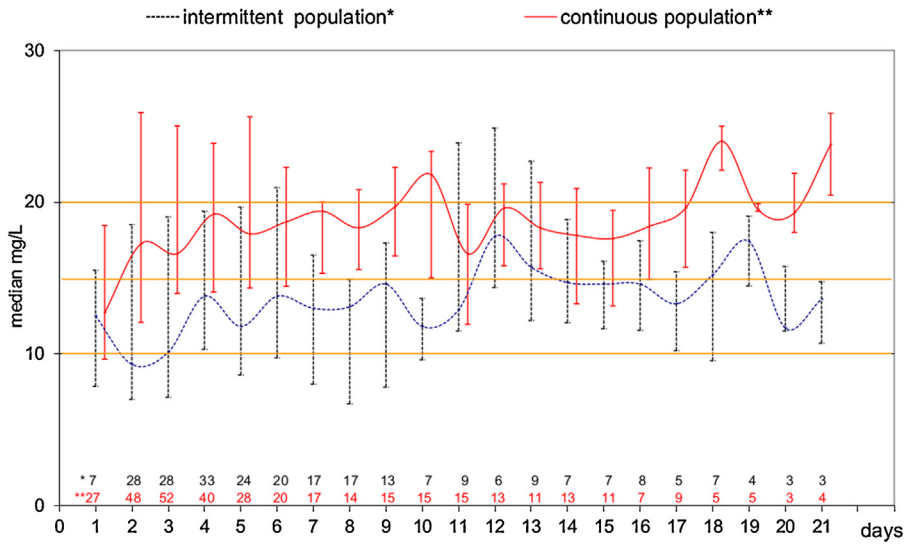

Figure 1 Vancomycin serum levels compared for intermittent versus continuous administration over 21 days; data showing median and interquartile ranges; */** indicating the number of patients measured.

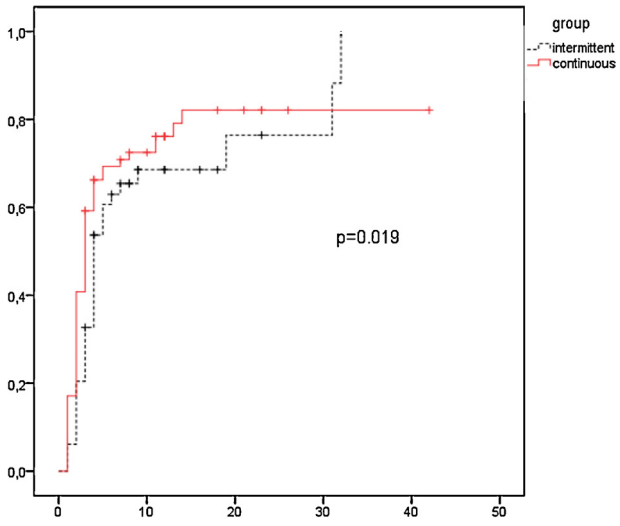

Figure 2 Cumulative incidence curves showing duration (days) until reference serum levels were achieved with vancomycin serum thresholds of 10—20 mg/L. In the continuous group, the serum levels were achieved significantly earlier ($p = 0.019$).

with the intermittent administration regimen. Furthermore, in patients with continuous application of vancomycin, TDM less frequently revealed serum levels below the 10 mg/L threshold but more often showed serum levels above 20 mg/L.

Regarding baseline characteristics, the study population was well balanced for most variables as well as for severity of disease. There were only small differences in infections observed during the course of the ICU stay, but the overall distribution of infections was in concordance with other publications in different settings [21,22]. Therapy recommendations for vancomycin were applied sufficiently with approximately 70% of all patient days being adherent to recommendations, with slightly more adherence in the continuous group. Based on previous studies, adherence to therapy recommendations can be beneficial for patients [23—25], and a threshold of 70% was defined as the quality target for the implementation of our intensive care unit therapy standards.

With special emphasis on therapy initiation, cumulative incidence analyses made it obvious that the continuous dosing regimen achieved target reference levels significantly earlier. This might be one of the most remarkable aspects of this therapy form, as the time to achieve appropriate coverage of pathogens was found to be one of the key interventions in sepsis therapy, especially for severe infections [26]. In this situation, the positive effects of high initial doses on the outcomes of infections have to be weighed against the risks of vancomycin-associated kidney failure [19]. Consequently, therapy targets have to be based on individual co-morbidities and possible alternative therapy options. In our study, TDM results more often showed serum levels above the 20 mg/L threshold for patients with continuous vancomycin treatment, but this was not paralleled by higher rates of acute kidney injury. Similar results were observed in a study by Saugel et al. in medical ICU patients [8]. In addition, we observed high rates of TDM levels below the 10 mg/L threshold, especially in the group with intermittent infusion of vancomycin.

Low antibiotic serum levels have been attributed as a risk factor for resistance development and therefore should be avoided [20]. This problem was also described for continuous vancomycin application and can be improved with an initial vancomycin loading dose, as shown in the study of Saugel et al. [8]. However, the specific reference thresholds remain under discussion [8]. Although some conclusions have been drawn from study data and are introduced into treatment recommendations [3], evidence for a specific level is limited [27]. Further discussion is ongoing related to the assumed pharmacological mechanism of vancomycin, with some authors pronouncing time dependent [9] versus – at least partly – concentration-dependent efficacy of vancomycin [28]. Based on current evidence summarized in the guidelines [3], vancomycin serum targets are suggested to be tailored based also on findings from microbiology. Therefore, the area under the curve (AUC) for vancomycin serum concentrations measured is related to the minimal inhibitory concentration (MIC) of the underlying pathogen. However, repeatedly sampling vancomycin serum levels is rarely possible, and serum trough levels of 15 mg/L vancomycin were described to be sufficient to achieve the target ratio of AUC/MIC of 400.

Interestingly, continuous administration was applied longer in our study compared with intermittent administration. Additionally, for a patient of body weight 80 kg and normal renal function, doses applied within the first 24 h were 2 g for intermittent exposure versus 3 g of continuous exposure. The related apprehension for cumulative renal toxicity is contradicted by our finding of reduced rates of renal impairment with continuous vancomycin therapy along with comparable ICU mortality rates. It is critical to independently evaluate renal impairment due to the clinically well-known fact that it is impossible to decide upon underlying causality and that severe infection can itself lead to organ failure [19,29]. Principally, intermittent vancomycin dosing, as described in Table 1, could also be adapted using an initial higher loading dose, or the first dosing interval could be reduced, to increase the overall drug exposure in these patients. In our data set, we were not able to assess such alternative dosing patterns with the intermittent dosing strategy and further studies are required to assess such options.

One major critique of this study is related to its observational nature, thus inheriting a higher variability of dosing compared with randomized controlled interventional studies. In this context, choice of antibiotic therapy as well as administration regimen was the responsibility of the ICU physician. Consequently, patients were non-randomly assigned to a specific study group. This observational study was performed as a secondary analysis of prospectively obtained data and is therefore also limited to the variables evaluated in the trial and to the number of patients observed [25]. As an example, it would have been interesting to analyze TDM results in relation to body weight, but these variables were not available in a significant number of patients. On the other hand, this phase IV clinical study's data reflect the current best state of practice independently of selected populations or with specific interventions not available in the clinical routine. Over past decades, optimal serum levels for vancomycin therapy have continued to be changed related to the ongoing evaluation of this valuable drug [3]. Furthermore, minimal inhibitory concentrations for pathogens (MICs) were not included in this analysis. This information was not incorporated, as vancomycin therapy often has to be initiated empirically to cover the relevant suspected pathogen spectrum without results from microbiological analyses, and recommendations are primarily given for initial therapy. An MIC creep for vancomycin has also been described lately, potentially questioning the future use of vancomycin as the prevalence of higher MICs increases, but this also supports the need for more rapid achievement of target levels [30,31].

Conclusion

Continuous infusion of vancomycin might be helpful to achieve determined target levels, but prospective trials are needed to demonstrate a potential patient benefit, especially incorporating the focus of infection and the MICs of pathogens.

Funding

Independent from this project, IN and ST received lecture fees from Roche Deutschland GmbH and Pfizer Deutschland GmbH. UT received lecture fees from MSD Sharp and Dohme, Germany. MD received grants from Fisher & Paykel, Forest, Gilead, Linde, and Pfizer, and payment for lecture fees from Abbott, Astellas, Astra Zeneca, Forest, Novartis, Gilead, Pfizer, MSD, Astellas, Astra Zeneca, Forest, Novartis, Gilead, Pfizer, MSD and Sobi. CS received a project grant from Novartis as well as lecture fees or grants for other projects from Abbott, Astellas, BDA, Forest, MSD, Pfizer, and Wyeth;

personal fees from the Ethical Committee Vienna Faculty of Medicine, Zon-Mw-Dutch Research Community, Care Fusion, Deltex, Fresenius, Hutchinson, MCN, Novartis, Pajunk, Grünenthal, Köhler Chemie, Roche, Orion Pharma, and Outcome Europe Sarl; grants from the University Hospital Stavanger, AiF, BMBF, DKH, DLR, ESF/Headquarters for Education, Youth and Science, German Academic Exchange Service, German Research Society, Headquarters for Education, Science and Research, GIZ, Inner University Grants, Stifterverband, European Commission; and personal fees from the B. Braun foundation and Georg Thieme Verlag.

Competing interests

All authors declare that they do not have any conflicts of interest concerning the specific subject of the study.

Authors' contributions

CS, IN and ST contributed to the conception and initiation of this study. KG, ST, MD and AK were responsible for data analysis. ST and IN drafted the manuscript; UT, MD, AK, AG and CS revised the manuscript critically. All authors approve the final manuscript.

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