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EVALUATION OF VANCOMYCIN INITIAL DOSING AND THE RESULTANT TROUGH LEVEL IN PAEDIATRIC PATIENTS

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This study aims to examine the vancomycin initial dosing and the resultant trough level in paediatric patients. In this retrospective observational study, all therapeutic drug monitoring (TDM) records of paediatric patients admitted to Sabah Women and Children Hospital (SWACH) from January 2011 to September 2013 were reviewed and 116 patients without renal disease were included in the study. Of the total, 38.8% were neonates, 32.8% were infants and 28.4% were children. The majority of the patients were intensive care patients (69.0%) and the most common clinical indication for vancomycin was sepsis (44.8%). The four initial dosing regimens identified were 40 mg/kg/day (38.8%), 30 mg/kg/day (31.0%), 60 mg/kg/day (25.0%) and 45 mg/kg/day (5.2%). The distribution of initial dosing regimen was significantly different between the three age groups (p<0.001). The proportion of those who achieved the target therapeutic range (10–20 mg/L) was 39.7% whereas the proportions of those who were in sub-therapeutic range (<10 mg/L) and supra-therapeutic range (>20 mg/L) were 43.1% and 17.2% respectively. The distribution of trough level was significantly different between those who received ≤40 mg/kg/day and those who received >40 mg/kg/day (p=0.007). The proportions of those who achieved the target therapeutic range (10–20 mg/L) in the 2 dosing groups were 30.9% and 60.0% respectively. In conclusion, the study showed that the initial dosing of >40 mg/kg/day is more likely to achieve the target therapeutic range (10–20 mg/L) compared to the initial dosing of ≤40 mg/kg/day.

***Keywords**:* Vancomycin, Paediatric, Initial dosing, Trough level

INTRODUCTION

Vancomycin, a glycopeptides antibiotic, acting on the bacterial cell wall, was first used clinically in 1958. It is primarily used in the treatment of infections with Gram positive organism resistant to beta lactam antibiotics such as methicillin resistant *Staphylococcus aureus* (MRSA), coagulase negative staphylococci and penicillin resistant *Streptococcus pneumonia* central nervous system infections (Broome and So 2011; Dehority 2010).

Even after 60 years in clinical use, it is still not clear what is the most appropriate initial dosing of vancomycin to be used in paediatric. Major paediatric dosing references for vancomycin recommend a daily dose of 40–60 mg/kg/day (Dehority 2010; Kim *et al.* 2010) with 40 mg/kg/day being the most widely used worldwide (Benner *et al*. 2009). In Malaysia, the dosing practices have relied solely on literature data from Caucasian infants (Lo *et al.* 2010).

Serum monitoring is important in optimising vancomycin therapy (Zhao *et al.* 2013; Pacifici and Allegaert 2012; Lo *et al*. 2010). In the past, the main reason for vancomycin monitoring was to prevent nephrotoxicity and ototoxicity. However, in recent

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years, the emphasis of vancomycin monitoring has moved from the prevention of largely reversible toxicity to ensuring optimum pharmacodynamic exposure with the hope of ensuring efficacy in serious infections and potentially to avoid the development of resistance (Gordon *et al.* 2012).

On the basis of evidence suggesting that *S. aureus* exposure to trough level of <10 mg/L can produce strains with vancomycin-intermediate *S. aureus* (VISA), the Infectious Diseases Society of America (IDSA), the American Society of Health–System Pharmacists (ASHSP) and the Society of Infectious Diseases Pharmacists have recently increased the lower limit of trough level from 5 mg/L to 10 mg/L in their 2009 guidelines (Liu *et al*. 2011). Today, most clinicians have adopted the higher trough level but ironically the approach to initial dosing has remained unchanged (Legal and Wan 2010), possibly due to the concerns for toxicity or the unfamiliarity of the clinicians with the new dosing guidelines.

At Sabah Women and Children Hospital (SWACH), currently there is no standard guideline on the initial dosing of vancomycin. The dosing is usually guided by the resultant trough level. The initial dosing commonly prescribed by the clinicians in the institution ranges from 30–60 mg/kg/day with the target trough level of 10–20 mg/L. The blood sample for trough level monitoring is taken within 30 minutes before the fourth dose.

The purpose of this study was to examine the vancomycin initial dosing, and the resultant trough level among paediatric patients of all age groups with normal renal functions. The resultant trough level of the initial dosing is of interest in the study as it may predict both the development of antibiotic resistance and the mortality of the patients especially the intensive care patients (Truong, Levkovich and Padiglione 2012). It was hoped that this study would be able to identify the initial dosing regimen that is most likely to achieve the trough level in the range of 10–20 mg/L (target therapeutic range) in an effort to avoid the potential emergence of vancomycin resistant pathogens as well as to maximise efficacy from vancomycin therapy.

MATERIALS AND METHODS

This retrospective observational study reviewed therapeutic drug monitoring (TDM) vancomycin data of paediatric patients admitted to SWACH between January 2011 and September 2013.

SWACH is a referral hospital for women and children patients in Sabah, Malaysia. The institution consisted of five paediatric wards that include Melur 1 (General Medical), Melur 2 (General Medical and Oncology), Melur 3 (General Medical and Surgery), PICU (Paediatric ICU) and NICU (Neonatal ICU). The NICU is further stratified into Level 1, Level 2 and Level 3 according to the severity of illness.

The past TDM request forms in the study period were retrieved from the TDM archive and the relevant information were transcribed onto the case report form. Information extracted from a patient's TDM records included age, weight, gender, race, diagnosis, vancomycin indication, dose, trough serum concentration, concomitant medications and ward.

The inclusion criteria were of patients 12 years old and below with the TDM results of the initial dosing of vancomycin. The exclusion criteria were the presence of at least one of the following: patients older than 12 years old, repeated serum measurements, patients on renal dosing of vancomycin which was defined as dosing of vancomycin at 24 hours interval or *stat* vancomycin dosing and/or the presence of one the following diagnosis in the TDM forms — end stage renal disease (ESRD), chronic renal failure (CRF), acute renal failure (ARF) and/or acute kidney injury (AKI).

For the analysis purpose, Melur 1, Melur 2 and Melur 3 were classified as non-intensive care wards and PICU and NICU were classified as intensive care wards. The initial dosing of vancomycin was divided into 2 groups: ≤40 mg/kg/day and >40 mg/kg/day based on the previous findings postulating that the empiric dose of 40 mg/kg/day is inadequate in paediatrics (Chhim, Arnold and Lee 2012; Kim *et al.* 2010; Benner *et al.* 2009; Frymoyer, Hersh and Guglielmo 2009; Glover, Cole and Wolfsdorf 2000; Chang 1995).

All vancomycin trough levels were measured by the ARCHITECT *i*Vancomycin assay [Abbott Laboratories (M) Sdn. Bhd, Selangor, Malaysia]. It is an in vitro chemiluminescent microparticle immunoassay (CMIA). The lower limit of quantitation (LLOQ) of the assay method is 3 mg/L. All vancomycin doses were given by intermittent intravenous infusion over at least 60 minutes. All blood samples were taken within 30 minutes before the fourth dose. The target therapeutic range is 10–20 mg/L.

Descriptive statistics were used to depict the demographic data and outcomes. Proportions were compared using Chi–Square Test of Independence. In circumstances where the assumptions for the Chi–Square Test of Independence cannot be met, Exact Tests was used (Mehta and Patel 2011). The association between nominal/ordinal and continuous variables was assessed by using Kruskal–Wallis test. Post–hoc paired comparisons were done by using Mann–Whitney U test. The p value of <0.05 was considered statistically significant. SPSS version 16 (SPSS Inc., Chicago, USA) was used for the data analysis.

The approval for conducting the study was obtained from the Medical Research Ethic Committee (MREC), Ministry of Health Malaysia.

RESULTS

From January 2011 to September 2013, the total number of TDM for vancomycin performed at SWACH was 713. After exclusions, the total number of patients included in the study was 116 (16.3%). The demographic and clinical data of the patients were shown in Table 1.

The clinical indications for vancomycin as stated by the clinicians in the TDM forms were shown in Table 2. The indications for vancomycin were unclear in 15.3% of the TDM forms as only the underlying diseases or health problems were stated. These included prematurity, congenital heart disease, chronic lung disease, biliary atresia, duodenal atresia, ileal perforation, severe dehydration, severe haemophilia A, omphalocoele, gastroparesis, congenital myopathy and Total Parenteral Nutrition (TPN) extravasation into peritoneal cavity.

The mean body weight in kilogram for the patients were 1.6 [SD = 0.9; 95% confidence interval (CI) = 1.3; 1.9] in neonates, 5.1 (SD = 3.3; 95% CI = 4.0; 6.2) in infants and 18.1 (SD = 6.2; 95% CI = 15.9; 20.3) in children. There was a significant association between the body weight and dosing regimen [$X^2(3) = 22.175$; $p<0.001$]. The mean ranks for the 30 mg/kg/day, 40 mg/kg/day, 45 mg/kg/day and 60 mg/kg/day dosing were 38.0, 67.7, 47.2 and 72.1 respectively. Post-hoc paired comparisons showed that there were significant differences in the body weight between the 30 mg/kg/day and 40 mg/kg/day dosing ($p<0.001$), 30 mg/kg/day and 60 mg/kg/day dosing ($p<0.001$) and 45 mg/kg/day and 60 mg/kg/day dosing ($p=0.023$). The median body weight in the 30 mg/kg/day, 40 mg/kg/day, 45 mg/kg/day and 60 mg/kg/day dosing were 1.4, 6.8, 2.2 and 8.4 kg, respectively.

The distribution of vancomycin initial dosing by age group was shown in Table 3. There was a significant difference in the distribution of the initial dosing between the three age groups ($p<0.001$). Generally, the neonates received a lower initial dosing of

vancomycin compared to the infants and the children groups. It was shown that 51.1% of the neonates were started on the 30 mg/kg/day dosing compared to only 26.3% and 9.1% in infants and children respectively.

Table 1: Demographic and clinical data of the patients.

Parameters	Number of patients, N (%)
Gender	
Male	76 (65.5)
Female	40 (34.5)
Age group	
Neonates (0–4 weeks)	45 (38.8)
Infants (1–23 months)	38 (32.8)
Children (2–12 years)	33 (28.4)
Ward	
Intensive care	80 (69.0)
Non-intensive care	36 (31.0)
Initial dosing	
30 mg/kg/day	36 (31.0)
40 mg/kg/day	45 (38.8)
45 mg/kg/day	6 (5.2)
60 mg/kg/day	29 (25.0)
Trough levels	
Sub-therapeutic (<10 mg/L)	50 (43.1)
Therapeutic (10–20 mg/L)	46 (39.7)
Supra-therapeutic (>20 mg/L)	20 (17.2)

Table 2: Clinical indications for vancomycin infusion.

Clinical indications	Number of patients, N (%)
Sepsis	52 (44.8)
Cancer related infection	11 (9.5)
Meningitis	8 (6.9)
Pneumonia	7 (6.0)
Abscess	6 (5.2)
Neutropenic fever	4 (3.5)
Catheter related infection	4 (3.5)
Blood culture positive	4 (3.5)
Endocarditis	1 (0.9)
Chronic otitis media	1 (0.9)
[†]Not clearly stated	18 (15.3)

Note: [†]Refer to text

The percentages of achieving the target therapeutic range (10–20 mg/L) in neonates, infants and children were 44.4%, 36.8% and 36.4% respectively. The percentages of having sub-therapeutic range (<10 mg/L) were 33.3%, 44.7% and 54.5% in the same order. The percentages of having supra-therapeutic range (>20 mg/L) were 22.2%, 18.4% and 9.1% also in the same order. The association between the age group and the trough level however, was not significant [$X^2(4) = 4.398$; p=0.355].

Table 3: Distribution of initial dosing between different age groups.

Age group	Dosing (mg/kg/day)				*p* value[a]
	30	40	45	60	
Neonates (0–28 days)	23 (51.1)	14 (31.1)	3 (6.7)	5 (11.1)	<0.001
Infants (1–23 months)	10 (26.3)	11 (28.9)	3 (7.9)	14 (36.8)	
Children (2–12 years)	3 (9.1)	20 (60.6)	0 (0.0)	10 (30.3)	

Notes: All values expressed as number of patients and percentage, N (%)
[a]Exact tests

Table 4 shows that there was no significant difference in the trough level between the different dosing regimens. However, when the dosing were reclassified as shown in Table 5, there was a significant difference in the trough level between those who received ≤40 mg/kg/day dosing and those who received >40 mg/kg/day dosing [$X^2(2) = 9.999$; p=0.007). Figure 1 shows the distribution of trough level by age group for dosing of ≤40 mg/kg/day and >40 mg/kg/day.

Table 4: Distribution of trough level between different initial dosing regimens.

Dosing (mg/kg/day)	Trough level (mg/L)			*p* value[a]
	<10	10–20	>20	
30	20 (55.6)	9 (25.0)	7 (19.4)	0.054
40	22 (48.9)	16 (35.6)	7 (15.6)	
45	1 (16.7)	3 (50.0)	2 (33.3)	
60	7 (24.1)	18 (62.1)	4 (13.8)	

Notes: All values expressed as number of patients and percentage, N (%)
[a]Exact tests

Table 5: Distribution of trough level between initial dosing ≤40 mg/kg/day and >40 mg/kg/day.

Dosing	Trough level (mg/L)			X^2(df)	*p* value[b]
	<10	10–20	>20		
≤40 mg/kg/day	42 (51.9)	25 (30.9)	14 (17.3)	9.999 (2)	0.007
>40 mg/kg/day	8 (22.9)	21 (60.0)	6 (17.1)		

Notes: All values expressed as number of patients and percentage, N (%)
[b]Chi-Square Test of Independence

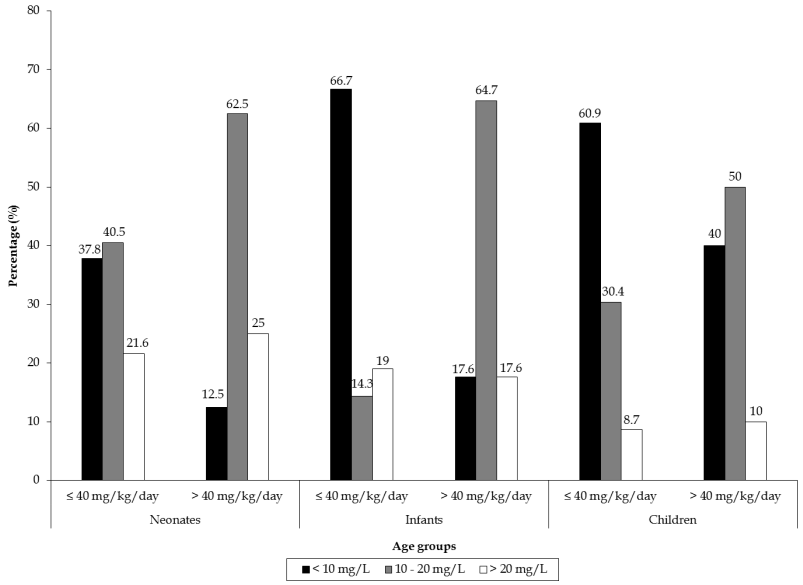

Fig. 1: Distribution of trough level by age group.

DISCUSSION

The study showed that the majority of paediatric vancomycin recipients admitted to SWACH were neonates and infants (71.6%), treated mainly for sepsis (44.8%) and most of them were intensive care patients (69.0%). These findings agree with the findings of previous studies that vancomycin is a primary therapeutic choice against Gram positive pathogens in newborns and infants (Marsot *et al.* 2012) and is mainly indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant staphylococci (Lasky *et al.* 2012).

There was a significant association between the body weight of the patients and the initial dosing. The post-hoc analysis revealed that for all the initial dosing pairs with significant difference, median body weights were significantly higher in those who received higher initial dosing compared to those who received lower initial dosing. This concurs with the current knowledge that body weight is one of the three main covariates important for optimising vancomycin dosage in paediatric population. When controlling for the other covariates, higher body weight would require higher dose of vancomycin. The other two

covariates are the age and the creatinine clearance (CL_{CR}) (Marsot *et al*. 2012). A more extensive list of other covariates affecting the dosing of vancomycin has been discussed recently (Marsot et al. 2012).

As shown in Table 3, there was a significant difference in the dosing regimens received by the three age groups. In general, the neonates received much smaller vancomycin initial dosing compared to their older counterparts. According to the Paediatric Protocols for Malaysian Hospitals (Imam, Phak and Thomas 2008), the general vancomycin dosing for neonates is 30 mg/kg/day. The general dosing for infants and children meanwhile ranges from 30–40 mg/kg/day (Imam, Phak and Thomas 2008). In comparison, reports from international researchers recommend the vancomycin dosing of 25–50 mg/kg/day in neonates and 45–60 mg/kg/day in infants and children (Avent *et al*. 2013). According to the MD Consult Drug Monograph (2014), the vancomycin dosing ranges from 20–45 mg/kg/day in neonates and 45–60 mg/kg/day in infants and children. Even though there are many guidelines existing on the vancomycin dosing, there is a general consensus of using lower dosing in neonates (Avent *et al*. 2013; Zhao *et al.* 2013). The result of this study showed that with the exception for the neonates, the dosing practice at this institution was towards the lower end of the dosing range as suggested by both the MD Consult Drug Monograph (2014) and Avent *et al*. (2013).

Even though the majority of the neonates received a lower initial dosing of vancomycin, the proportion of them achieving the target therapeutic range (10–20 mg/L) was higher than both that of infants and children whom received a higher initial vancomycin dosing. This may be explained by the lower clearance of vancomycin in neonates compared to the infants and children. The lower vancomycin clearance can be attributed to the immature renal function in neonates. As vancomycin is almost exclusively eliminated by the renal route, the vancomycin elimination capacity is lower in neonates compared to that of infants and children (Zhao *et al*. 2013). This explains why lower vancomycin dosing is needed to achieve the target therapeutic range in neonates. The renal function maturity of the neonates is positively correlated with age (Marsot *et al.* 2012). According to Cukuranovic and Vlajkovic (2005), the adult levels of renal blood flow, concentration capacity and glomerular filtration are reached after 12 months, 18 months and 24 months of life respectively.

The study observed that the number of patients with sub-therapeutic range was higher than those who achieved the target therapeutic range of 10–20 mg/L. When analysed for the association between the initial dosing regimen and the trough level, there was no significant difference in the trough level between the four initial dosing regimens. This may be explained by the small sample size. After regrouping the initial dosing into ≤40 mg/kg/day and >40 mg/kg/day, it was shown that the distribution of trough level between the two groups differed significantly (p=0.007). Table 5 shows that the patients who received the initial dosing of >40 mg/kg/day were more likely to achieve the target therapeutic range and less likely to have sub-therapeutic range compared to those who received the initial dosing of ≤40 mg/kg/day. The proportions of having supra-therapeutic range were almost the same between the two groups. The above observation was seen almost identical across all age groups as shown in Figure 1. This observation was consistent with previous studies that were in contention that a starting dose of <40 mg/kg/day might not be optimal to achieve the recommended trough level of ≥10 mg/L (Chhim, Arnold and Lee 2012; Kim *et al.* 2010; Benner *et al.* 2009; Glover, Cole and Wolfsdorf 2000; Chang 1995).

The study found that 69.8% of the paediatric patients received the initial dosing of ≤40 mg/kg/day with 40 mg/kg/day being the most commonly used. The empiric dosing regimen of 40 mg/kg/day was first proposed in 1980 based on the pharmacokinetic data in 55 paediatric patients with a recommendation of higher dose at 60 mg/kg/day for those patients with staphylococcal central nervous system infection (Glover, Cole and Wolfsdorf

2000). However, the target lower limit of the trough level in the study at that time was >5 mg/L, which was lower than the current recommendation of ≥10 mg/L. This raises the question of the need to employ a higher initial dose to achieve the target therapeutic range of 10–20 mg/L.

A failure to achieve the target therapeutic range is detrimental as previous studies suggested that low level of vancomycin early in the treatment course of MRSA infections might predict therapeutic failure (Truong, Levkovich and Padiglione 2012) and the potential for the emergence of VISA, heteroresistance VISA (hVISA) and vancomycin-resistant *S. aureus* (VRSA) (Hu *et al.* 2013; Sakoulas *et al.* 2006; Charles *et al.* 2004; Howden *et al.* 2004). The major implications of the development of these resistant pathogens are prolonged illness, greater risk of death and higher treatment costs.

The concerns regarding vancomycin toxicity, especially nephrotoxicity, are the main reason why many clinicians prefer the conventional 40 mg/kg/day. This safety issue stemmed from a number of impurities present in the initial formulation, which was termed the "Mississippi Mud" due to the brown colour of the compounds (Moellering 2006). However, today's formulation is a much safer preparation without those impurities. Although reports of nephrotoxicity and ototoxicity during vancomycin therapy do exist, they are difficult to interpret as most vancomycin therapies are usually accompanied by other nephrotoxic and ototoxic agents (Elyasi *et al.* 2012; Hazlewood *et al.* 2010; Glover, Cole and Wolfsdorf 2000). No matter how much toxicity is related to vancomycin, many researchers were convinced that problems could be avoided by careful monitoring of serum concentrations (Levine 2006).

The results of this study indicate that the vancomycin initial dosing of ≤40 mg/kg/day failed to produce the desired target therapeutic range of 10–20 mg/L most of the time, thus a need to review the current dosing practice. The observed high proportion of patients who were under-dosed after the initial dosing requires interventions, especially in the infants and children groups which have very high proportions of those who were in the sub-therapeutic range (see Fig. 1). One of the interventions is to increase the vancomycin initial dosing to at least 45 mg/kg/day as suggested by Avent *et al*. (2013) and MD Consult Drug Monograph (2014) in infants and children. For the neonates, the initial dosing is more complex and should be tailored according to the age group in weeks and body weight as suggested by the Micromedex drug database (Drug Information 2014). The alternative intervention is to use a standardised vancomycin loading dose (LD). This dosing strategy is advocated mainly in critically ill patients whose vancomycin volume of distribution (V_d) and clearance are altered due to their pathophysiological conditions. The vancomycin V_d in septic patients for example may increase significantly as a result of the increase in capillary permeability as a response to sepsis. The hyperdynamic state of sepsis may also increase the cardiac output and renal blood flow which in turn increase the renal elimination of vancomycin. This phenomenon results in a rapid drop of serum vancomycin level (Roberts and Lipman 2006). As a result, higher than normal vancomycin dose is needed to achieve the target therapeutic range; hence the use of LD as LD is proportional to the target trough level and V_d. Other pathophysiological conditions that may increase V_d are oedema, pleural effusion and ascites (Truong, Levkovich and Padiglione 2012). The V_d is also known to be larger in neonates, especially in those with very low body weight due to their larger volume of extracellular fluid compared to the infants and children (Marsot *et al.* 2012). A standardised loading dose of 20–25 mg/kg is suggested by Liu *et al.* (2011) in seriously ill infants and children followed by the maintenance dose of 45–60 mg/kg/day. In neonates, a loading dose of 15 mg/kg is suggested by MD Consult Drug Monograph (2014) followed by the maintenance dose of 20–30 mg/kg/day.

There were several limitations in the study. Firstly, this was a retrospective, observational single-centre study. Secondly, there was no evaluation on the serum creatinine of the patients which is an important covariate in optimising vancomycin dosing.

Thirdly, there was no evaluation on the association between the initial dosing regimens and clinical outcomes. The results of the study however may be used as a guide to form the hypothesis for future studies on the appropriate vancomycin dosing in paediatrics. It is also advisable that future studies on paediatric vancomycin dosing should separate the neonates from the infants and children due to their complex pharmacokinetic and physiological properties.

CONCLUSION

In conclusion, the study demonstrates that the initial dosing of vancomycin of >40 mg/kg/day is more likely to achieve the current therapeutic vancomycin trough level of 10–20 mg/L than the initial dosing of ≤40 mg/kg/day. At minimum, earlier achievement of the target therapeutic range would reduce the workload related to ordering and interpreting unnecessary vancomycin levels. At best, it might reduce the likelihood of antibiotic failure (Legal and Wan 2010). However, further studies with more robust designs on the relationship between initial dosing, clinical outcomes and toxicities are necessary before the recommendation to increase the vancomycin initial dosing in paediatric patients can be made. In practice, it is imperative for the clinicians to weigh between the risk of patients developing the toxicities and the risk of accelerating the emergence of vancomycin–resistant pathogens in selecting the right doses of vancomycin in paediatric patients.

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