Crystalloid resuscitation is associated with decreased treatment delays and improved systolic blood pressures in a blood-constrained setting

Mark T Yost [ID] ,[1] Matt Driban,[2] Fanny Nadia Dissak Delon,[3] Mbiarikai A Mbianyor,[4] Thompson Kinge,[5] Richard Njock,[6] Daniel Nkusu,[7] Jean-Gustave Tsiagadigui,[8] Melissa Carvalho,[1] Rasheedat Oke,[1] Alain Chichom-Mefire,[4] Catherine Juillard,[1] S Ariane Christie [ID] [1]

[1]Department of Surgery, University of California Los Angeles, Los Angeles, California, USA
[2]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[3]University of Bamenda, Bamenda, Cameroon
[4]Faculty of Health Sciences, University of Buea, Buea, Cameroon
[5]Limbe Regional Hospital, Limbe, Cameroon
[6]Laquintinie Hospital, Douala, Cameroon
[7]Catholic Hospital of Pouma, Pouma, Cameroon
[8]Edea Regional Hospital, Edea, Cameroon

Correspondence to
Dr Mark T Yost; yost.mark13@gmail.com

ABSTRACT

Objectives We analyzed resuscitation practices in Cameroonian patients with trauma as a first step toward developing a context-appropriate resuscitation protocol. We hypothesized that more patients would receive crystalloid-based (CB) resuscitation with a faster time to administration than blood product (BL) resuscitation.

Methods We included patients enrolled between 2017 and 2019 in the Cameroon Trauma Registry (CTR). Patients presenting with hemorrhagic shock (systolic blood pressure (SBP) <100 mm Hg and active bleeding) were categorized as receiving CB, BL, or no resuscitation (NR). We evaluated differences between cohorts with the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. We compared time to treatment with the Wilcoxon rank sum test.

Results Of 9635 patients, 403 (4%) presented with hemorrhagic shock. Of these, 278 (69%) patients received CB, 39 (10%) received BL, and 86 (21%) received NR. BL patients presented with greater injury severity (Highest Estimated Abbreviated Injury Scale (HEAIS) 4 BL vs 3 CB vs 1 NR, p<0.001), and lower median hemoglobin (8.0 g/dL BL, 11.4 g/dL CB, 10.6 g/dL NR, p<0.001). CB showed greater initial improvement in SBP (12 mm Hg CB vs 9 mm Hg BL vs 0 NR mm Hg, p=0.04) compared with BL or no resuscitation, respectively. Median time to treatment was lower for CB than BL (12 vs 131 min, p<0.01). Multivariate logistic regression adjusted for injury severity found no association between resuscitation type and mortality (CB adjusted OR (aOR) 1.28, p=0.82; BL aOR 1.05, p=0.97).

Conclusions CB was associated with faster treatment, greater SBP elevation, and similar survival compared with BL in Cameroonian patients with trauma with hemorrhagic shock. In blood-constrained settings, treatment delays associated with blood product transfusion may offset the physiologic benefits of an early BL strategy. CB prior to definitive hemorrhage control in this resource-limited setting may be a necessary strategy to optimize perfusion pressure.

Level of evidence and study type III, retrospective study.

BACKGROUND

Approximately 5 million people die in low- and middle-income countries (LMICs) each year due to injury.[1] Multiple studies in LMICs have identified

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Though balanced blood product transfusion represents the gold standard resuscitation in traumatic hemorrhage, the lack of safe blood in low- and middle-income countries (LMICs) such as Cameroon limits this practice. Trauma patients in Cameroon require a significant amount of blood but receive far less than needed and experience disproportionately worse outcomes. As a result, hemorrhagic shock is a major cause of preventable deaths in Cameroonian patients with trauma. Analysis of clinical patterns associated with real-world resuscitation practices can guide the development of a context-appropriate resuscitation protocol and optimize injury survival in blood-constrained settings.

WHAT THIS STUDY ADDS

⇒ Current resuscitation practices in Cameroonian patients with trauma with hemorrhagic shock demonstrate that crystalloid-based (CB) is the dominant treatment strategy and is associated with decreased time to treatment compared with blood product resuscitation. Blood transfusion was associated with treatment delays and modest improvements in blood pressure compared with CB resuscitation. When adjusted for injury severity, the use of blood resuscitation strategy was not independently associated with improved survival in this Cameroonian context. In a blood-constrained context, insufficient blood transfusion volume and/or treatment delays associated with blood product transfusion may offset the physiologic benefits of blood resuscitation.

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hemorrhage as the most common preventable cause of death.[2–4] Balanced whole-blood-like product transfusion and prompt hemostatic control remain the gold standard for traumatic hemorrhage resuscitation and are associated with decreased morbidity and mortality.[5–9] However, LMIC hospitals often lack access to sufficient safe blood to support resuscitation, leading to resuscitation delays and likely contributing to preventable mortality.[10–14] Although expanding the availability of safe blood through

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The findings of this study should serve as the foundational evidence basis for the development of an appropriate hemorrhagic shock protocol in the Cameroonian context. Since blood products are rarely available in this setting, such a hemorrhagic shock protocol should prioritize initial CB resuscitation to rapidly render treatment and maintain end-organ perfusion. However, the protocol should prioritize blood transfusion if available blood can be administered without delay. Future studies that implement hemorrhagic shock protocols should collect hospital course and clinical outcome data over time. These protocols must collaborate with facility blood banks to equitably distribute blood transfusion among all pertinent illnesses.

the development of blood banking remains critically important, understanding the clinical patterns and outcomes associated with real-world resuscitation practice is needed to guide trauma providers to optimize injury survival in blood-constrained settings.

Sub-Saharan Africa (SSA) has the greatest unmet blood transfusion needs of any global region.[11 15] Although Cameroon has a national blood policy, Cameroonian blood banking is hospital-based, and patient-related donors supply the majority of donated blood products.[10 12 16 17] Use of patient-related donors increases the risk of bloodborne pathogen transmission.[17–20] Further, cultural beliefs against blood donation and fear of HIV testing during blood donation screening have greatly curtailed volunteer blood donor participation.[21 22] For these reasons even referral centers in Cameroon have extremely limited available blood products, as the National Blood Transfusion Program (NBTP) estimates that donors only provide about 10% to 20% of the 400 000 to 600 000 pints of blood required annually in the country.[22–24]

A recent review of trauma deaths in Cameroon identified hemorrhagic shock to be a major contributor to preventable deaths and a national trauma quality improvement committee highlighted the need to improve both recognition and treatment of hemorrhagic shock.[25] However, little is known about current trauma resuscitation practice or associated outcomes in this blood-constrained setting. The Cameroon Trauma Registry (CTR) is an ongoing prospective multisite trauma registry with the specific objective of providing data capable of supporting trauma system improvement.[26] In this study, we analyzed current resuscitation practices among patients with hemorrhagic shock as a first step toward developing a context-appropriate hemorrhagic shock protocol in Cameroon. We hypothesized that more patients would receive crystalloid-based (CB) resuscitation with a faster time to administration compared with blood product (BL) resuscitation.

METHODS
Study design
We conducted an observational cohort study using prospectively collected CTR data from injured patients presenting to four hospitals in Cameroon between October 2017 and December 2019.

Setting
The four hospitals that participated in the national CTR data collection are located in the Southwest and Littoral regions of Cameroon. The first hospital is a public tertiary referral hospital with a 3-million-person catchment area. Two regional hospitals serve catchment areas of 100 000 to 300 000 people, respectively. Finally, a district hospital serves a catchment population of less than 100 000 people.[26 27]

When a Cameroonian emergency department (ED) patient requires intravenous crystalloid, the patient or patient's family must present an order slip to the hospital pharmacy and pay out of pocket for all materials required for intravenous administration (syringes, catheters, intravenous tubing, etc). After payment, the patient's family brings these items to the ED, where a nurse administers the fluids.

After a Cameroonian doctor orders a blood transfusion, either the nurse or the patient's family brings the paper order slip to the blood bank. The blood bank is usually located in a building separate from the ED on the hospital campus. The blood bank confirms the blood order and performs a cross-match from a patient sample collected by the nursing staff. If the patient's blood is not available, the blood bank asks the patient's family and friends to undergo cross match testing to determine if they have a matching blood type (eg, patient-related donation). If a match in this group does not exist, the patient's family must contact other blood bank locations to ascertain if they have the needed blood type. The amount of blood varies between hospitals. At times there are only 1 to 2 units of blood available for the entire patient population of smaller hospitals.

Participants and data sources
The study analyzed all injured patients who presented to affiliated hospitals and enrolled in the CTR during the aforementioned study period. Patients were approached by trained Cameroonian research assistants for informed verbal consent. Parents and/or guardians provided verbal consent for patients under the age of 18 years old. Research assistants documented obtaining verbal consent on the registry form. The need for signed informed consent for adults and parents/guardians was waived by the Institutional Review Board (IRB). Data were collected on paper forms by the research assistants and uploaded to an encrypted REDCap database hosted on the University of California, San Francisco server.[28]

Statistical methods, variables, and data analysis
We extracted data on all CTR patients who presented with evidence of hemorrhagic shock. We defined hemorrhagic shock as a systolic blood pressure (SBP) less than 100 mm Hg and evidence of active bleeding. An SBP cut-off of less than 100 mm Hg is the most sensitive measure since nearly 80% of Cameroonian patients with trauma dying at the hospital perish in the ED before disposition and 30% of Cameroonian patients with trauma who died after arriving at the hospital alive presented with normal vital signs.[25] We defined active bleeding as observation of external bleeding on presentation to the ED. Although the CTR records focused on assessment with sonography for trauma and diagnostic peritoneal lavage, these procedures were performed in less than 1% of all CTR patients. Additionally, diagnostic imaging in this CTR version records results as normal or abnormal which limits the ability to precisely discern evidence of internal hemorrhage. Patients with hemorrhagic shock were categorized as receiving either BL resuscitation, CB resuscitation, or no fluid resuscitation (NR) and we compared all three cohorts. All patients in the BL cohort received crystalloid prior to blood transfusion. Although the CTR did not explicitly measure whole blood or packed red blood cell components

transfused, it is likely that BL patients received whole blood.[29] CB patients only received intravenous crystalloid fluids and no blood products. For each cohort, we compared demographics, injury severity, physiologic, and clinical data.[27] Demographics such as cellphone ownership, urban/rural residence, and agricultural land ownership serve as proxies for estimating socioeconomic status (SES) according to *EconomicClusters* analysis.[30 31] We defined mortality as hospital mortality.

We summarized categorical variables as frequencies and proportions whereas we summarized continuous variables as median and IQR. We presented missing data as frequencies and proportions if data missingness was present for analyzed variables. We evaluated differences between resuscitation cohorts with the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. We compared time to treatment between the CB and BL cohorts with the Wilcoxon rank sum test. Time to treatment is defined as the time from patient arrival to time of first infusion of BL or CB. We used multiple logistic regression to evaluate associations between resuscitation strategy and trauma death. For all analyses, we used an alpha of 0.05. All statistical analysis was performed using Stata V.16.[32] We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines in the reporting of methods, results, and discussion.[33]

RESULTS

Of the 9635 patients enrolled in the CTR, 403 patients (4%) presented with hemorrhagic shock. Patients with hemorrhagic shock had a median age of 29 years (IQR 23–38 years) and were composed of 75% males. Patients with hemorrhagic shock presented with a median Highest Estimated Abbreviated Injury Scale (HEAIS) score of 3 (IQR 2–4) and 52 (13%) patients died.

Among patients with hemorrhagic shock, 278 patients (69%) received CB resuscitation, 39 patients (10%) received BL resuscitation, and 86 patients (21%) received NR (table 1). The BL patients were significantly older (35 years) than the CB and NR patients (both 28 years, p=0.03). A smaller proportion of NR patients (54%, n=46) were male than the CB (81%, n=226) and BL (82%, n=32) cohorts (p<0.001). We did not perform Fisher's test analysis of injury mechanism and disposition categorical variables due to lack of sufficient data that limited the validity

of analysis for comparisons of more than two groups. Nevertheless, the frequencies and proportions of the injury mechanism and disposition variables are listed to provide additional injury context in this setting.

BL patients presented with greater injury severity as measured by HEAIS (4 BL vs 3 CB vs 1 NR, p<0.001) and a greater proportion of polytrauma (51.3% BL vs 44.6% CB vs 4.7% NR, p<0.001) (table 2). NR patients had lower median heart rate on arrival (78 beats per minute (bpm) NR vs 94 bpm CB vs 96 bpm BL, p<0.001) and higher median SBP (94 mm Hg NR vs 90 mm Hg CB vs 88 mm Hg BL, p=0.003). BL patients had a lower median hemoglobin (8.0 g/dL BL) than the CB (11.4 g/dL) and NR (10.6 g/dL) cohorts (p<0.001). CB patients demonstrated a greater change in SBP after resuscitation (+12 mm Hg) compared with the BL cohort (+9 mm Hg) and NR cohorts (+4 mm Hg) (p=0.04). Time to treatment was 12 min in the CB cohort compared with 131 min in the BL cohort (p<0.001).

Multivariable logistic regression analysis adjusted for injury severity found no association between resuscitation type and mortality (CB adjusted OR (aOR) 1.28, p=0.82 vs BL aOR 1.05, p=0.97) (table 3).

DISCUSSION

In this study, we analyzed current resuscitation practices for patients with hemorrhagic shock in Cameroon as a first step toward developing a context-appropriate resuscitation protocol. CB resuscitation is the predominant strategy for treatment of hemorrhagic shock and is associated with a decreased time to treatment than blood product resuscitation. Blood transfusion was performed in less than 10% of patients with hemorrhagic shock and appeared to be triggered by high perceived injury severity, more extreme vital sign abnormalities, and lower hemoglobin levels. We can infer that there are no statistically significant differences between resuscitation cohort and SES *EconomicCluster* proxy variables.[30 31] Moreover, blood transfusion was associated with considerable treatment delays and modest incremental improvements in blood pressure compared with CB resuscitation. Despite the physiologic superiority of blood as a resuscitation product, when adjusted for injury severity, the use of blood resuscitation strategy was not independently associated with improved survival in this setting. These findings suggest

Table 1 Demographic and injury mechanism data of patients with hemorrhagic shock (n=403) categorized by resuscitation type

| | Crystalloid-based (n=278) | Blood product (n=39) | No resuscitation (n=86) | |
	Percentage (n)	Percentage (n)	Percentage (n)	P value
Age (median, IQR)	28 (23–38)	35 (25–42)	28 (19–36)	0.03*
Male sex	81.3 (226)	82.1 (32)	53.5 (46)	<0.001**
Urban residence	86.3 (240)	79.5 (31)	93.0 (80)	0.19
Missing	1.8 (5)	5.1 (2)	0	
Own cellphone	85.6 (238)	87.2 (34)	93.0 (80)	0.28
Missing	1.1 (3)	2.6 (1)	0	
Own agricultural land	8.3 (23)	7.7 (3)	17.4 (15)	0.06
Missing	4.7 (13)	7.7 (3)	1.2 (1)	
Mechanism				
RTI	61.5 (171)	66.7 (26)	48.8 (42)	
Stab wound	21.2 (59)	23.1 (9)	12.8 (11)	
Struck by person/object	5.4 (15)	2.5 (1)	16.3 (14)	
Fall	4.3 (12)	2.5 (1)	11.6 (10)	
Other/missing	7.6 (21)	5.1 (2)	10.5 (9)	

*p<0.05, **p<0.01.
RTI, road traffic injury.

Table 2 Physiologic and clinical data of hemorrhagic shock patients (n=403) categorized by resuscitation type

	Crystalloid-based (n=278)	Blood product (n=39)	No resuscitation (n=86)	
	Median (IQR)	Median (IQR)	Median (IQR)	P value
Polytrauma (%, n)	44.6 (124)	51.3 (20)	4.7 (4)	<0.001**
GCS	15 (14–15)	15 (8–15)	15 (15–15)	<0.001**
Missing (%, n)	0.7 (2)	0	0	
HEAIS	3 (3–4)	4 (3–5)	1 (1–2)	<0.001**
Missing (%, n)	2.2 (6)	0	2.3 (2)	
Arrival HR (bpm)	94 (75–107)	96 (81–113)	78 (65–93)	<0.001**
Missing (%, n)	2.5 (7)	5.1 (2)	3.5 (3)	
Arrival SBP (mm Hg)	90 (80–96)	88 (72–96)	94 (85–97)	0.003**
Hgb (g/dL)	11.4 (10.4–13.1)	8.0 (6.8–9.1)	10.6 (10.4–10.8)	<0.001**
Missing (%, n)	76.6 (213)	28.2 (11)	97.6 (84)	
Change in HR (bpm)	−4 (−15 to +5)	−5 (−28 to +16)	+4 (−8 to +6)	0.50
Missing (%, n)	52.9 (147)	23.1 (9)	94.2 (81)	
Change in SBP (mm Hg)	+12 (+2 to +28)	+9 (−2 to +21)	0 (−4 to +3)	0.04*
Missing (%, n)	52.5 (146)	20.5 (8)	94.2 (81)	
Time to treatment (min)	12 (7–22)	131 (70–240)	—	<0.001**
Missing (%, n)	4.0 (11)	23.1 (9)	—	
Disposition (%, n)				
Discharged home	26.3 (73)	20.5 (8)	90.7 (78)	
Admitted ward	18.3 (51)	12.8 (5)	2.3 (2)	
Admitted ICU	2.2 (6)	5.1 (2)	0	
Direct to OR	7.2 (20)	20.5 (8)	1.2 (1)	
Died	14.0 (39)	28.2 (11)	2.3 (2)	
Left AMA	23.7 (66)	10.3 (4)	1.2 (1)	
Transferred	7.2 (20)	2.6 (1)	1.2 (1)	
Other/missing	1.1 (3)	0	1.2 (1)	

*p<0.05, **p<0.01.
AMA, against medical advice; bpm, beats per minute; GCS, Glasgow Coma Scale; HEAIS, Highest Estimated Abbreviated Injury Scale; Hgb, hemoglobin; HR, heart rate; ICU, intensive care unit; n, number of patients; OR, operating room; SBP, systolic blood pressure.

that in a severely blood-constrained context, either insufficient blood transfusion volume or treatment delays associated with blood product transfusion may offset the physiologic benefits of blood resuscitation. Although CB resuscitation is known to be an inferior overall strategy for the treatment of hemorrhagic shock with considerable potential for delayed morbidity, it nevertheless may be the best option to maintain early organ perfusion in this context.[34]

The results of this study should serve as an initial step toward the development of a hemorrhagic shock protocol that is appropriate for the Cameroonian context. Though patients with trauma in SSA require a significant amount of the limited blood supply, these patients receive far less blood than needed and experience disproportionately worse outcomes compared with the

Table 3 Multivariable logistic regression for mortality

	Adjusted OR	95% CI	P value
Age	1.02	0.99 to 1.04	0.26
Male sex	0.87	0.33 to 2.27	0.78
HEAIS	8.32	4.66 to 14.84	<0.001
Resuscitation type			
None	Reference	—	—
Crystalloid-based	1.28	0.15 to 10.82	0.82
Blood	1.05	0.11 to 10.48	0.97

**p<0.01.
HEAIS, Highest Estimated Abbreviated Injury Scale.

rest of the world.[10–12] Although other LMICs have implemented massive blood transfusion (MBT) protocols, current resuscitation patterns at Cameroonian hospitals in this study demonstrate that reliance on an MBT is not feasible.[2 9] Due to the profound scarcity of available blood in Cameroonian hospitals, a hemorrhagic shock protocol should prioritize initial crystalloid resuscitation to rapidly render treatment and maintain end-organ perfusion. Though increase in SBP in this study is a crude measure for organ perfusion, other research concludes that crystalloid resuscitation intermittently perfuses organs in the absence of blood products.[34 35] While emphasizing crystalloid resuscitation, the protocol should allow blood transfusion to supersede crystalloid if blood is available and able to be administered without delay. Although this recommendation aligns with advanced trauma life support (ATLS) education, prohibitive costs and incompatibility with local capacities of standardized trauma education courses such as ATLS prevent LMIC provider participation.[35–38] This accommodation reflects the reality of limited blood transfusions in Africa and also conforms with previous advocation of clear fluid resuscitation in blood-constrained settings.[10–12 34] Significant controversy exists between CB and no intervention if no blood is available. Though a randomized controlled trial would best address this controversy, this article contains non-randomized, real-world data that demonstrate what treatment practices currently occur in this LMIC context. Whereas standardized trauma protocols (STPs) in LMICs can increase fluid resuscitation and lower mortality rates, a Cameroon-specific STP should collect patient data regarding clinical progress and

hospital course over time, as CB resuscitation trauma patients experience delayed complications such as renal acidosis and dilutional coagulopathy.[34 39]

Furthermore, more research is needed to further understand the clinical nuances of blood transfusion demand in Cameroon. A comprehensive hemorrhagic shock protocol including blood transfusion must be developed with facility blood bank collaboration to equitably distribute this resource among other clinical illnesses (obstetrics, malaria, etc). Although the Cameroon NBTP has announced blood transfusion demand and supply deficits on a national scale, researchers must determine which hospitals and clinical conditions require the greatest proportions of blood products.[22 23] Concurrently, Cameroon must expand public health initiatives to encourage voluntary blood donation and increase the national supply of blood products. Such an endeavor would require significant financial, public health, and political support as blood banking in SSA remains a very stigmatized issue.[17 20 21]

This study contains several limitations. Data missingness may reflect the practices influenced by the scarcities of Cameroonian health system. Specifically, it is possible that many patients lack recorded follow-up vital signs due to the large volume of clinical responsibilities placed on the limited amount of healthcare providers.[40 41] Multiple imputation for missing variables tends to become unreliable with data missingness greater than 10%. Machine learning demonstrates that non-random variable missingness greatly contributes to trauma research, as the sickest patients are most likely unable to provide complete data.[42] We included the percentage of data missingness to provide an accurate depiction of real-world prospective data collection in an LMIC. Finally, the inability to perform a reliable Fisher's exact test of the injury mechanism and disposition categorical variables due to small sample size limited study conclusions.

Moreover, another limitation of this study is the inability to differentiate between early versus late mortality in the analysis. It is important to consider this limitation as crystalloid resuscitation in patients with trauma is associated with complications more than 24 hours after treatment.[34] Likewise, the CTR data in this study period did not record the volume of blood or crystalloid administered to patients, limiting investigation of the effect of treatment volume on outcomes. An additional limitation is that the CTR did not record colloid resuscitation during the study period of data collection. Data regarding intravenous fluid volume and colloid administration have subsequently been added to the latest versions of CTR to support more comprehensive volume resuscitation analysis in the future. Additionally, the lack of balanced product transfusion in the Cameroonian context may affect clinical outcomes.[6 7] Although SSA possesses a significant unmet need for packed red blood cells, the unmet needs for blood components such as plasma and platelets are even larger.[11] This profound lack of blood and blood component supply impacts providers' capacity to follow resuscitation guidelines developed in high-income countries (HICs) and may skew the results of the study BL cohort. Further, survivor bias is present in the CTR data as there is no formal system of prehospital care in Cameroon. Although prior CTR analyses recorded that 22% of all trauma deaths presented as dead on arrival to the ED, it is impossible to measure the number of unreported deaths that occur outside the hospital.[25] Nevertheless, survivor bias does not invalidate these findings since research must understand the optimal treatment for injured patients who reach the hospital. Though the NR group has the lowest injury severity, the NR cohort remains important because a significant portion of patients evaluated by LMIC trauma care providers are discharged without treatment. The demonstration of all three cohorts—CB, BL, and NR—best depicts real-world clinical practice in this context and serves to instruct providers regarding the outcomes of their clinical decisions.

CONCLUSION

Injured Cameroonian patients with hemorrhagic shock treated with CB transfusion received treatment more rapidly, demonstrated greater elevation in SBP, and did not exhibit increased mortality on regression analysis when compared with patients receiving BL resuscitation. BL resuscitation was associated with greater injury severity and significant treatment delays, which may offset its physiologic benefits.

ORCID iDs
Mark T Yost http://orcid.org/0000-0001-6277-7729
S Ariane Christie http://orcid.org/0000-0002-0430-7187

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