

Running head: PRINTO criteria for CID in JDM underestimate skin disease

Title: Analysis of published criteria for Clinically Inactive Disease in a large Juvenile Dermatomyositis cohort shows that skin disease is underestimated

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ABSTRACT

Objective:

Recent criteria (from the Pediatric Rheumatology International Trials Organisation) to classify patients with clinically inactive disease (CID) in Juvenile Dermatomyositis (JDM) require at least three of four conditions to be met: creatinine kinase (CK) ≤ 150 U/L, Childhood Myositis Assessment Scale (CMAS) ≥ 48 , Manual Muscle Testing of 8 groups (MMT8) ≥ 78 and physician global assessment of overall disease activity (PGA) ≤ 0.2 . We tested these criteria in the UK cohort of JDM patients.

Methods:

1114 patient episodes were assessed for the 4 items in the CID criteria. Each episode was analysed to determine whether skin disease was present. The Disease Activity Score (DAS) tool was measured in 59 patients.

Results:

307 episodes achieved CID based on the 3 muscle criteria (but PGA > 0.2); 65.8% had rash and 35.2% had abnormal nailfold capillaries. When PGA ≤ 0.2 was one of the 3 criteria, the frequency of skin signs was significantly lower (23.1% and 8.7% respectively). If PGA was considered an essential CID criterion (P-CID), patients with active skin disease were less likely to be defined as CID (median DAS skin score 0/9, versus 4/9 in patients meeting 3 muscle criteria, $p < 0.001$). P-CID led to an improvement in the positive predictive value (85.4%) and the positive likelihood ratio of 11, compared to the current criteria (72.9% and 5.1 respectively).

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Conclusion:

When existing CID criteria were assessed without PGA, there was a high frequency of skin disease. Incorporating PGA as an essential CID criterion helps prevent the misclassification of patients with active skin disease.

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INTRODUCTION

Juvenile dermatomyositis (JDM) affects approximately 2-3 children/million/year, and although rare, is the most common childhood form of idiopathic inflammatory myopathy (IIM),(1, 2). Scoring tools have been developed to assess disease activity and damage in JDM,(3) in a standardised manner to assist clinical trials and allow comparisons between different cohorts. The Pediatric Rheumatology International Trials Organisation (PRINTO) recently analysed these activity measures, and defined thresholds for the state of clinically inactive disease (CID),(4). Patients were clinically inactive if they met at least 3 of 4 criteria, defined as: creatinine kinase (CK) ≤ 150 U/L, Childhood Myositis Assessment Scale (CMAS) ≥ 48 , Manual Muscle Testing of 8 groups (MMT8) ≥ 78 and physician global assessment of overall disease activity (PGA) ≤ 0.2 .

These criteria are currently weighted towards muscle disease: although muscle symptoms are the main focus of monitoring and treatment, it is important that skin inflammation is not neglected. Skin disease is often recalcitrant to treatment and may be associated with poor long-term outcomes such as calcinosis,(5, 6), poor quality of life and decreased physical function,(7, 8). Therefore, we propose that skin disease should be represented in any definition of CID. At present, only 3 of 4 criteria are needed to define CID. Therefore if all 3 muscle criteria are normal, the PGA may be disregarded. This risks potentially ignoring disease activity of the skin or other organs. The purpose of this study was to apply the PRINTO CID criteria to the UK cohort of JDM patients, and test the hypothesis that in clinical practice, there may be alternative definitions that would improve the performance of the criteria.

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PATIENTS and METHODS

Patients

1114 discrete patient episodes involving 258 patients with JDM were analysed from the UK JDM Cohort and Biomarker Study,(9). Informed written consent was obtained. All patients had a diagnosis of JDM according to Bohan and Peter criteria,(10, 11). 74.6% were female and 80.9% were Caucasian. At the time of the patient episode the mean (\pm sd) age was 11.9 (\pm 3.6) years. The mean age at diagnosis was 6.7 (\pm 3.4) years, with mean disease duration 4.4 (\pm 3.1) years.

Data collection

Clinical data were collected prospectively from patients at recruitment, then 3–4 monthly for the first 2 years and then at least once a year. Data collection included signs and symptoms and disease activity measures: CMAS, MMT8, PGA and laboratory tests. Data related to skin disease (rash, Gottron's papules, ulceration, nailfold changes, calcinosis) were retrieved for all patient episodes. All data for the UK JDM Cohort and Biomarker Study are stored in a Structured Query Language (SQL) platform database with Access front end data retrieval.

59 of the patients were clinically assessed using the JDM Disease Activity Score (DAS),(12) tool. This was measured prospectively by 2 physicians, BA and RC-M at the same time as clinical assessment of the patient. The DAS tool consists of 6 components, resulting in a 20 point scale, with higher scores indicating greater disease activity. The tool has 2 sub-sections, the DAS muscle score (total 0-11) addressing functional status

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and the presence or absence of weakness, and the DAS skin score (total 0-9) related to skin disease including skin involvement type, distribution, vasculitis and Gottron's papules. For the purposes of this study, the DAS tool was scored in its entirety (DAS total score 0-20), and separated into its muscle and skin sub-sections.

Data analysis

Patient episodes were included in the study if data for all four of the PRINTO CID criteria,(4) were available. CID could be achieved if all 4 criteria were met or if only 3 out of 4 were met. On this basis, patient episodes were divided into groups (Table 1).

Statistical analyses

Continuous normally distributed variables were reported as mean (\pm SD) and continuous non-normally distributed variables as median values (range). Categorical data were analysed using the Chi-square test. One-way analysis of variance (ANOVA) was used to test the difference in DAS scores between groups with a Tukey's correction for multiple testing. A p-value <0.05 was considered significant.

We compared the performance of the original criteria against 'P-CID', an alternative definition of CID where PGA is regarded as an essential criterion together with either 2 of the 3 muscle criteria, using diagnostic statistics. From the original cohort of 1114 patient episodes, both definitions of CID were tested using a reference group of patient episodes; those within 4 months of diagnosis (active) and on medication, and those off all medication for 6 months or more (inactive, or clinical remission as defined by the International Myositis Assessment and Clinical Studies Group (IMACS) consensus guidelines,(13)). 4 months after diagnosis was set as a time period as we considered

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that these patients would have active disease. In order to demonstrate that P-CID improved the performance of the CID criteria, separate analyses were performed including sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios (with corresponding confidence intervals).

Data were stored in a central Access database (Microsoft 2007) and analysed with Excel (Microsoft 2010). GraphPad Prism version 5.00 for Windows was used for statistical analyses.

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RESULTS

Amongst our cohort of 1114 patient episodes from 258 JDM patients, 665 episodes (59.7%) met the criteria for CID (Figure 1). Of these 665 episodes, 254 (38.2%) from 119 patients met all 4 criteria (Group I), while 411 (61.8%) from 165 patients met 3 of 4 criteria. Of the episodes where only 3 of 4 criteria were met, 104 had a PGA ≤ 0.2 (Group II), whilst the remaining 307 had CID based on the 3 muscle criteria, with a PGA > 0.2 (Group III).

To test if each of the criteria were equally redundant, the 411 episodes were divided based on which of the CID criteria was not met (Figure 2A-D). The median CK value in the group with CK > 150 U/L was 206U/L (Figure 2A) and the majority of outliers had values less than 400 (range 152-650). CMAS scores in the group not meeting the CMAS threshold were clustered about a median value of 45, although values of 28 and 34 were noted in the case of 2 outliers (Figure 2B). For patient episodes not meeting the MMT8 threshold, scores were clustered close to 78 ((Figure 2C), median 73, range 71-77). However, unlike CK, CMAS and MMT8, it was striking that the distribution of PGA scores when PGA > 0.2 , spanned the entire spectrum of scores from 0.3 to 8.5 ((Figure 2D), median 1.0).

Frequency of skin disease

In clinical practice the most common reason for ongoing disease activity in the face of normal muscle assessment, is skin inflammation. To address this, the frequency of skin signs was analysed according to the specific CID criteria that were met (Table 2). Most clinicians feel that a PGA > 1.0 represents active disease; 44% of patient episodes in

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Group III had PGA >1.0 despite normal muscle criteria, suggesting ongoing disease activity that did not involve muscles.

In Group I skin signs were still present, with almost 30% having a skin rash, and 11% having abnormal nailfold changes. Group II had no significant differences in skin abnormalities when compared to Group I. In Group III, the frequencies of skin signs were much higher and these data closely paralleled results in Group IV. The omission of PGA from the definition of CID (Group III) significantly increased the frequency of JDM skin signs compared to Group II for rash (χ^2 57.28, $p < 0.0001$), Gottron's papules (χ^2 30.74, $p < 0.0001$), nailfold changes (χ^2 26.84, $p < 0.0001$) and calcinosis (χ^2 10.93, $p = 0.0009$). There were no significant differences in the rate of ulceration.

DAS tool scores

Our results suggested that PGA was an important criterion since it identified ongoing skin disease. To confirm this hypothesis, we used the DAS tool,(12) to perform a detailed analysis of muscle and skin disease in 59 JDM patients (Figure 3). As expected, DAS total scores were low (median 0, range 0-2) in Group I (Figure 3A), suggesting that the combined criteria successfully excluded patients with active disease. There was no increase in DAS total scores when Group II (median 1, range 0-6) were compared to the reference Group I. However, in Group III, there was a significant increase in DAS total score compared to Group I (median 5, range 2-9, ANOVA $p < 0.01$).

To further explore the role of PGA within the CID criteria, we re-analysed the above data after splitting the DAS total score into its skin and muscle sub-sections. The DAS skin score (Figure 3B), mirrored the results from the DAS total scores in that there were no

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significant differences between Group I (median 0, range 0-2) and Group II (median 0, range 0-4). Group III (median 4, range 1-7) had significantly worse DAS skin scores than Group I and Group II. In contrast, there were no significant differences in DAS muscle scores between Groups I, II and III (median 0 in all 3 groups, Figure 3C), confirming that there was almost no muscle disease activity.

Diagnostic performance of revised criteria

These results suggest that a raised PGA in the context of normal muscle markers identifies patients who have ongoing skin inflammation. As CID when the PGA was met (P-CID) appeared more stringent than the 3 muscle based criteria (Figure 1), we asked if this would reduce its diagnostic utility. We compared the performance of the original criteria against P-CID (PGA should be an essential criterion together with either 2 or 3 muscle criteria). Both definitions of CID were tested using the originally identified 1114 patient episodes to create 2 reference groups;

1. Active disease – defined as patients within 4 months of diagnosis date and taking medication (total 111 episodes).
2. Inactive disease – defined as patients off all medications for 6 months or more (total 59 episodes).

We applied the PRINTO criteria to these 2 groups and separated the patient episodes according to the number of criteria met (supplementary data, Table 1):

Consequently we calculated sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (PLR and NLR) based on the current criteria and P-CID (Table 3).

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P-CID led to an improvement in the positive predictive value (85.4%) and a positive likelihood ratio of 11, compared to the current criteria (72.9% and 5.1 respectively) without an appreciable deterioration in the negative predictive value and negative likelihood ratio. The specificity also increased to 93.7% (compared to the current criteria 81.9%), however P-CID led to a decrease in the sensitivity (69.5%, compared to the current criteria 91.5%).

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DISCUSSION

Many patients with JDM have prolonged disease courses and require long term treatment, therefore it is important to be able to define CID to aid assessment of their condition and guide treatment decisions. To this end, it was important that PRINTO proposed criteria for CID in JDM which were based on disease activity measures that are in routine clinical use. Our study formally tested these criteria in a large independent cohort of JDM patients and asked if they performed adequately in a “real world” clinical setting.

Based on the PRINTO criteria, nearly 60% of our patient episodes met the definition for CID. As 3 measures are specific to muscle disease, we asked if there was redundancy between these items. Indeed, omission of 1 of the 3 muscle criteria had little impact on the disease activity scores in that domain. In contrast, if PGA was not one of the 3 criteria, this led to a clear increase in PGA scores, despite normal muscle criteria. Our results identified a subset of patients, with high PGA in the face of normal muscle criteria that exhibited a high frequency of skin abnormalities. We predicted that these patients had active skin disease, but as our longitudinal cohort study data could not easily distinguish between damage and active disease e.g., atrophic Gottron’s papules, we prospectively assessed 59 patients using the DAS tool. In this carefully curated patient cohort, it was clear that patients in Group III had significantly higher DAS skin scores than patients from Groups I or II, confirming that use of muscle criteria alone failed to detect patients with active skin disease.

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Although the majority of the DAS tool specifically identifies clinical activity, a few of the skin items may detect damage, such as atrophic changes within the skin involvement section, and telengectasia in the vasculitis section. However when these items were removed from the analysis, the results were unchanged (data not shown).

A recent report from Norway retrospectively analysed long term follow up of an inception cohort of 59 JDM patients and found a similar rate of CID (49%) to our study,(14). Only 48% of the Norwegian patients meeting CID criteria had a normal score based on the Myositis Intention to Treat Activity Index (MITAX), a tool measuring disease activity in 7 distinct organ domains. However if the skin domain was excluded from the MITAX tool, 87% of patients meeting CID had a normal MITAX score. These results are consistent with our findings that the PRINTO CID underestimates skin disease. One limitation of our study is that we did not have accurate data on disease activity in other organs. Although we show that patients with high PGA in the face of normal muscle criteria have active skin disease, it possible that the elevated PGA also relates to disease in other organs.

When compared to the existing PRINTO criteria, the use of P-CID improved the specificity and the positive predictive value of the CID tool but reduced sensitivity suggesting our modification increased the stringency of the tool. In this analysis we considered patient episodes within 4 months of diagnosis to be representative of patients with clinically active disease. However this analysis may underestimate the specificity of the CID tool as a small number of patients within this group had no evidence of active disease and may reflect patients with a milder disease course or those who are early responders to treatment.

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We also considered the use of PGA and MMT8 alone to define CID, but this did not offer better results than our proposed P-CID tool. However this 2 item tool would be a viable option to be considered in a further validation study examining CID criteria.

We therefore propose that the existing PRINTO criteria require modification, either with the use of PGA as an essential criterion or by adding items that specifically measure skin disease activity. These changes would ensure that active JDM skin disease is not overlooked in the definition of CID and need to be tested in future studies.

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TABLES

Table 1 - Groups according to disease activity and criteria met

Group	Status	Criteria met	PGA	Other criteria
I	CID	4	PGA met ≤ 0.2	All met
II	CID	3	PGA met ≤ 0.2	Either CK or CMAS or MMT8 not met
III	CID	3	PGA not met > 0.2	CK, CMAS and MMT8 all met
IV	Active	0 or 1	-	-

CID = clinically inactive disease; CK = creatinine kinase; CMAS = Childhood Myositis

Assessment Scale; MMT8 = Manual Muscle Testing of 8 groups; PGA = physician global assessment of overall disease activity.

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Table 2 – Frequency of skin signs in JDM patients meeting clinically inactive criteria

	Rash	Gottron's papules	Ulceration	Nailfold changes	Calcinosis
Group I; PE 254, n 118	76 (29.9)	32 (12.6)	1 (0.4)	28 (11.0)	19 (7.5)
Group II; PE 104, n 70	24 (23.1)	11 (10.6)	1 (1.0)	9 (8.7)	6 (5.8)
Group III; PE 307, n 131	202 (65.8)	123 (40.1)	9 (2.9)	108 (35.2)	60 (19.5)
Group IV; PE 208, n 127	159 (76.4)	117 (56.3)	26 (12.5)	100 (48.1)	36 (17.3)
χ^2 between Group I and II	1.71	0.29	0.43	0.45	0.33
p value	ns	ns	ns	ns	ns
χ^2 between Group I and III	71.57	52.44	5.11	44.16	16.72
p value	p<0.0001	p<0.0001	p=0.024	p<0.0001	p=0.0009
χ^2 between Group II and III	57.28	30.74	1.27	26.84	10.93
p value	p<0.0001	p<0.0001	p=0.259	p<0.0001	p=0.0009

(number of episodes, % in brackets).

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CID= clinically inactive disease; PGA = physician global assessment of overall disease activity; PE = patient episodes; n = number of patients; χ^2 = chi squared test with corresponding p value; ns = not significant.

Group I – Clinically inactive disease, all 4 criteria met; Group II – Clinically inactive disease, 3 criteria met (PGA met ≤ 0.2 and either CK or CMAS or MMT8 not met); Group III - Clinically inactive disease, 3 criteria met (PGA not met > 0.2 and CK, CMAS and MMT8 all met); Group IV – Active (0 or 1 criteria met).

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Table 3 – Performance characteristics of current and revised clinically inactive disease criteria

	Current CID criteria	CI	Alternative definition of CID (P-CID)	CI
Sensitivity	91.5	80.5 to 96.8	69.5	56.0 to 80.5
Specificity	81.9	73.3 to 88.3	93.7	87.0 to 97.2
PPV	72.9	61.1 to 82.3	85.4	71.6 to 93.5
NPV	94.8	87.7 to 98.0	85.2	77.4 to 90.8
PLR	5.1	3.4 to 7.6	11.0	5.3 to 23.0
NLR	0.1	0.04 to 0.2	0.3	0.2 to 0.5

PPV = positive predictive value; NPV = negative predictive values; PLR = positive likelihood ratio; NLR = negative likelihood ratios.

CID = clinically inactive disease, CI = confidence intervals, P-CID = clinically inactive disease when the PGA is met.

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FIGURE LEGENDS

Figure 1

Analysis of 258 patients from the UK JDM cohort and biomarker study according to the clinically inactive disease (CID) criteria

Flowchart describing the prevalence of CID in 1114 patient episodes.

Figure 2

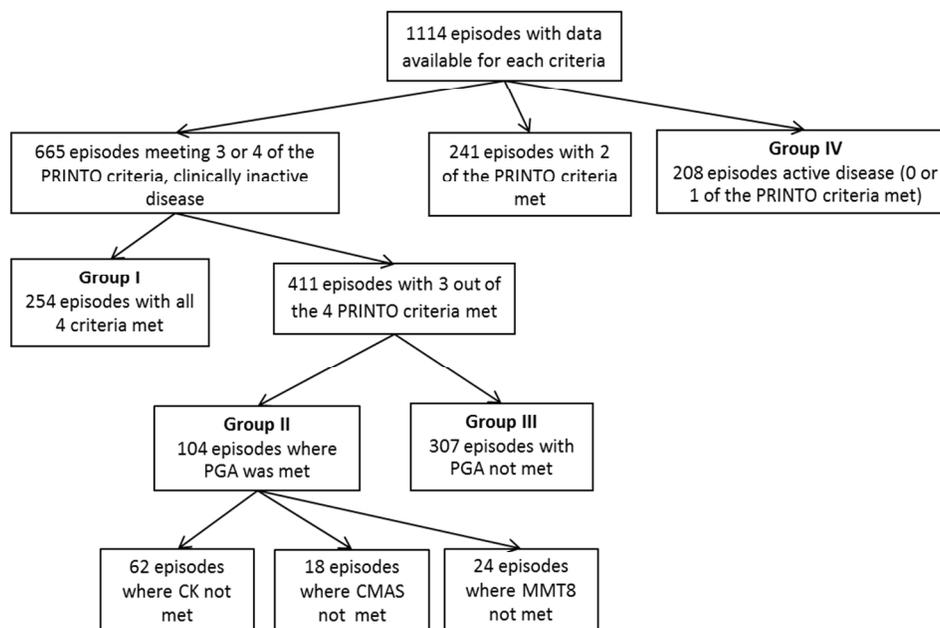
Analysis of disease activity and laboratory results in patient episodes which met 3 of 4 CID criteria

A-D. Each panel shows data analysed when 1 of the 4 criteria was not met (**A.** CK, **B.** CMAS, **C.** MMT8, **D.** PGA) in 411 episodes. Median values demonstrated.

Figure 3

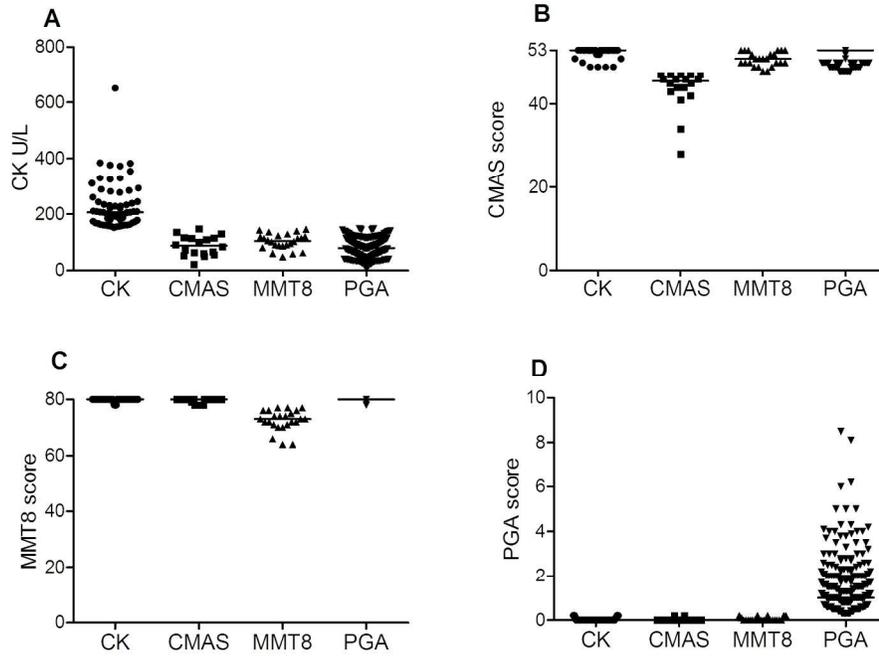
JDM disease activity scores (DAS) in 59 patients meeting criteria for clinically inactive disease (CID)

Scatter plots: **A.** DAS total score, **B.** DAS skin score, **C.** DAS muscle score in JDM patients meeting all 4 criteria for CID (Group I), meeting 3 of 4 criteria (either PGA met ≤ 0.2 (Group II) or PGA not met > 0.2 (Group III)), or meeting only 0 or 1 criteria (active disease, Group IV). Median values demonstrated. Only significant results shown, * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.



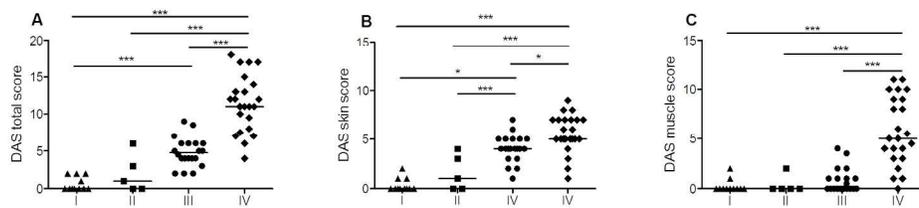
194x126mm (150 x 150 DPI)

Accepte



203x143mm (300 x 300 DPI)

Accept



228x61mm (300 x 300 DPI)

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