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REVIEW

Assessment of opioid and benzodiazepine withdrawal symptoms in critically ill children: current state of the art

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Abstract - Prolonged administration of benzodiazepines and/or opioids to children in a paediatric intensive care unit (PICU) may induce physiological dependence and withdrawal symptoms. We reviewed the literature for relevant contributions on the nature of these withdrawal symptoms and on availability of valid scoring systems to assess the extent of symptoms in children. Symptoms of benzodiazepine and opioid withdrawal can be classified into three groups: central nervous system (CNS) overstimulation, gastrointestinal dysregulation and autonomic dysfunction. In children, symptoms associated with CNS overstimulation and autonomic dysfunction may overlap after long-term use of benzodiazepines or opioids. Symptoms of gastrointestinal dysfunction in the PICU population have only been described for opioid withdrawal. Four scoring systems for use in children have been described. Two of these provided good reliability and validity to determine withdrawal symptoms: the Withdrawal Assessment Tool version 1 (WAT-1) and the Sophia Observation withdrawal Symptoms-scale (SOS).

Keywords - Opioids, benzodiazepine, withdrawal symptoms, paediatric intensive care

Introduction

Ventilated, critically-ill children commonly receive sedative and analgesic drugs to ease their mental burden, and the anxiety and pain induced by frightening or painful interventions and environmental factors in the paediatric intensive care unit (PICU). Intravenous opioids (e.g. morphine and fentanyl) and benzodiazepines (e.g. midazolam) are the most commonly used drugs for this purpose [1,2].

A common complication of sedation, especially when lasting more than one week, is physiological dependency and the risk of withdrawal symptoms. Withdrawal symptoms may develop when a drug that causes physical dependence is suddenly stopped, reduced too quickly or antagonized [3,4].

Most of our knowledge of physical dependence and withdrawal symptoms has been derived from research in newborns of drug-addicted mothers [5,6]. Since the 1990s, withdrawal syndromes have been recognized in older children who have been iatrogenically exposed to opioids, benzodiazepines and other drugs in the PICU [7]. Two retrospective and one prospective randomized controlled trial have been reported on opioid and/or benzodiazepine withdrawal after long-term administration of analgesics or sedatives in the adult ICU setting [8-10]. The incidence of withdrawal syndrome has been described in only two studies so far; one reported withdrawal symptoms in 32.1% (9/28) and the other in 100% (11/11) [8,9]. However, each of these studies used a different assessment tool which makes it difficult to describe symptoms in a uniform manner. Reported symptoms are mostly agitation, irritability, anxiety, insomnia, tachycardia, hypertension, and sweating. High total doses and exposure to medication for longer than seven days, are risk factors for developing withdrawal symptoms in adult ICU patients. This knowledge may serve to gain a better insight into problems of tolerance, dependence, and withdrawal in paediatric intensive care, which are still insufficiently recognized [11]. Recognition of withdrawal syndrome in PICU patients is difficult because the symptoms may strongly overlap with clinical signs of inadequate sedation, such as agitation, anxiety, and movement disorder.

The purpose of this review is to discuss the nature of withdrawal symptoms, their frequency, reported incidences and risk factors as well as available tools for assessing withdrawal symptoms in children in a PICU.

Withdrawal symptoms

The signs and symptoms of withdrawal can be classified into three distinct categories: overstimulation of the central nervous system (CNS), gastrointestinal dysfunction, and autonomic dysregulation or sympathetic hyperactivity [4,12,13]. Table 1 lists the signs and symptoms of withdrawal in children relating to either opioids or benzodiazepines, or their combined use, broken down into these three categories.

Opioid withdrawal symptoms

Common manifestations of CNS overstimulation are: tremors, increased muscle tension, anxiety, restlessness, irritability, and insomnia [14-23]. In addition, Lane *et al.* [19] and French and Nocera [17] described the development of choreoathetoid movements as a withdrawal symptom of fentanyl administration in five children and one child respectively, as well as intermittent muscle contractions and uncontrolled movements after long-term use of fentanyl. The Moro reflex is seen as an opioid withdrawal symptom in neonates [5,13]. However, as the Moro reflex disappears between the ages of 1 and 3 months, it is never observed in older children. It was nevertheless one of the items in the assessment tool used by

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Franck *et al.* [16] in 1.5- to 28-month-old children. In view of the age limitation we feel it is not feasible to use this symptom as a withdrawal symptom for all PICU patients [4]. The most frequent gastrointestinal symptoms of opioid withdrawal are vomiting and diarrhoea [15,16,18,20-22]. In addition Carnevale and Ducharme [15] reported reduced oral intake. Autonomic phenomena are: fever, sweating, sneezing, yawning, tachycardia, and hypertension [16,17,20-22]. Note that increases in heart rate and blood pressure should be related to the normal values for the child's age and disease. In summary, the clinical signs of opioid withdrawal in children (Table 1) are largely congruent with those in newborn babies of drug-addicted mothers [5,13].

Benzodiazepine withdrawal symptoms

Classical characteristics of benzodiazepine withdrawal described for the domains of adult psychiatry and care of drug addicts are: severe anxiety, involuntary muscle tremors, confusion, insomnia, perception disorders, depression, and generalized convulsions [12,24]. Table 1 lists the withdrawal symptoms for benzodiazepines observed in children. Strikingly, most symptoms have been described on the basis of single case-reports and case series with small numbers of patients. Only two articles describe larger patient groups of 40 and 53 patients, respectively [25,26]. Symptoms observed in these two studies were different, however, and the observation forms used included no more than five and seven symptoms, respectively. These qualitative and quantitative limitations, notably in the case studies, provide only limited insight into the symptoms of benzodiazepine withdrawal. The benzodiazepine studies were all of a descriptive nature, in contrast to the opioid studies. Regarding CNS overstimulation, in a case-report Sury *et al.* [23] first described withdrawal symptoms resulting from long-term use of midazolam in children. Three children, aged 4, 11, and 12 years, received midazolam as a sedative for 7, 14 and 17 days, respectively. Within 24 hours after discontinuation they showed signs of hallucinations, irritability, confusion, restlessness/agitated behaviour and generalized convulsions. These are all manifestations of CNS overstimulation. Other studies report tremors, anxiety, agitation, restlessness, inconsolable crying, muscle twitching, and myoclonic movements of the extremities [14-16,25-29]. Regarding sympathetic hyperactivity or autonomic dysregulation, a case study of two children observed tachycardia and fever as benzodiazepine withdrawal reactions [28]. Others observed perspiration, insomnia and severe coughing [16,26]. Regarding gastrointestinal dysfunction, one case study reported vomiting in a 14-day-old newborn whose stomach had distended as a result of air swallowing [28]. This single case report provides insufficient evidence to include this symptom as a benzodiazepine withdrawal symptom. Dysfunction of the gastrointestinal tract as a symptom of benzodiazepine withdrawal has not been described in adults [8,24]. In summary, the major symptoms of benzodiazepine

Table 1. Reported signs and symptoms of benzodiazepine and opioid withdrawal in children

	CENTRAL NERVOUS SYSTEM OVERSTIMULATION	GASTROINTESTINAL DYSFUNCTION	AUTONOMIC DYSFUNCTION
Opioids	Increased muscle tone	Vomiting	Tachypnoea
	Myoclonus	Poor feeding	Yawning
	Ataxia	Diarrhea	Sneezing
	Abnormal movements		Hypertension
	Pupil dilation (>4mm)		Mottling
	High pitched crying		
Benzodiazepines	Muscle twitching		Frequent suction required
	Inconsolable crying		
	Grimacing		
	Jitteriness		
	Visual, auditory hallucinations		
	Disorientation		
	Seizures		
	Movement disorder		
Opioids & Benzodiazepines	Tremor		Fever
	Anxiety		Sweating
	Agitation/Crying		Tachycardia
	Irritability		
	Insomnia/sleep disturbance		
	Choreoathetoid movements (of upper extremities)		

withdrawal in children are anxiety, tremors, and other involuntary muscle movements, irritability, perspiration and insomnia. These correspond with the classical manifestations of benzodiazepine withdrawal in adults [12,24].

Combined benzodiazepine-opioid withdrawal symptoms

Differences between opioid and benzodiazepine withdrawal symptoms are marginal [12]. Symptoms associated with CNS overstimulation and sympathetic hyperactivity largely overlap after long-term use of benzodiazepines or opioids in children (see Table 1). However, benzodiazepine withdrawal is not associated with symptoms of the gastrointestinal tract [8,12].

Several studies found it hard to determine whether the withdrawal symptoms were specifically caused by benzodiazepines dependence because in these studies opioids (morphine, fentanyl) were administered for sedation as well [14,16,25,27,29]. This illustrates the practical limitations of describing specific benzodiazepine-related withdrawal symptoms in the PICU. From clinical experience we know that a combination of benzodiazepines and opioids is usually administered in order to provide for both sedation and analgesia. As reflected in the literature, this may last from several days to weeks [1,30]. Given the overlap in symptoms, it is hard to ascribe withdrawal symptoms to either opioids or benzodiazepines [15,16,27].

Frequency of withdrawal symptoms

Table 2 contains information from three studies that examined the frequency of signs and symptoms of withdrawal in critically ill children [16,31,32]. These were the only studies which prospectively observed the frequency of withdrawal symptoms. As this information is drawn from disparate groups using several methods, comparisons are subjective. With respect to these limitations symptoms such as tremors, agitation, inconsolable crying, motor disturbance, sleeplessness, diarrhoea, loose stools and sweating appear emerge as highly prevalent symptoms of withdrawal. In an earlier study we provided a comprehensive overview of frequency of occurrence of all 24 different withdrawal symptoms after tapering off or cessation of benzodiazepines and/or opioids in children [32].

Incidences of benzodiazepine and opioid withdrawal syndrome

Only four published studies describe incidences of withdrawal symptoms after long-term use of benzodiazepines or opioids in children [18,25,26]. In a retrospective study, Fonsmark *et al.* [26] found that 14 of 40 (35%) sedated children (6 months-14 years) on ventilatory support developed withdrawal symptoms. A prospective study of abrupt discontinuation of midazolam in critically ill children (0-11 years) reported adverse side effects in 17% of the 53 patients [25]. Opioid withdrawal symptoms were seen in 13/23 (57%) children aged 0-22 months after prolonged continuous fentanyl administration [18]. A prospective study of the pattern of analgesic and sedative infusions in ventilated children (1 month -15 years) in a Brazilian PICU reported that withdrawal syndrome was diagnosed in 46 of 124 (34%) patients [33]. However, methods differed between these four studies. Katz *et al*. [18] used the Neonatal Abstinence Score (NAS) developed by Finnegan *et al.* [5] which has only been validated for use in newborns. Both Hughes *et al*. [25] and Fonsmark *et al.* [26] recorded withdrawal symptoms through self-developed observation lists with no more than five behavioural items. Fonsmark *et al.* included 'sweating' as a physiological item [26]. The authors did not provide data on reliability and validity of their observation lists [25,26]. In the study of Sfoggia *et al.* assessment of withdrawal symptoms was based on daily interviews with the physician [33]. Neonates receiving extracorporeal membrane oxygenation (ECMO) therapy comprise a specific PICU population. From 9 to 57% of children on ECMO showed symptoms of opioid withdrawal (NAS > 8) [34,35].

Influencing factors of withdrawal symptoms

Various authors have shown that dosing and duration of benzodiazepines or opioids administration influences development of withdrawal symptoms [17,18,26]. Katz *et al.* [18] found a total fentanyl dose of 2.5 mg/kg or higher or a fentanyl infusion for at least nine days to result in withdrawal symptoms in 100% of cases. Arnold *et al.* [34] found that neonates receiving ECMO therapy with total doses greater than 1.6 mg/kg fentanyl or an ECMO duration of longer than five days had a significantly greater incidence of withdrawal symptoms, as reflected by the NAS. In another study in ECMO patients the authors demonstrated that neonates who received total fentanyl doses higher than 1.2 mg/kg were thirteen times more likely to experience opioid withdrawal after ECMO [35]. No study has established the total morphine doses that may be associated with withdrawal symptoms.

A retrospective study by Fonsmark *et al.* [26] found a total midazolam dose higher than 60 mg/kg to be associated with the occurrence of withdrawal symptoms. In a previous study we found a 0.51 ($p < 0.001$) correlation between total doses of midazolam and maximum sum score on the Sophia Benzodiazepine and Opioid Withdrawal Checklist [32]. The correlation between total doses of opioids and the maximum sum score was 0.39 ($p < 0.01$). Furthermore, there was a significant correlation (0.52; $p < 0.001$) between duration of use and maximum sum score. Several authors found correlations between withdrawal symptoms and total cumulative doses (mg/kg) of midazolam or opioids [8,16-18,26,31,36]. These studies suggest that children in a PICU receiving benzodiazepines and/or opioids for five days or longer, are at risk of developing withdrawal symptoms. Benzodiazepine and/or opioid withdrawal symptoms may occur if these medications are abruptly stopped or tapered off too rapidly in children showing physical dependence [4]. Manifestations typically occur 8-48 hours after discontinuation.

We conclude that both a longer duration of administration and higher total doses of midazolam and opioids are clearly related to the occurrence of withdrawal symptoms, and may therefore be considered risk factors. We suggest that tapering off (weaning) too rapidly increases the risk of withdrawal symptoms. Strategies to reduce the incidence of withdrawal symptoms should begin by making efforts to reduce doses of benzodiazepines and/or opioids, which makes the patient less risk for withdrawal. On the other hand, based on a few prospective studies, several authors recommend a daily tapering rate of 10-20% for children on benzodiazepines and/or opioids for more than five to seven days [16,20-22]. This strategy,

Table 2. Frequency of reported withdrawal symptoms

SYMPTOMS	STUDY (SIZE/METHOD)		
	Franck et al. [16] 693 observations n=15 (%)	**Franck et al. [31] 1040 observations n=83 (%)**	**Ista et al. [32] 932 observations n=76 [a] (%)**
Central nervous system irritability			
Agitation			21.1
Anxiety			14.8
Crying / agitated 26-75% of interval	33.8		
Increased muscle tension		16.6	13.0
Motor disturbance /Movement disorder	15.9	5.8 / 7.5 [c]	19.8
Slight muscle jerks			7.0
Uncoordinated, robust movements		5.8 / 7.5	12.8
Tremors	35.7	7.9 / 10.3 [c]	2.8
Spontaneous			
In response to stimuli			
Inconsolable crying			7.3
High pitched crying			3.6
Grimacing			10.1
Sleep pattern			
Sleeps <1 hour			14.6
Sleeps >1 and <3 hours			57.7
Sleeping <25% of the interval	51.7		
Seizures			0.3
Pupil dilatation			1.2
Pupil > 4mm	36.4	19.3	
Hyperactive Moro reflex	1.3		
Hallucinations	0.7		1.1
Gastro-intestinal dysfunction			
Vomiting	3.9	7.6	4.5
Diarrhea	42.4	20.1	17.8
Increased gastric residuals after feeding			12.4
Poor feeding			1.6
Autonomic dysfunction			
Tachycardia			9.3
Tachypnoea			29.6
Respiratory rate high for age	7.9		
Respiratory rate often > baseline for this child		44.2	
Hypertension			14.6 [b]
Fever			17.6
Temperature > 37.8°C		25.1	
Temperature > 37.2°C	81.5		
Sweating	10.6	13.2 / 13.3 [c]	12.9
Sneezing	2.4	9.1 [d]	1.0
Yawning	5.3	9.1 [d]	1.9
Nasal stuffiness	7.9		
Mottling			9.2

a performed within 24 hours after weaning off midazolam/opioids; b hypertension only determined in patients with arterial line n=560 (observations); c pre-stimulus observation/ post-stimulus observation; d Items was defined as yawning or sneezing

however, did not prevent withdrawal symptoms. Adult sedative and analgesic guidelines recommend that daily dose decrements of opioids should not exceed 5-10% in high-risk patients [37]. Playfor *et al.* support use of this practice in the PICU in spite of the fact that there is little evidence for its efficacy [38]. So we are left with a great need for effective weaning strategies in a PICU, general hospital or in particular circumstances at home.

Measuring withdrawal symptoms in children

An accurate diagnosis of withdrawal must be made. Withdrawal symptoms vary from patient to patient in number, severity and presentation. However, in many PICU patients they are relatively subtle, and could easily be mistaken for responses to other bothersome factors. Children will also manifest agitation, anxiety, insomnia, irritability, fever, tachycardia, hypertension, and sweating in response to inadequate sedation or pain management, ventilator distress, infection, noisy environment, paradoxical reactions, or delirium [39-44]. In accordance with Tobias [4], we maintain that the diagnosis of withdrawal symptoms remains one of exclusion. For example, fever or vomiting should never be attributed to withdrawal until other possible causes have been excluded. Key confounders such as the ones mentioned above must be excluded as well. Symptoms are more likely to be withdrawal symptoms if they are time-related to a decrease or cessation of benzodiazepines and/or opioids.

The task of assessing seriously ill children for signs of tolerance, dependence, or withdrawal notably falls to the paediatric critical care nurse [12]. This requires a particular awareness, knowledge of

Table 3. Tools for clinical assessment of withdrawal symptoms in critically ill children

INSTRUMENT	POPULATION AGE	OBSERVATION ITEMS				STRUCTURE		PSYCHOMETRIC EVALUATION			WITHDRAWAL CUT-OFF SCORES
		CNS	GI	Auto	Other	Total items	Score-range	Number of obs.	Reliability	Validity	
Sedation withdrawal score (SWS) [47]	Children	Tremor, irritability, HT, high pitched cry, convulsions, hyperactivity	Vomiting, diarrhoea	RR, T, sweating, sneezing		12 Numerical	0-24	ND	ND	ND	<6 -, 6-12 don't decrease, 12-18 revert to former regimen, >18 seek advice
Opioid Benzodiazepine Withdrawal Scale (OBWS) [16]	15 paediatric patients (6 weeks-28 months)	Crying/ agitation, tremors, sleeplessness, movement disorder, HMR, Hallucinations	Vomiting, diarrhoea	RR, T, sweating, sneezing, PD, yawning	Nasal stuffiness, frequent suction required	21 (16 withdrawal symptoms) Numerical	0-16	693	IRR: *r* = 0.8	*Content* ND *Construct* sen=50% spec=87%	≥ 8 withdrawal
Withdrawal Assessment Tool version 1 (WAT-1) [31] [adapted version of the OBWS]	83 children 35 months (7 months-10 yrs) [a]	Tremor, Uncoordinated/ repetitive movement, Yawning or sneezing, State [c]	Loose / watery stools, vomiting/ retching/ gagging	T >37.8°C, sweating	State [c], Startle to touch, Time to gain calm state (SBS≤0)	11 Numerical	0-12	1040	*Internal [d]:* PRINCALS, 4 factors IRR N=30 paired observations ICC = 0.98 Cohen's kappa = 0.80	*Content* ND *Construct* sen= 0.87 spec = 0.88 *Sensitivity to change* ND	≥ 3
Sophia Observation withdrawal Symptoms-scale (SOS) [48]	79 children 3.4 months (0-16 yrs) [b]	Agitation, anxiety, tremors, HT, inconsolable crying, grimacing, sleeplessness, motor disturbance, hallucinations	Vomiting, diarrhoea	Tachycardia, tachypnoea, Fever (≥ 38.5°), sweating		15 Numerical	0-15	932	*Internal [d]:* MDS, 3 dimensions IRR N=23 paired observations ICC = 0.97 Cohen's kappa = 0.73-1.0 (items)	*Construct* 85 experts *Construct* + [e] *Sensitivity to change* +	≥ 4

CNS, Central Nervous System irritability; GI, Gastro-intestinal dysfunction; Auto, Autonomic dysfunction; Obs., observations; IRR, interrater-reliability; ND, no data, not described in article; *r*, correlation coefficient; sen, sensitivity; spec, Specificity; SE, Standard error; HT, hyper tonicity (increased muscle tone/tension); HMR, hyperactive Moro reflex; RR, respiratory rate; T, temperature/fever; SBS, state behavioral scale [50]; PD - pupil dilation (> 4 mm), yrs – years; PRINCALS, principle components analysis; MDS, multidimensional scaling; ICC, Intraclass Correlation Coefficient; +, performed; [a] median (IQR); [b] median (range); [c] (asleep/awake/calm or awake/distressed); [d] Internal consistency; [e] significant correlations between total doses of midazolam /opioids and maximum sum score of withdrawal symptoms [32]

and insight into these phenomena. For clinical purposes a validated and reliable assessment tool would be very helpful.

The Neonatal Abstinence Score (NAS) used to be the tool of choice in clinical practice and research studies [17,18,20,21,45,46]. This tool has some limitations, however. First, it was developed to assess the severity of withdrawal in neonates exposed to opioids *in utero* [5]. Second, it includes certain reflexes such as the Moro reflex that occur only in children below the age of three months; and this implies that these reflexes cannot be used in the total PICU age group. Third, cut-off points for patients other than newborns of addicted mothers are not defined. For these reasons the NAS is less useful in PICU patients, who will typically receive both opioids and benzodiazepines. Other authors designed observation checklists themselves, which include five to thirteen symptoms [20,25,26]. These observation checklists have not been properly validated for use in children [20,26].

Four new instruments for assessing withdrawal symptoms in children have been published, namely: Sedation Withdrawal Score (SWS) [47], Opioid and Benzodiazepine Withdrawal Scale (OBWS) [16], Withdrawal Assessment Tool version 1 (WAT-1) [31] and Sophia Observation withdrawal Symptoms-scale (SOS) [48]. Table 3 provides details on symptoms and the psychometric properties of these instruments that are used in practice and in research.

Symptoms and signs included in the four scales largely overlap, except for hyperactive Moro reflex, high-pitched crying, sneezing, yawning, seizures and pupil dilation and the requirement for frequent suction [16,31,47]. Given the inherent age restriction for the Moro reflex this item cannot be included in a scale for all ages. The SOS includes three other signs and symptoms – anxiety, grimacing and tachycardia – which the other three scales do not contain. However, the literature identifies these signs and symptoms as withdrawal symptoms [49].

The authors of the SWS state that it is clinically sensitive but present no validity and reliability data to support this [47]. The OBWS is the first instrument with prospective validation. Its specificity was found to be 87%, which implies that the scale correctly classifies 87% of the children without withdrawal symptoms. Its sensitivity was just 50%, however, which implies that the scale is not better than chance prediction. In summary, although both the SWS and OBWS include relevant withdrawal symptoms associated with benzodiazepine and/or opioid withdrawal in children, we feel that psychometric issues have been given insufficient attention.

The reliability and validity of the WAT-1 and the SOS look promising (Table 3). We believe the SOS is more sensitive than the WAT-1 in assessing signs and symptoms of benzodiazepine withdrawal. On the basis of validity analysis, Franck and colleagues suggest that the WAT-1 is better in detecting symptoms of opioid than those of benzodiazepine withdrawal [31]. This might be problematic for use in the PICU given the fact that benzodiazepine withdrawal symptoms are frequent. Symptoms such as agitation, anxiety, tremors, insomnia, fever, sweating, and tachycardia have been described in both benzodiazepine and opioid withdrawal. Symptoms such as movement disorder, grimacing, inconsolable crying and hallucinations have only been observed as benzodiazepine withdrawal. The latter three symptoms were included in the SOS but not in the WAT-1. Instead, Franck *et al.* incorporated three items from the State Behavioral Scale [31]. A methodological underpinning of this approach is lacking however. The WAT-1 and SOS are nevertheless comparable with respect to demographic characteristics of test study population and psychometric properties. Validation is a never-ending process and it would be worthwhile to compare both assessment tools in a multicentre study with emphasis on sensitivity to change.

Conclusion

This review provides an overview of the English-language literature on withdrawal symptoms in children in intensive care, and on available instruments to ascertain this phenomenon in children aged from 0 to 16 years. Emphasis is placed on studies that describe symptoms of withdrawal as a consequence of long-term administration of benzodiazepines and/ or opiates. Also, high total doses, duration of administration of opioid, and/or benzodiazepine infusion and ECMO therapy were described as risk factors in developing withdrawal symptoms in PICU patients. These factors are also described in adult studies. The diagnosis of withdrawal in patients must be made carefully and the occurrence of withdrawal symptoms must be time-related to a decrease or cessation of benzodiazepines and/or opioids. Attention should be paid to key confounders such as inadequate pain or sedation management, ventilator distress and delirium, which may mask withdrawal symptoms. Key confounders must be excluded as well. With regard to assessment tools, the WAT-1 and the SOS seem clinically useful for children and could facilitate prevention of withdrawal syndrome.

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