

# Childhood-onset Bipolar Disorder: The Perfect Storm

## CME EDUCATIONAL OBJECTIVES

1. Demonstrate the severity of childhood-onset bipolar illness and its long-term negative effects on individuals and their families.
2. Restate some of the diagnostic and societal controversies that have limited research in childhood-onset bipolar disorder.
3. Summarize solutions as to how the controversies could be surmounted and treatment-related studies could be fostered.

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*Dr. Post has disclosed the following relevant financial relationships: Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Pfizer, and Vallidas: Consultant; and AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline: Member of Speakers' Bureau.*

*doi: 10.3928/00485718-20090924-06*



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A convergence of unfortunate circumstances has generated “the perfect storm” of inadequate treatment of youth with childhood-onset bipolar disorder. Although this condition affects a minority of children, many youth are afflicted and experience long delays in receiving their first treatment. Compared with adult-onset forms of the illness, the childhood-onset form of bi-

polar disorder carries a poor prognosis throughout adulthood. Yet continued obstacles affect efforts to appropriately identify and treat children. There is only a small amount of treatment-related research yielding several Food and Drug Administration (FDA)-approved medications for children 10 to 19 years. Additionally, there are virtually no medications approved for children with this disorder who are younger than 10 years, despite evidence from various sites sug-

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gesting that a sizable number of children experience first symptoms in the earliest years of life.

The “storm” continues to build. Affected families are reluctant to speak up for fear of stigma associated with “going public” with their child’s diagnosis. Many researchers are unable to act since they have been under direct scrutiny for pharmaceutical collaboration. Ultimately, the government will likely need to mandate that funds be allocated to research, or funding from a private foundation will likely be required. Some may wonder if the storm will dissipate on its own. However, there are multiple individual storms described below surrounding childhood-onset bipolar illness, which are individually problematic but also cause further trouble when they are combined.

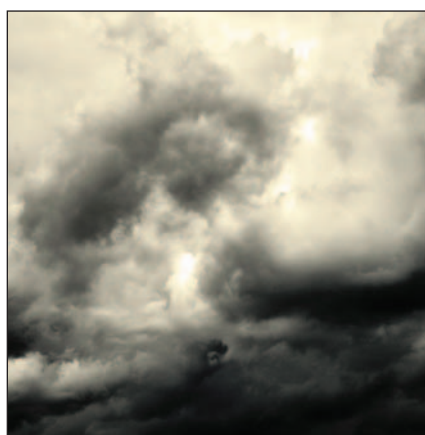
### FIVE CONVERGING STORMS

#### **Storm 1: The Diagnosis is Common, Impairment is Severe, and Treatment is Difficult**

There are more than 1 million youngsters suffering with a diagnosis of childhood- or adolescent-onset bipolar illness in the United States.<sup>1,2</sup> Three decades ago, the diagnosis was rarely used, and youngsters with the disorder were almost unheard of. The idea that children with high levels of moodiness may actually suffer from a psychiatrically defined mood disorder represents a paradigm shift in a field that formerly considered mood swings to always be a developmental characteristic of youth. The median age of onset of the disorder was in the late 20s, but more recently it has decreased into the teenage years. Although increasing numbers of children are being identified, adults with the disorder are in parallel reporting early ages of onset when systematically asked.

Therefore, now nearly 50% to two-thirds of adult outpatients with well-diagnosed bipolar illness in the United

States report having experienced the onset of the first episode of their illness (depression or mania) before 19 years. These data are based on the National Institutes of Mental Health (NIMH)-sponsored Systematic Treatment Enhancement Program for bipolar disorder (STEP-BD) and data from the Bipolar Collaborative Network (BCN) in which the average age of the adults is 42 years.<sup>3,4</sup> We now recognize that bipolar disorder is best understood as a



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pediatric-onset illness in the majority of cases and further understand that what is known as adult bipolar disorder is a heterogeneous illness, which, in part, may be parsed by age of onset.

Moreover, the STEP-BD and the BCN both found that their patients with the earliest onsets of bipolar illness compared with those with adult onsets had a much more adverse course of illness throughout their lives. This included more episodes, rapid cycling, substance abuse, suicide attempts, and many other indices of morbidity and disability. In addition, the BCN validated this self-

reported difficult prior course of illness and relative treatment-resistance of those who had childhood-onset bipolar illness with prospective clinician ratings during naturalistic treatment. These findings showed that those adults who had childhood onsets of their bipolar disorder experienced more severe depression, more time depressed, more days of mood cycling within a single day, and fewer days well (euthymic), compared with those with adult-onset illness.<sup>4</sup>

Additionally, we found that patients in the BCN with childhood onsets of their illness (before 13 years) were not first treated with pharmacotherapy for either depression or mania until an average of 15 years after the onset of their illness.<sup>4</sup> Those with adolescent onsets (ages 13 to 18) were not treated for an average of 10 years, while adults were treated after an average of 3 to 5 years. A new analysis reveals that the duration of the delay to first treatment is a predictor of more severe and persistent illness in adulthood, independent of the age of onset.<sup>5</sup> These data also raise the potentially optimistic view that the long delays in treatment were part of the reason for the more adverse courses, and that with earlier, more appropriate interventions, the childhood-onset illnesses would have a more favorable outcome. This remains to be directly demonstrated.

Because the precise definitions and symptom thresholds for the diagnosis have evoked considerable controversy with only partial resolution,<sup>6-8</sup> this has further inhibited the conduct of treatment studies in an expeditious fashion. Thus, we currently have little systematic data to guide the clinical therapeutics of individual children and their differential clinical presentations. Some expert consensus treatment guidelines exist, but these have been based on admittedly sparse treatment literature and apply directly only to those with bipolar I illness.<sup>9</sup>

What we do know from children currently evaluated and followed in formal

clinical research settings is that treatment is complicated, and it also takes a great deal of time to achieve acute mood stabilization.<sup>10-12</sup> One recent study<sup>13</sup> indicated that those with bipolar disorder associated with full-blown manias (bipolar-I [BP-I]) or less severe hypomania (bipolar II [BP-II]) required approximately 9 months to achieve acute mood stabilization. The category of children whose manic manifestations do not last for a minimum of 4 days required for BP-II, but whose moods oscillate dramatically, often multiple times within a day, are called bipolar not otherwise specified (BP-NOS). These children are the most controversial diagnostically, yet they were severely impaired and required the longest time (ie, 2.75 years on average) to be stabilized.

These data are mirrored by many other investigative groups. Geller et al<sup>14</sup> found that most children with bipolar diagnoses eventually showed some improvement and a brief period of recovery. However, the majority relapsed over a period of 2 to 4 years of prospective observation and the children remained ill about two-thirds of the time during prospective follow-up. The most recent installment in this longitudinal study found that 50% of the subjects who reached 18 years during the follow-up period continued to meet full criteria for bipolar-I disorder.

Wozniak et al<sup>15</sup> have reported similar rates of persistence of bipolar-I disorder after a 5-year follow-up. Of those not meeting criteria for bipolar-I disorder, most suffer from either subthreshold mania, full or subthreshold depression, or are receiving treatment for mood disorder, suggesting a very high level of persistence beyond bipolar-I criteria. A clinical caveat in the interpretation of these data, however, is that these children were treated “as usual” in the community, and this did not involve (in the majority) the recommended treatment with mood stabilizers or atypical

antipsychotics.<sup>10,14</sup> How these children might have fared with more appropriate consensus-recommended treatment still remains to be ascertained.

DeBello and her group<sup>16</sup> published a brief follow-up of children also treated in the community. They found that these individuals, too, ran a parallel course of illness with many improving transiently, relapsing often, and remaining highly symptomatic for long periods of time, despite their naturalistic treatment.

### Storm 2: Diagnostic Controversy Continues

At one end of the continuum, some individuals do not believe that mania can exist in very young children. It is particularly noteworthy in this regard that a similar state of disbelief was present some 40 years ago about the potential existence of childhood-onset depression, when many argued that it could not occur or be adequately recognized in prepubertal children.<sup>17</sup> It is now widely recognized and accepted that children can have very severe depression at early ages. Moreover, in parallel with the findings with bipolar illness noted above, the data now also indicate that adults with recurrent (unipolar) depression that began in childhood run a much more difficult course than those with adult onsets of their depression.

Others on the continuum of diagnostic controversy argue that childhood-onset bipolar disorder might exist, but they rarely see it, and it is overdiagnosed. One study in 2007 reported that 10 years prior, there were 20,000 doctor visits of children in the United States for a diagnosis of bipolar illness, but, recently, this number had increased to 800,000 visits per year.<sup>2</sup> These children, however, were only those who were labeled bipolar and were in treatment with a physician who made the diagnosis. This does not include a large number of children in the general community who may have the illness but are not yet diagnosed nor are

in the medical system. Many have dismissed the figures and surmised that the diagnostic criteria have widened such that the huge increases represent misdiagnosis and overdiagnosis, although some suggest surmised that the illness was also previously under recognized.

This view is consistent with the data from the two large academic networks noted above that in extremely well-diagnosed adults (average age 42 years) with bipolar illness, nearly one-quarter indicated that their illness (first depression with dysfunction or first mania) began before 13 years.<sup>3,4</sup> Thus, even some 25 or more years ago when these adults were youngsters, many were experiencing manic and depressive symptoms, which would very likely meet modern diagnostic criteria for mania and depression. However, the illness was not recognized nor treated. Now it is widely recognized and treated in the community<sup>2</sup> and in many academic centers.<sup>13,14,16,18,19</sup>

Few experts raise the possibility that there are real increases in the illness that present extraordinary problems that need to be addressed in a timely fashion.<sup>1</sup> Some systematic studies indicate that there is a real increase in prevalence, although perhaps not to such an extent reflected in the study noted above.<sup>2</sup> In a major review of the field, Lange and McInnis<sup>20</sup> found a large number of studies confirming the existence of a cohort (or a year of birth) effect; that is, every birth cohort since World War I has had an increased incidence and younger age of onset of both unipolar and bipolar disorder in the United States and in several other countries, as well. These investigators indicated that this increase was not an artifact of diagnostic changes, and the same instruments and criteria were utilized over these periods of time.

At the same time, the Lange and McInnis<sup>20</sup> review noted that there is also evidence of an anticipation (or generational) effect. This reflects the fact that if a parent had experienced the onset of a bipolar ill-

ness at 25 years, and one of their children developed the disorder, it would occur an average of 10 years earlier (ie, at about 15 years). In addition, this generational effect might be associated with a more severe or rapidly recurring (cycling) course. Both genetic and environmental mechanisms for the anticipation effect have been suggested and are possible.

Despite the data from multiple sources and the actual presence of numbers of children with bipolar presentations who arrive for evaluation and treatment in doctors' offices and in academic centers, controversy continues for a variety of reasons. Some groups claim that children must look identical to adults, even though the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* sets the criteria for the presence of bipolar disorder only for adults.<sup>21</sup> These proponents insist that although it is not strictly defined in DSM-IV as a feature of bipolar disorder, there must be extended episodes of mania and depression with clear well intervals, not ultra-fast mood fluctuations within a day (ultradian cycling). Additionally, continuity with adult illness must be demonstrated.

The recent 8-year follow-up study of BP I children with an average age of 11 years by Geller et al<sup>8</sup> did much to address and resolve these controversies. They found that children in the study were ill in an affective episode about 60% of the weeks of follow-up, and that many who reached 18 years or older continued to experience classic manic episodes. Their BP I children also continued to show large amounts of ultradian cycling, which is also characteristic of the children with a BP-NOS diagnosis.<sup>13</sup> In addition, it is also not widely recognized that some 20% of adults (average age 40 years) with bipolar disorder also manifest ultradian cycling, and this is more prevalent in those with childhood onsets.<sup>22-24</sup>

Another area of controversy about the diagnosis in children is where the

predominant mood is irritability as opposed to euphoria. The problem arises that irritability is a prominent presentation of children with almost any childhood-onset diagnosis; therefore, one must have and rely heavily on the other elements of mania to confirm the diagnosis. However, this argument has been resolved with regards to the question of depression. Similar to irritability, one could argue that sadness is also ubiquitous in various forms of discouragement, demoralization, and unhappiness across diagnostic categories. Yet researchers and clinicians have agreed that sadness of distinct quality and quantity, coupled with additional symptoms, reaches the threshold for diagnosis of major depression. DSM-IV included the requirement for the presence of elevated or irritable mood and at least five of nine other manic symptoms for those with irritability and four of nine manic symptoms for those with elevated mood (euphoria). Further, DSM-IV defines the irritability of mania as "extreme."

Wozniak and Biederman<sup>25</sup> have made the case that these children with irritability who meet the other criteria for mania are, in fact, bipolar, and support their case by a variety of data, including a high incidence of positive histories of bipolar illness in the families of these individuals. These authors demonstrate that although extreme irritability alone does not render a diagnosis of mania, when combined with additional symptoms, validity of the disorder is established.<sup>26</sup> Conversely, Leibenluft and colleagues<sup>27</sup> at the NIMH state that those with extreme chronic irritability, without appropriate durational criteria for BP-I or BP-II, fit what they call the "broad phenotype" or severe mood dysregulation (SMD). SMD is unlikely to be related to bipolar illness because it is associated with a lower incidence of family history of bipolar illness than one might expect. Leibenluft and colleagues<sup>7</sup> believe that those with SMD

have a different illness, one that would perhaps evolve into unipolar depressive or some other nonbipolar illness in adults. In partial agreement, Biederman et al<sup>28</sup> consider that many of these children without euphoria or grandiosity have severe attention-deficit/hyperactivity disorder (ADHD) with co-occurring conduct disorder, such that a separate category of SMD is not necessary.

Most problematic, however, is that neither the narrow nor broad phenotype has yet been linked to optimal treatments and outcomes. Even if one could make these diagnostic distinctions with certainty, the clinician currently would still be at a loss as to how to proceed therapeutically. Most in the field agree that these and other diagnostic controversies will ultimately be settled by long-term prospective follow-up studies, as has begun with the data of Geller et al.<sup>8</sup> However, these extended longitudinal studies take years to complete, and more immediate (even if temporary and tentative) solutions to the controversies are urgently needed.

### **Storm 3: There are No Data Linking the Controversial Bipolar Subtypes or their Imitators to Effective Treatment**

Although the precise descriptors and boundaries for childhood bipolar illness remain uncertain, especially for the BP-NOS diagnosis, almost no one disagrees about the severity of these children's illness. Their explosive behavior and mood changes render family life difficult, and social relationships with other children are virtually nonexistent. Their behavior causes a very high incidence of being expelled from regular and even specialized educational facilities. In addition, Tillman et al<sup>29</sup> recently reported that nearly three-quarters of children with bipolar illness at both age ranges 6 to 9 years and 10 to 16 years are psychotic (have hallucinations or delusions), and many are suicidal or homicidal.

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Thus, even if the SMD children described by Ellen Liebenluft<sup>27</sup> and colleagues do not prove to have bipolar illness and follow another illness trajectory into adulthood, they still require appropriate treatment. Although there remain too few pharmacological treatment studies of children with BP-I illness, it is even more problematic that there are no systematic studies of the therapeutics of children with BP-II or BP-NOS, and only one for the broad phenotype SMD (in which lithium failed to show efficacy). In addition to studies on efficacy, current treatments have known side effects. In addition, parents and clinicians are even more concerned about “unknown” side effects or adverse effects on development that might result from aggressively psychopharmacologic treatment during childhood.

We were told almost a decade ago that more parents were asking for treatment information about childhood-onset bipolar illness from the Depression and Bipolar Support Alliance (DBSA) and the National Alliance for the Mentally Ill (NAMI) than any other issue. They said they were not getting systematic information because little exists. There is also a marked shortage of child psychiatrists in the United States, and in particular in those who specialize in the treatment of bipolar disorder. Without a systematic treatment literature, when physicians from other disciplines and other specialties have to step in and take on the treatment of these children, a new series of problems arise.

Although there are no FDA-approved medications for bipolar children younger than 10 years, several of the atypical antipsychotics are now approved for those 10 to 17 years and lithium for those 12 years and older. In contrast, there are 19 FDA-approved medications for the treatment of ADHD, which by definition starts in youngsters before 7 years. Complicating the problem are the agreed-upon findings that a high per-

centage of those with childhood-onset bipolar disorder have comorbid ADHD, although this comorbid condition decreases markedly with age.

Given these circumstances, many of the young children with bipolar disorder are initially treated with stimulants and antidepressants intended for those with uncomplicated ADHD, without



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the coverage of the first-line consensus recommendations of mood stabilizers and atypical antipsychotics. Thus, treatment is not only often delayed, but sometimes inappropriate.<sup>4</sup>

### **Storm 4: Counterproductive Focus**

The convergence of a fourth storm is adding further difficulties. A surge in diagnosis and treatment of pediatric bipolar disorder has led all too often to a “head-in-the-sand” attitude of denial that children could possibly require dramatic psychiatric intervention. Not recognized or cited is that there are not enough clinical therapeutic studies being conducted to inform the physicians, patients, and families about best treatment approaches for the bipolar subtypes or even their imi-

tators, such as SMD in young children.

The data are unequivocal that bipolar disorder in children is also difficult to treat, socially and educationally incapacitating, and even life threatening. The suicide rate in 14- to 19-year-olds is one of the fastest growing in the population of the United States and markedly contributed to by those with depressive and bipolar disorders. Nearly 10% to 15% of adults with bipolar disorder will die over the course of their lifetimes from suicide.<sup>30</sup> Adolescents with bipolar illness are also at inordinately high risk of also developing substance abuse problems,<sup>31,32</sup> often with additional extraordinary costs. For example, Kemp et al<sup>33</sup> found that 30% of the men in a prison near Cleveland who agreed to be interviewed had bipolar disorder that had not been previously diagnosed nor treated, and this was most often complicated by substance abuse.

Moreover, the medical mortality that is associated with bipolar disorder in adults is also extraordinary. Individuals with depression and untreated bipolar disorder are at markedly increased risk for heart attacks, strokes, diabetes, lung disease, and a variety of life-shortening or life-ending medical complications. A recent study indicated that patients with severe mental disorders who were treated in the public health sector lost an average 13 years of life expectancy (in Virginia) and 25 to 30 years of life expectancy (in some Western states) compared with those in the general population in these same areas of the country.<sup>34</sup> Only a very small component of this loss is related to suicide. Lack of appropriate psychiatric care is directly leading to lack of appropriate medical care, and the two are intimately intertwined.

### **Storm 5: Lack of Access to Evaluation and Treatment**

More than 30 million individuals in the United States do not have medical insurance. Many of the others who have it do not have adequate coverage for a chronic, recurrent medical disorder such as bipolar illness, even if they have virtually unlim-

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ited coverage for related chronic recurrent disorders, such as epilepsy or diabetes. This may change with new legislation, but the contexts of treatments may remain highly imbalanced. For a child with diabetes, not only are visits encouraged, but education about the illness and management is accepted as a necessary part of the treatment regimen and supported by nurses, social workers, case workers, physicians, and the like. With such good treatment and education to closely monitor and regulate glucose levels, the medical complications of diabetes, which used to plague many in their early 40s, have now been generally delayed to the sixth and seventh decades of life.

The opposite is occurring in the medical management of bipolar disorder. Youngsters who need concerted treatment are often not identified or treated appropriately. Individual, parental, and family psychoeducation, as well as focused psychotherapy, have been repeatedly demonstrated to be better than treatment as usual on a variety of outcome measures when combined with drug treatment.<sup>35</sup> Yet these systematic approaches are rarely utilized in the general community and may not be reimbursable for those with adequate insurance coverage without “red tape” to go through. Even with good initial therapeutic results, lack of adequate follow-up treatment paradigms affects these individuals, and children and adolescents with bipolar disorder typically have repeated relapses and recurrences even after they have been stabilized.<sup>8,13,14,18</sup>

Even when adequate care and coverage are available, the most effective and well-tolerated treatments for the short- and long-term have yet to be adequately defined. Treatment most often involves complex combination therapy,<sup>36-38</sup> but few studies have systematically examined how to deploy these complicated regimens.<sup>36,39</sup>

### THE NEEDED SOLUTIONS

Many of the solutions (for these converging difficulties of child onset bipolar

disorder) are readily available, feasible, and not inordinately expensive, but are not pursued with any sense of urgency.

A strategic plan needs to be enacted to facilitate the acquisition of new treatment-related information. Among many other approaches, efforts could include: 1) using agreed-upon common terminology; 2) mandated funding, not only for controlled-clinical trials, but also practical clinical trials, which could compare the effectiveness and tolerability of two



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active treatments; and 3) establishing a childhood-onset treatment outcome network to collect and disseminate information about the most effective and well-tolerated approaches that are currently widely used in practice. Such efforts, outlined below, in addition to the traditional ongoing pharmaceutical industry-sponsored, randomized, placebo-controlled clinical trials for older children, would do much to overcome rapidly the relative absence of treatment-related information for prepubertal youngsters with bipolar disorder.

### Solution 1

Some of these children with bipolar-like variants will ultimately be excluded from the agreed upon definitions in the new iterations of DSM-V once prospective studies identify the differential trajectories of these children. However, this does not mean we can ignore or exclude them in treatment-related studies. It is important that not only the classic subtypes of childhood-onset bipolar illness, but its more controversial variants (such as BP-NOS, SMD, or conduct disorder with ADHD, etc.), be intensively investigated to define their optimal treatment strategies in children of various age groups, including very young children.

### Solution 2

It is necessary that either the NIMH or a private foundation step into a role of funding research. Such an initiative could rapidly foster the conduct of comparative clinical trials of a practical sort to define which individuals respond to which treatment and which treatments are the best tolerated. Such practical clinical trials have been advocated by March et al<sup>40</sup> and other experts in the field and do not even require a placebo arm to be highly informative. Studies without a placebo arm are what the majority of parents want when considering entering their children in clinical trials.<sup>41</sup> Such practical, randomized, open comparative trials of two active agents could be performed at a single site or several sites, and not involve the expense of the traditional multi-site randomized, controlled trials (RCT) with a placebo group, which are typically required by the FDA for approval of a new drug.

### Solution 3

The formation of a treatment outcome network would rapidly provide preliminary information about actual treatment practices in the community and what ap-

proaches appear effective and well tolerated in the long term. Currently, all of the treatment-related experience in the community is completely unavailable to other practitioners or the public. Such a framework could then evolve to include more formal clinical trials, such as those that were fostered in adult networks for depression. These trials include the Sequential Treatment Alternatives to Relieve Depression (STAR\*D), STEP-BD, Stanley Foundation Bipolar Network (SFBN), and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies.

### FUTURE CONSIDERATIONS

It is unlikely that these and other approaches will occur without a congressional mandate or the generosity of a private donor. NIMH funding has been flat (until the recent stimulus infusion), and its priorities are widely and thinly spread. Numerous investigators in the field have called for increased treatment research efforts in childhood onset bipolar illness, including those at a Research Forum on Childhood Onset Bipolar Disorder at the 2006 meeting of the American Academy of Child and Adolescent Psychiatry, so far with little evidence of success.

A parallel experience has also taken place in the area of adult-onset bipolar disorder. There has been an acknowledged shortfall in the NIMH funding of psychopharmacologic treatment studies in adult bipolar disorder, compared with other major mental disorders, for more than 3 decades.<sup>42,43</sup> Despite repeated calls for increased funding and intensive study in this relatively neglected area, it has not occurred. There is little reason to assume that childhood-onset bipolar illness will fare any better, particularly in the face of all the problematic areas of diagnostic controversy, young age of the children involved, and lack of public and advocacy group support. About 40 years ago, a national initiative was launched for the study and treatment of schizophrenia,

which completely reversed the understudy of that diagnosis. Now, a similar initiative is needed to avoid further tragic delays in the definition of optimal treatment approaches to childhood-onset bipolar disorder and its variants.

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