



A narrative review of gender dysphoria in childhood and adolescence: definition, epidemiology, and clinical recognition

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Background and Objective: Within the past decade, more transgender and gender diverse youth that experience gender dysphoria seek transition-related medical care, thus there is a growing and continued need to improve knowledge and expertise in this topic. This narrative review aims to provide a comprehensive discussion of current definitions and diagnostic criteria related to gender dysphoria, understanding that determinants of an individual's gender identity is likely influenced by multiple constructs, and providing the readers with an approach to clinical recognition and evaluation of a child or adolescent with gender dysphoria.

Methods: We conducted a PubMed search including literature in the English language using key words: gender dysphoria, transgender, gender-diverse youth, gender identity. We considered publications between 1995–2022. Specifically, publications from 2012–2022 were considered to support recommended approach to evaluation for gender dysphoria.

Key Content and Findings: There is increasing evidence on the contributions of genetics, hormone influences and neurobiology on gender identity. Furthermore, data on the benefits of access to gender affirming therapy continue to emerge. Transgender youth are at increased risk of psychiatric comorbidities such as depression, anxiety, and life-threatening behaviors. As such, studies underscore the importance of early recognition, mental health support and medical intervention through hormone treatments for pubertal suppression and/or gender-affirming hormone therapy in decreasing mental health burdens and improving quality of life among the transgender youth.

Conclusions: While there have been significant strides in our understanding of gender-related issues in youth, there remains a significant gap in knowledge related to medical care, and how the medical community can further support these individuals. Further studies on the biological basis of gender diversity, continuing to explore genetic, endocrine, and neuroanatomic influences, may aid in redefining gender constructs and decrease social stigmas associated with it. Guidelines and approach to care for transgender youth are now more widely available, primarily aimed at initial identification and intervention, but with strong recommendations of continuing multidisciplinary care that will provide support and expertise during the physical and psychosocial interventions, while ensuring continued communication and discussion of treatment recommendations and ongoing management.

Keywords: Gender dysphoria; transgender; gender-diverse youth; gender identity

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Introduction

Concepts of gender variance have evolved over the years and continue to do so. In the past 10 years alone, the number of transgender/gender-diverse children and adolescents has increased. Current data indicates approximately 0.1–0.2% of the general population consider themselves as transgender/gender non-conforming (1). The impact of geographical differences relates to cultural norms, with upward trends in numbers of individuals identifying as transgender in areas with increasing awareness and societal acceptance. There is still paucity of data for children and adolescents. However, more recent studies, particularly in adolescents, show that the prevalence of gender diversity can range from 2–9% (2,3). Interestingly, there seems to be a change of the sex ratio within the past decade favoring birth-assigned females. In a study based in Toronto, the proportion of assigned-at-birth males and those assigned at birth as females from 1995 to 2005 was 2.1:1 but changed to 1:1.8 from 2006 to 2013 (4). A similar trend was noted by de Graaf *et al.*, in a cohort from London, with the percentage of birth-assigned boys being referred significantly decreased when the two cohorts were compared (2000–2006 *vs.* 2007–2017), and that boys assigned at birth were referred at a younger age than girls assigned at birth (5).

Increased public awareness brought about by heightened media representation, de-stigmatization and increased understanding of gender and gender diversity, are among the proposed explanations for this upsurge in numbers. More youth considered as transgender and gender diverse, particularly those that experience gender dysphoria, seek transition-related medical care, thus there is a growing and continued need to improve knowledge and expertise in this topic. We present this article in accordance with the Narrative Review reporting checklist (available at <https://pm.amegroups.com/article/view/10.21037/pm-21-95/rc>).

Methods

Literature search was done using the PubMed online database, limited to years from 1995 to 2022, written and published in English language, using search terms gender dysphoria, transgender, gender-diverse youth. All article types were included for review. Articles that were published in languages other than English was excluded. Other inclusion criteria included articles that targeted the pediatric age groups (children and adolescents). We specifically included the articles that discuss the biological basis, clinical approach to individuals with gender identity concerns, comorbid mental and physical health conditions, and selected

considerations about health care access of individuals with gender dysphoria (*Table 1*). Although we briefly include gender affirming therapy in our review, detailed discussion of related therapy is out the scope of this review.

Definition of terms and diagnostic criteria for gender dysphoria

The World Health Organization describes gender as, “characteristics of women, men, girls and boys that are socially constructed” (6). This includes various things such as norms, behaviors, and the roles that are associated with being male or female. Gender expression is how people show their gender to others. Gender is often used interchangeably with sex, which is typically assigned at birth, based on the combination of physical characteristics such as genitalia, chromosomes, and hormone levels (7). Gender incongruence happens when an individual’s gender identity does not correlate to the sex that was delegated at birth. The distress or unease of this incongruence results to gender dysphoria (GD), which when significant enough, can be diagnosed formally using the Diagnostic Statistical Manual of Mental Disorders or DSM-V classification system (8). The term gender identity disorder has been substituted by the term gender dysphoria, thus emphasizing the view that a transgender identity, rather than being considered pathological, should focus on the suffering associated with gender incongruence. In addition, the 11th edition of International Statistical Classification of Diseases and Related Health Problems (ICD-11) had revisions that helped redefine gender identity-related health (9). The diagnostic categories of “transsexualism” and “gender identity disorders of children” were substituted by “gender incongruence of adolescence and adulthood” and “gender incongruence of adulthood”. These categories were also removed from mental and behavioral disorders, and were reclassified into a new section for “conditions related to sexual health”. This change moves toward the direction of destigmatizing gender incongruence and gender diversity, and not being labeled as mental health conditions (10).

The criteria used for diagnosis of gender dysphoria are not the same for children (*Table 2*), compared to those used for adolescents and adults, as described below (*Table 3*).

Biological basis of gender dysphoria

What determines a person’s gender identity is likely influenced by multiple constructs, including biology,

Table 1 The search strategy summary

Items	Specification
Date of search	June 1, 2021 to December 31, 2022
Database searched	PubMed
Search terms used	Gender dysphoria, transgender, gender-diverse youth, gender identity
Timeframe	January 1, 1995 to December 31, 2022
Inclusion and exclusion criteria	Articles not available in English were excluded. Study type considered include clinical trial, randomized controlled trial, review, systematic review, and meta-analysis
Selection process	Each author independently searched and selected relevant literature

Table 2 DSM-5 criteria for gender dysphoria in children (8)

A marked incongruence between one's experienced/expressed gender and assigned gender, of at least six months duration, as manifested by at least six of the following

A strong desire to be of the other gender or an insistence that one is of the other gender (or some alternative gender different from one's assigned gender)

In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing

A strong preference for cross-gender roles in make-believe play or fantasy play

A strong preference for the toys, games or activities stereotypically used or engaged in by the other gender

A strong preference for playmates of the other gender

In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities

A strong dislike of one's sexual anatomy

A strong desire for the primary and/or secondary sex changes that match one's experienced gender

The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Table 3 DSM-5 criteria for gender dysphoria in adolescents and adults (8)

A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by at least two of the following

A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)

A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)

A strong desire for the primary and/or secondary sex characteristics of the other gender

A strong desire to be of the other gender (or some alternative gender different from one's assigned gender)

A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)

A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)

The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

social interactions within one's environment, as well as cultural dictates (11,12). Results of research focusing on biological determinants of gender development support the hypotheses of genetic, endocrine, and neuroanatomic influences on gender. Twin studies suggest a role of genetic factors in gender incongruence, with concordance rate for gender incongruence noted to be higher in monozygotic twins than in dizygotic twins (13,14). Effects of polymorphisms and gene variants that can influence sex differentiation of the brain during early development have also been explored, under the assumption that these alterations contribute to gender identity. Some studies that aimed to identify polymorphisms in a subject's sex hormone-related genes that encode for sex-steroid receptors were not successful in showing genetic relation associated with gender incongruence (15,16). However, a more recent study by Foreman *et al.*, investigated both single nucleotide polymorphisms and repeat length polymorphisms in 12 different sex hormone signaling genes in cisgender male controls and transgender women (17). This study showed that gender dysphoria was significantly associated with the number of alleles and genotypes that were studied (17). Another study by Fernández *et al.*, assessed the role of estrogen receptors alpha (ER α), beta (ER β), androgen receptor (AR), and aromatase (CYP19A1) on brain differentiation of humans (18). They showed that specific genotype and allele combinations of these receptors are involved in the genetic basis of gender-diversity, and that ER β plays an important role in brain differentiation of humans (18).

As for endocrine influences, observations in individuals with disorders of sex development resulting to excess testosterone production and prenatal exposure show the impact testosterone has on the fetal brain and development in regards to male gender identity later in life (19). Research involving individuals diagnosed with congenital adrenal hyperplasia (CAH) show that females with CAH have 2D:4D finger ratio comparable to males without CAH. This suggests that in early fetal life, sexual dimorphism in skeletal development is associated with differences between the exposure to androgens in males and females (20,21). Previous studies that has looked into 2D:4D finger ratio in transgender individuals have contradictory results, however, in 2020, Siegmann *et al.* presented new data and results of a meta-analysis that showed higher (feminized) 2D:4D finger ratio in male to female transgender individuals when compared to the male controls (22).

Similar to results of investigations on effect of genetics and

hormone exposure, studies in neuroanatomy and functional neuroimaging in transgender individuals have been inconclusive; however, a main hypothesis for GD assumes that an individual's perceived gender can be related to sexual differentiation of the brain and suggests that in transgender individuals, a deviation between sex differentiation of the brain and reproductive organs can occur, as a result of genetic factors and/or effects of testosterone during fetal development (19,23,24). Some areas of the brain that have been suggested to demonstrate differences between people with and without gender dysphoria include the bed nucleus of the stria terminalis, hypothalamic uncinate nucleus, kisspeptin-expressing neurons and the putamen (25). Studies utilizing functional magnetic resonance imaging explored functional connectivity patterns of resting state networks in the brains of prepubertal children and adolescents with gender dysphoria and compared it with non-gender dysphoric control groups, which showed GD-specific and sex-atypical patterns in adolescents with GD, but not found in prepubertal children (26). In another study which compared magnetic resonance imaging related to cortical thickness, functional connectivity, surface area, and gray matter volume of female to male (FTM) transgender individuals to cisgender controls, the FTM group was noted to demonstrate thicker mid-frontal, precuneal-parietal, and lingual cortex compared to both male and female controls, although, in areas with reported anatomical sex differences among the controls, FTM transgender individuals adhered to those patterns of gender which had been allocated at birth (27). The group likewise showed not as strong functional connections from the pregenual anterior cingulate to the insular cortex, and the temporo-parietal junction when compared to controls (27). It is important to note though, that results of these investigations remain limited by the small number of participants, and that additional research to look into neurostructural or functional differences prior to and subsequent to gender-related hormonal therapy are needed.

Epidemiology

There is an increase in the number of children and adolescents who are seeking help for gender identity concerns. It is unclear if this increase reflects an actual increase in the proportion of individuals with gender dysphoria, or due to recent increase in awareness and reduction of social stigma around this condition which eventually resulted in higher numbers of individuals seeking care (28,29). Reported estimates of the prevalence

of gender dysphoria (0.6–1.7%) are highly variable and irreproducible due to variability of the data source, study population (clinic patients *vs.* school student), and methods used for measurement (self- or parent-reported concerns *vs.* diagnosis of gender dysphoria established by a clinician). For example, studies that use data from clinic visits can only capture individuals who seek medical care and ignore a percentage of individuals who do not. In contrast, studies that are performed outside of the healthcare setting (such as school students) include the subset of individuals who do not seek medical care. However, these studies use questionnaires designed to measure self-identification as gender dysphoric, and therefore might amplify the actual prevalence of gender dysphoria since a percentage of those individuals do not fit the DSM-V criteria for gender dysphoria (29). As such, more research is needed in this area to investigate the epidemiology of gender dysphoria in children and adolescents.

Female sex at birth, older age of initial presentation to medical care, and non-Hispanic white race and ethnicity increased the likelihood of receiving diagnosis and treatment (30). Youth that received gender-affirming medical care had mental health outcomes similar to general population (31), and those that present during earlier pubertal stages demonstrated better mental health and well-being than older adolescents presenting and receiving care later (32). In a cross-sectional study that compared psychological well-being in three groups: transgender adolescents before starting puberty-suppression treatment, transgender adolescents undergoing treatment, and cisgender peers, poorer psychological functioning was noted in transgender adolescents who have not received treatment yet (33). The study also showed improved psychological functioning after starting transgender care with puberty suppression. The results of these studies underscore the importance of early recognition, mental health support and medical intervention through hormone treatments for pubertal suppression and/or gender-affirming hormone therapy. In addition, transgender individuals have been shown to receive sub-optimal healthcare. Riggs *et al.* studied 188 transgender individuals in Australia and correlated their mental and physical health to their experiences with general practitioners. The authors found that in contrast to receiving discrimination from general practitioners, having comfort with- and receiving respect had positive correlation with their mental health (34). Another study by Clark *et al.* showed similar findings on Canadian individuals, in addition to multiple studies from different countries (35–37).

Evaluation of a child or adolescent with gender incongruence and gender dysphoria

The primary care provider has an essential role in providing a routine discussion about gender identification in health supervision visits. They should promptly recognize those with gender identity concerns and provide them with the appropriate counseling, and referral to appropriate specialty care. Parents and families might be able to identify signs and symptoms of gender dysphoria, but often these may be subtle or indirect, with children or adolescents also unaware or unsure of their gender identity.

Children and adolescents with gender identity concerns and/or their families may also delay seeking advice or medical care which can be due to fear of stigma associated with being transgender or gender diverse, or due to lack to health care access (38). Primary care providers should be aware that children and adolescents who have gender dysphoria might be concerned about expressing their thoughts about their identity to their families and peers. This might be due to fear of social stigmatization from being labeled as a lesbian, gay, bisexual, transgender, and queer (LGBTQ). LGBTQ adults report that experiences of interpersonal discrimination and violence that can range from emotional, verbal and physical forms (39). The same is true for transgender youth, who also commonly report negative experience that directed toward expressing their gender identity in term of accessing appropriate bathroom facilities or participating in gender specific activities, and other forms of school victimization (40,41). A survey that was performed on high school students in New Zealand in 2014 showed 65.2% of those who identified themselves as transgender didn't disclose their transgender identity. The survey also showed that gender dysphoria related symptoms started before the age of 12 years in 45% of those who had gender dysphoria (42).

During an assessment, detailed history is essential to identify gender identity concerns. Special attention should be given to concerns that persists over a long interval of time rather than transient thoughts about their gender identity (43). The health care provider may choose to use one or more of the available gender dysphoria screening tools as an objective way to measure individual's dissatisfaction about their gender identity (44). The Utrecht Gender Dysphoria Scale (UGDS) and its newer version; Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS) are widely used questionnaires. While the UGDS included only the sex assigned at birth (male *vs.*

female), the UGDS-GS is more inclusive of the additional categories of gender identity spectrum (i.e., genderqueer, nonbinary or cisgender) (44).

The age at which a youth presents with gender-related concerns is an important determinant of how to approach assessment and further care, as it may also dictate the degree or type of treatment and support the youth needs through-out the process of gender exploration. The health care provider should have a good understanding of developmental changes in childhood and adolescence. Prepubertal children who are gender-diverse may have a more fluid and changing trajectory of gender identity, thus their gender-related needs may vary over time (45). While this is also true for adolescents, understanding that this stage of cognitive, psychosocial and emotional maturation plays a crucial role in gender-identity development may aid in developing a more individualized approach to care.

The provider should ask non-judgmental questions aimed at eliciting information about gender nonconforming behaviors or preferences and inquire about the level of social support that they have (46). Research has demonstrated that children who received social support during their gender affirming medical care tend to exhibit better psychological well-being (32,47). Furthermore, parental support during the gender transition has shown stronger association with improved life satisfaction, improved self-esteem and decrease the likelihood of experiencing mood disorder in children with gender dysphoria (48). In contrast, an increased risk of suicide, homelessness and HIV infection were identified in gender diverse people who have less social support (38,49).

Parents should be educated that the presence of one or two gender non-conforming behaviors does not mean that a child or adolescent is gender diverse or transgender, and that exploration of gender expression is a part of a developmental process. Additionally, it is essential to discuss that a subset of individuals with gender identity concerns will abandon their concerns over time. However, it is challenging to predict which individuals will have persistent gender identity concerns which will eventually progress into a fully developed gender dysphoria. A survey done in 2017 involving 25 youth gender centers in Europe, United States and Chile noted 63% of youth being treated in these centers were transgender males (50). Percentages of persistence lie between 10–39%, with the critical period for demonstrating persistence or desistence somewhere between 10–13 years of age (51,52). The more extreme the experience of gender incongruence, the higher the likelihood that it may persist (53). Transgender with bisexual and homosexual orientation are also more likely

to persist (54).

While understanding that being transgender and gender diverse is not a mental health disorder, as emphasized in the joint position statement from the Endocrine Society and Pediatric Endocrine Society, attention should be devoted to screening for associated mental health concerns related to the distress of gender incongruence, or gender dysphoria (55). Appropriate and prompt referral to a mental health specialist is recommended, ideally those with experience in evaluating youth with gender dysphoria, given the intricacy and possible co-existence of other mental health concerns, and ruling out possible confounding mental illness. It is important to note that mental health illness may be contributing to etiology, complicating, or being a consequence of gender dysphoria. For example, disordered eating is common in adolescents with gender dysphoria with underlying thoughts to either suppress or accentuate physical body feature of desired gender (56). Also, transgender youth are at increased risk of depression, anxiety, and life-threatening behaviors, up to 2–3 times more frequent than cisgender controls (7,57). Individuals with gender dysphoria are also more likely to have other neurocognitive or diagnoses, such as autism spectrum disorder (ASD) or attention/deficit/hyperactivity disorder (ADHD) (58). In a recent study that compared 4,173 individuals with gender dysphoria to 16,648 controls, ASD and ADHD were identified in 6% and 17.9%, respectively (58). It is worth mentioning that having autism in a gender-dysphoric individual can limit ability to fully express their thoughts and feelings, therefore, further complicating their condition (46).

Safe sex practice and sexual health is crucial topic to be discussed with youth with gender dysphoria. Transgender individuals (particularly transgender women) are at increased risk of HIV and sexually transmitted infections (59-61). Therefore, counselling about condom use, pre-exposure prophylaxis and post-exposure prophylaxis are essential. Health care providers should be mindful when they ask about sexual practices. World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) guidelines that were published in 2022 recommends asking questions about the sexual organs that individual's partner has, and the sexual organs used during the sexual relationship rather than asking about the gender of their partner (62).

It is considered unethical for health care providers managing individuals with gender dysphoria to deliver care that aims to make them congruent with their sex assigned at birth (38). Instead, they should be a part of

multidisciplinary team to facilitate the transgender care. Ideally, this should be through a specialty center that would allow access to continued mental health care, hormone treatment and/or surgical therapy. Medical-social worker role is crucial given the multiple challenges that a person with gender dysphoria might experience in terms of safety, access to housing, education, and health care. Treatment options are tailored to the individual, guided by age, stage of puberty development, capacity to provide consent, and degree of parent/family support (63). Dialogue with the child or adolescent and their parents or legal guardian should focus on assessing their specific aims for therapy. Separate and multiple sessions with the patient is necessary to gain perspective of the youth's cognitive, emotional and psychosocial development, as well as their own perspective and goals of the transition process (64). With the complexity of diagnostic and decision-making of the process of gender affirmation, involvement of several specialists that will work with the transgender youth and their families is often needed (63). The goal of the multidisciplinary team is to provide support and individual expertise during the physical and psychosocial interventions, while ensuring continued communication and discussion of treatment recommendations and ongoing management. The core group of specialists would typically include appropriately trained mental health professionals, clinicians with expertise in hormone therapy, surgeons and care coordinators (63).

The process of gender transition refer to the act of altering one's physical, social, and/or legal characteristics to match their affirmed gender identity (65). For pre-pubertal children, this transition is primarily a social process, adopting gender-affirming names, hairstyles, clothing, pronouns and use of restrooms or other facilities. During this social transition, continued assessment of the person's feelings and response to the social transformation would allow both the individual and gender care provider to have a better understanding on how to proceed. A study conducted by Olson *et al.*, where parents and pre-pubertal transgender children from a community-based national sample as well as age and gender matched controls completed anxiety and depression measures, support the benefits of social transition, with transgender youth reporting depression and self-worth that are comparable to their cis-gender peers (66). Emergence, persistence or worsening of gender dysphoria during onset of pubertal changes may indicate need for further medical intervention.

Hormonal therapy can be provided by an endocrinologist

to either halt the progression, change, assist in acquiring with secondary physical characteristic of desired gender or both (63). Prior to starting the hormonal therapy, discussion about its reversible and irreversible effects with the adolescent and their parents is crucial (67). Pubertal suppression by Gonadotropin-releasing hormone (GnRH) is usually offered as early as Tanner stage 2. Pubertal suppression prevent progression of secondary sexual characteristics which alleviate their gender dysphoria as well as give them additional time to further explore their gender identity before proceeding to the next step in medical treatment (67). WPATH and endocrinology societies recommend starting gender affirming hormone therapy around the age of 16. Gender affirming hormonal therapy helps them gain the secondary sexual characteristic of desired gender. Studies have shown that short term gender affirming hormonal therapy is relatively safe (63). However, literature is sparse about the long-term effects of gender affirming hormonal therapy. Discussion about the possible risks and measures to decrease them is important. For example, counseling against tobacco smoking to decrease risk of thrombosis in estrogen therapy is important (43). Fertility is another aspect that can be impacted during the medical and surgical therapy period (63). It is reported that estrogen can affect the quality and the quantity of the sperm in trans-women. Similarly, testosterone therapy can lead to reversible amenorrhea in trans-men. Therefore, counseling them about measures of fertility planning like sperm cryopreservation in transgender women and oocytes cryopreservation in transgender men should be done in advance (43).

The role of gender-affirmation surgery (GAS) usually comes after hormonal therapy (62). GAS is a group of surgical procedure that aims to affirm an individual's body with their gender identity. These include subcutaneous mastectomy, breast augmentation, vaginoplasty, metoidioplasty, phalloplasty and facial feminization/masculinization surgery (62,68-71). Most of these surgeries are performed after the age of 18 except for "masculinizing" mastectomy, which can be done at the of 16. GAS have shown multiple benefits to the patients, including an improvement of quality of life, satisfaction with appearance and body image, and decrease in gender dysphoria (62,68-71). Being a major surgery, the decision of GAS must be shared between the surgeon and the patient, and must be based on deep awareness of the patient own goals, expectations, associated risks and complications, and after exploration of all the alternative therapy options.

Conclusions

The care for transgender and gender diverse youth has evolved significantly throughout the years, but there remains a significant gap in knowledge related to medical care, and how the medical community can further support these individuals. Although further understanding on the biologic basis of gender identity is still needed, the changes in terminologies and the move to declassify gender-related issues as mental health disorders have been instrumental in changing the perspective towards transgender and gender diverse persons. Increased awareness and early recognition of gender-related issues in youth, accompanied by continued education about current evidence-based practices to deliver optimal health care, would allow for improved outcomes in transgender and gender diverse individuals' mental health, quality of life, and overall well-being.

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