



MINI REVIEW

What is new in Chicago Classification version 4.0?

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ABSTRACT

Since publication of Chicago Classification version 3.0 in 2015, the clinical and research applications of high-resolution manometry (HRM) have expanded. In order to update the Chicago Classification, an International HRM Working Group consisting of 52 diverse experts worked for two years and utilized formally validated methodologies. Compared with the prior iteration, there are four key modifications in Chicago Classification version 4.0 (CCv4.0). First, further manometric and non-manometric evaluation is required to arrive at a conclusive, actionable diagnosis of esophagogastric junction (EGJ) outflow obstruction (EGJOO). Second, EGJOO, distal esophageal spasm, and hypercontractile esophagus are three manometric patterns that must be accompanied by obstructive esophageal symptoms of dysphagia and/or non-cardiac chest pain to be considered clinically relevant. Third, the standardized manometric protocol should ideally include supine and upright positions as well as additional manometric maneuvers such as the multiple rapid swallows and rapid drink challenge. Solid test swallows, postprandial testing, and pharmacologic provocation can also be considered for particular conditions. Finally, the definition of ineffective esophageal motility is more stringent and now encompasses fragmented peristalsis. Hence, CCv4.0 no longer distinguishes between major versus minor motility disorders but simply separates disorders of EGJ outflow from disorders of peristalsis.

KEYWORDS

achalasia, esophageal motility, esophageal pressure topography, gastroesophageal reflux disease, per-oral endoscopic myotomy

1 | HISTORICAL EVOLUTION OF CHICAGO CLASSIFICATION

Although the first major version of the Chicago Classification (CC) was published in 2009, the Chicago Classification began in Paris in 2007 as an idea by three of the authors (JEP, AJB, MF) to form an international collaboration to eliminate competitive factions that were impeding progress in the field.¹ Inspired by the seminal contributions of Ray E. Clouse (1951–2007) who pioneered the transformation of esophageal

motility data into the color topography plots that have become so commonplace today, the group decided to cooperatively build the International High-Resolution Manometry (HRM) Working Group.² In fact, the first description of the “Chicago Classification” was in a publication authored by Fox and Bredenoord in 2007 (CCv0.5) setting the stage for the inaugural meeting of the International HRM Working Group in San Diego in 2008 that eventually led to CCv1.0 in 2009.^{1,3} CC was conceptualized as a standardized approach to the interpretation of clinical HRM studies enabling clinicians worldwide

to 'speak the same language' ending the Tower of Babylon situation in which differing names and definitions were applied to the same conditions. Additionally, it was decided to apply metrics that had been validated against independent measurements of esophageal function (eg, radiology) and to adopt a hierarchical diagnostic system in which disorders of esophagogastric junction (EGJ) function (eg, achalasia) were prioritized over major disorders of peristalsis that were rarely if ever seen in health and minor disorders of peristalsis that, despite being outside the normal range, were not conclusively pathological. In adopting a standardized nomenclature, objective metrics and a structure based on robust, physiological principles, CC has spurred a tremendous amount of research and collaboration resulting in an evolving schema, open to refinement and revision. The first major CC update (CCv2.0), endorsed by several international motility societies, followed from a meeting of the International HRM Working Group in Ascona in 2011.⁴ Subsequently, an expanded International HRM Working Group met in Chicago in conjunction with DDW 2014 to formulate the CCv3.0 that was formally presented at Ascona II in 2015.⁵ By this time, the CC had become the quintessential classification scheme of esophageal HRM findings, used worldwide to identify and categorize esophageal motor pathology.

2 | NOVEL OVERARCHING PRIORITIES OF CHICAGO CLASSIFICATION v4.0

In the 5 years since publication of CCv3.0, both the clinical and research applications of HRM have expanded, with the introduction of novel metrics and the widespread adoption of new therapies, in particular, endoscopic myotomy. Hence, an International HRM Working Group, now 52 members strong, worked for two years to develop the Chicago Classification version 4.0 (CCv4.0) presented in this issue of *Neurogastroenterology and Motility*. The aims of the CC initiative remain to optimize the diagnosis and management of esophageal motility disorders. However, its success in that pursuit hinges on its generalizability, clinical applicability, and continued refinement. Thus, in addition to providing an updated classification scheme, novel priorities of CCv4.0 were to involve diverse expert representation, to apply more rigorous methodology in literature review and consensus development, to standardize the HRM protocol, and to provide guidance on therapeutic considerations (Table 1).

2.1 | Diverse working group & rigorous methodology

In order to develop a rigorous classification scheme generalizable across regions, practice types, and socioeconomic structures, the CCv4.0 working group included 52 experts with diversity across age, gender, motility experience, and geography. There was representation from five continents and 20 countries, representing six Neurogastroenterology and Motility societies from around the

Key points

- Formal rigorous methodology was applied across a diverse and large group of experts to develop a generalizable and accepted classification scheme
- The recommended standard high-resolution esophageal manometry protocol includes supine and upright positions as well as supportive provocative manometric maneuvers
- Specific manometric patterns (EGJ outflow obstruction, distal esophageal spasm, and hypercontractile esophagus) require additional data and/or supportive history to be considered clinically relevant and indicate need for treatment
- The definition of ineffective esophageal motility is more stringent and encompasses fragmented peristalsis.

world. The working group was divided into seven subgroups, each tasked with developing statements specific to topics targeted for improvement or refinement based on the group experience with CCv3.0: (a) devising a standardized HRM protocol, (b) achalasia, (c) esophagogastric junction (EGJ) outflow obstruction (EGJOO), (d) distal esophageal spasm (DES), (e) hypercontractile esophagus, (f) ineffective esophageal motility (IEM), and (g) EGJ barrier metrics. The formally validated RAND Appropriateness Method (RAM) was used through several on-line independent surveys to facilitate equal contribution among group members. Evidence was assessed according to GRADE by two working group members external to the subgroup when statement structure permitted. Although it was anticipated that the majority of the literature would be assessed as low or very low level evidence by the GRADE construct that is weighted by randomized controlled trials and meta-analyses, the external expert review provided an additional unbiased evaluation.

2.2 | Standardized HRM protocol

Consistent with the structure of CCv3.0, motility laboratories generally adhere to a standard protocol of 10 supine wet swallows.⁶ However, that protocol is often insufficient to establish a definitive motility diagnosis that explains symptoms and guides therapy. This risks misdiagnosis and misdirected treatment of motility disorders, in particular EGJOO and hypercontractile esophagus. CCv4.0 addressed this clinical challenge with a subgroup dedicated to the development of a standardized HRM protocol. Based on literature review and multiple RAM surveys, the final CCv4.0 standardized HRM protocol includes wet swallows in both the supine and upright positions, as well as a supine multiple rapid swallow, and an upright rapid drink challenge. However, it is reasonable to limit the testing protocol to 10 supine or 10 upright wet swallows, for example in cases of clear-cut achalasia, particularly if there is risk of aspiration.

TABLE 1 Key priorities and updates in CCv4.0

Key priorities	Specific aim	Updates
Diverse representation	Develop a generalizable and accepted classification scheme	<ul style="list-style-type: none"> • 52 working group members • Diversity in age, gender, years of experience, practice type • Experts from 20 countries
Rigorous methodology	Minimize bias and ensure equal contribution among members	<ul style="list-style-type: none"> • Seven subgroups • RAND Appropriateness Method • GRADE assessment of supportive literature by non-voting member
Standardized HRM Protocol	Generate an efficient and comprehensive protocol that is sufficient to diagnose each esophageal motility disorder and promote collaboration	<ul style="list-style-type: none"> • Includes supine and upright testing postures along with relevant thresholds • Incorporates provocative and/or supportive manometric maneuvers
Provide Guidance on Therapeutic Considerations	Identify which manometric patterns are clinically relevant by themselves and which require supportive history and/or data to indicate need for therapy	<ul style="list-style-type: none"> • EGJOO, DES, and hypercontractile esophagus must be accompanied by obstructive symptoms to be considered clinically relevant • EGJOO requires confirmation of outflow obstructive physiology on non-HRM testing

Abbreviations: DES: distal esophageal spasm; EGJOO: esophagogastric junction outflow obstruction; GRADE: Grading of Recommendations Assessment, Development and Evaluation.

CCv4.0 also highlights the role of ancillary manometric evaluations such as response to rapid drink challenge, solid food swallows, or pharmacologic provocation to identify the causes of symptoms and elicit evidence of obstruction. Postprandial studies may also be helpful to identify rumination.

The advantages and disadvantages of this comprehensive standardized protocol was a point of debate throughout the CCv4.0 initiative. In addition to increasing diagnostic accuracy and reliability, standardization of the HRM protocol should enhance the ability for collaboration across laboratories. A forthcoming technical review provides rationale for inclusion of each aspect of the standardized protocol. The CCv4.0 group also acknowledged that some laboratories have limited resources necessitating that only part of the protocol is applied.

2.3 | Esophageal motor patterns of clinical relevance versus unclear relevance

While achalasia represents a well-defined esophageal motor pathology with specific treatments, many esophageal manometric patterns are incidental findings that are not indicative of clinical pathology and do not require intervention. In such instances, aggressive interventions can lead to poor patient outcomes. Hence, a key priority in CCv4.0 was to distinguish between actionable pathology and non-specific manometric findings. Initially, the working group explored an alternate classification scheme to distinguish between manometric patterns of unequivocal clinical relevance and those of unclear clinical relevance. However, consensus could not be attained and the CCv4.0 group opted to maintain the established classification scheme based on esophageal physiology. Nonetheless, the clinical relevance

of specific manometric patterns is referenced throughout CCv4.0 and patterns with unclear clinical relevance are indicated by asterisks in the figures, replacing the distinction between major and minor motility disorders in CCv3.0. CCv4.0 also recognizes that manometric findings in clinical practice do not always fit cookie cutter definitions for conclusive manometric diagnoses. Hence, CCv4.0 describes manometric scenarios that may be suggestive, but inconclusive, of a disorder and provides further guidance on using supportive manometric maneuvers and adjunctive tests to increase diagnostic confidence.

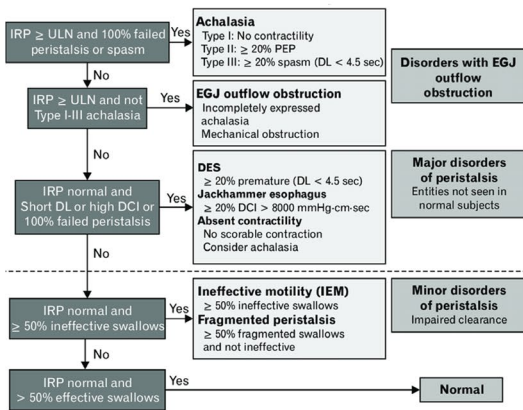
2.4 | CCv4.0 updates of esophageal motility disorders

Based on the working group's experiences with CCv3.0, disorder-specific working groups reviewed all diagnoses. Achalasia and absent contractility have stood the test of time and remain largely unchanged. EGJOO and IEM underwent a complete redefinition. Changes to DES and hypercontractile esophagus were considered, but there were insufficient data to merit major revision; however, both require further investigation and future update.

2.5 | Disorders of EGJ outflow

The median integrated relaxation pressure (IRP) of 10 wet swallows (supine or upright) is the first branching point of the CCv4.0 schema (Figure 1). An elevated median IRP warrants consideration for disorders of EGJ outflow (ie, achalasia, EGJOO). Importantly, CCv4.0 delineates IRP thresholds for supine versus sitting positions and for different HRM systems.

CC v. 3.0



CC v. 4.0

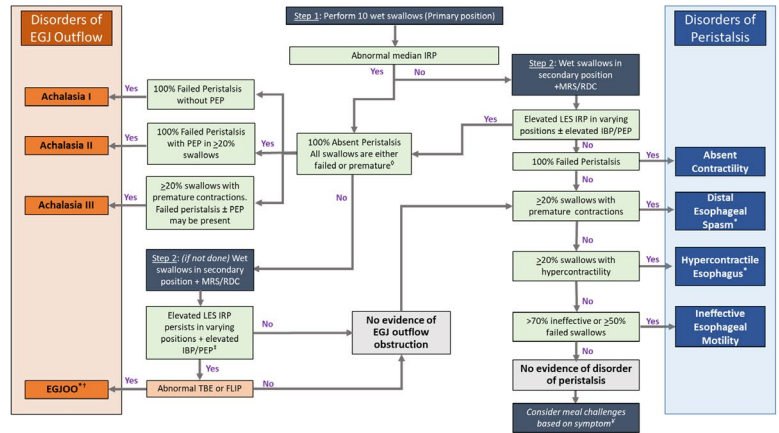


FIGURE 1 Classification schemes for 1A) Chicago Classification v3.0, 1B) Chicago Classification v4.0. Key differences in CCv4.0 include the inclusion of supine and upright position and provocative manometric maneuvers (‡, ¥), the more stringent and refined criteria for EGJOO and IEM, and as the indication that EGJOO, DES, and hypercontractile esophagus are manometric patterns of unclear clinical relevance (*). Patients with EGJ obstruction and presence of peristaltic swallows fulfill strict criteria for EGJOO and may have features suggestive of achalasia or other patterns of peristalsis defined by criteria for disorders of peristalsis: EGJOO with spastic features, EGJOO with hypercontractile esophagus, EGJOO with ineffective motility, or EGJOO with no evidence of disordered peristalsis (‡)

2.5.1 | Achalasia

Achalasia remains the prototypical esophageal motor disorder with the most supportive data. The conclusive manometric criteria for achalasia type I and II are consistent with prior CC iterations requiring an elevated median IRP (either in the supine and/or upright position) and 100% failed peristalsis. Panesophageal pressurization remains a defining feature of type II achalasia, although CCv4.0 notes that the distinction between type I and II is somewhat arbitrary and does not portend distinct treatment outcomes aside from advanced cases with minimal esophageal pressurization and/or severe esophageal dilation. On the other hand, very high levels of pressurization within panesophageal pressurization may represent embedded esophageal spasm potentially masking type III, or spastic, achalasia.

Type III achalasia requires an elevated median IRP (either in the supine and/or upright position) with spasm (premature contraction (distal latency <4.5 s) with distal contractile integral > 450 mmHg-s-cm) in at least 20% of swallows. Prior CC iterations were ambiguous in terms of whether a diagnosis of type III achalasia required 100% failed peristalsis. CCv4.0 now clarifies this point and requires 100% *absent* peristalsis defined as either failed peristalsis or spasm. Patients who have an elevated IRP, elevated intrabolus pressurization, and swallows with a mixture of spasm and “normal” peristalsis meet criteria for EGJOO. These patients should be labeled as EGJOO with spastic features. Having spasm in a greater number of swallows increases confidence that this is more akin to type III achalasia. Per-oral endoscopic myotomy with extension of the myotomy proximally is the accepted first-line treatment for type III achalasia (except when opioid-induced). The mechanism of opioid-induced esophageal dysfunction is distinct from primary achalasia and opioid cessation, and conservative therapeutic approaches should be preferred. We stress that the CC pertains to primary motility disorders,

not motility patterns secondary to medication use, mechanical obstruction, previous surgery or endoscopic interventions.

2.5.2 | EGJ outflow obstruction

As with prior CC iterations, a diagnosis of EGJOO is considered when the median IRP is elevated but peristalsis is sufficiently intact to preclude a diagnosis of achalasia. However, while some cases of EGJOO represent LES dysfunction and variant or evolving achalasia, a substantial proportion of EGJOO in the supine position is unrelated to LES dysfunction (eg, effect of artifact, sliding hiatal hernia, mechanical obstruction, or opioid effect). Consequently, interventions to disrupt the LES are not appropriate for most cases of EGJOO and irreversible interventions such as myotomy should be reserved for a well vetted subgroup. Hence, a focal point of CCv4.0 was to refine the identification of actionable EGJOO. New criteria for EGJOO stipulate an elevated IRP in both supine and upright positions as well as at least 20% of swallows with intrabolus pressurization (without meeting criteria for achalasia). Furthermore, a manometric diagnosis of EGJOO should always be considered inconclusive, requiring that there also be obstructive symptoms of dysphagia and/or non-cardiac chest pain AND supportive evidence of obstructive physiology from a non-HRM test. Supportive testing may be in the form of a timed barium esophagram (TBE) or functional lumen imaging probe (FLIP). Additional manometric maneuvers may also strengthen the confidence in an EGJOO diagnosis including response to rapid drink challenge, solid test swallows, or pharmacologic provocation.

EGJOO should be described in the context of the associated peristaltic pattern to provide supportive evidence for a primary motility diagnosis. As already mentioned, the distinction between type III achalasia and EGJOO with spastic features hinges on the

presence of some “normal” peristalsis and these entities can be difficult to distinguish; features of spasm on supportive testing can help inform clinical decisions. Similarly, EGJOO with hypercontractile features may represent reactive hypercontractility to obstruction or the hypercontractility may be a primary motility disorder that can also involve the LES. On the other hand, EGJOO with ineffective motility or EGJOO with no evidence of disordered peristalsis is more likely normal or a manifestation of reflux physiology, especially if there is minimal evidence of abnormal intrabolus pressurization or panesophageal pressurization. Generally, a cautious treatment approach should be applied to EGJOO; particularly, for the latter phenotypes (EGJOO-ineffective motility or EGJOO-normal peristalsis) and adjunctive tests should be utilized to confirm the diagnosis.

2.6 | Disorders of peristalsis

In the CCv4.0 schema, a disorder of peristalsis is considered if the median IRP is normal or the median IRP is elevated but criteria for a conclusive manometric diagnosis of EGJOO were not met. Disorders of peristalsis include absent contractility, DES, hypercontractile esophagus, and IEM.

2.6.1 | Absent contractility

Absent contractility remains unchanged in CCv4.0, defined by a normal median IRP and 100% failed peristalsis. For cases meeting criteria for absent contractility with an IRP at the upper limit of normal, CCv4.0 reiterates the need to investigate and exclude achalasia with supportive manometric measures (eg, rapid drink challenge, solid test meal) and adjunctive tests (eg, TBE, FLIP).

2.6.2 | Distal esophageal spasm

CCv4.0 maintains the CCv3.0 criteria of $\geq 20\%$ premature contractions for DES but requires that there also be dysphagia and/or non-cardiac chest pain for it to be a clinically relevant diagnosis. The working group raised several concerns about DES; however, none became formal recommendations given the lack of supportive data. In terms of clinical relevance, DES is a rare finding and, when encountered, often falls within the spectrum of type III achalasia. Having spasm in a greater number of swallows increases confidence that this is more likely a primary spastic disorder. However, the majority of manometric DES patterns likely represent a secondary response to reflux in patients with gastroesophageal reflux disease in which case antireflux rather than anti-spasmodic management should be recommended. Alternatively, opioids can lead to a DES pattern in which case opioid cessation should be recommended. Further investigation is needed to distinguish among phenotypes of manometric DES.

2.6.3 | Hypercontractile esophagus

CCv4.0 revised the nomenclature to switch jackhammer to a subtype and relabel the disorder as hypercontractile esophagus. CCv4.0 maintains the CCv3.0 criteria of $\geq 20\%$ hypercontractile swallows for this classification and requires that there also be dysphagia and/or non-cardiac chest pain to be a clinically relevant diagnosis. The most critical discussion of hypercontractile esophagus regarded the heterogeneity of motility patterns meeting the definition: jackhammer with repetitive prolonged contractions, single peak hypercontractile swallows, and hypercontractile swallows with a vigorous LES after-contraction. Among the three patterns, jackhammer is typically the most symptomatic with the greatest likelihood of responding to intervention. However, despite these concerns, the working group acknowledged the lack of supportive data and made no formal recommendations other than that jackhammer esophagus be considered a subgroup of hypercontractile esophagus rather than being synonymous with it in CCv4.0. Generally, a cautious treatment approach should be applied to hypercontractile esophagus, particularly in the absence of a jackhammer pattern.

2.6.4 | Ineffective esophageal motility

Based on emerging data, the CCv4.0 definition of IEM is more stringent, requiring more than 70% of swallows as ineffective (rather than at least 50% in prior CC iterations), or $\geq 50\%$ failed swallows. In CCv4.0, the definition of an ineffective swallow also encompasses fragmented swallows, and fragmented peristalsis is no longer a motor disorder in CCv4.0.

2.7 | EGJ barrier metrics

In addition to defining motility disorders, a major utilization of manometry is in characterizing EGJ barrier function as it pertains to both dysphagia and reflux disease. A major advantage of HRM is in the ability to image the dynamic nature of EGJ contractility and to easily isolate that attributable to the crural diaphragm as opposed to the LES. However, EGJ barrier metrics were not a part of prior CC iterations. The priority of CCv4.0 was to provide guidance on classifying EGJ morphology, and this is detailed in the main document and technical review. Future iterations will characterize the EGJ anatomy and function as it pertains to both motility disorders and reflux disease.

3 | SUMMARY

In summary, although much has changed with CCv4.0, the essence remains. Compared with CCv3.0, there are four key modifications to the schema (Figure 1 and Table 2). First, further manometric and non-manometric evaluation is required to arrive at a conclusive, actionable diagnosis of EGJOO. Second, EGJOO, DES, and hypercontractile esophagus are three manometric patterns that must be accompanied by obstructive esophageal symptoms to be considered clinically relevant (ie, actionable).

TABLE 2 Manometric Definitions: CC3.0 vs CC4.0

Diagnosis	CCv3.0 Definition	CCv4.0 Definition
Disorders of EGJ Outflow		
Type I Achalasia	Median IRP elevated & 100% failed peristalsis	Median IRP elevated (supine and/or upright) & 100% failed peristalsis
Type II Achalasia	Median IRP elevated & 100% failed peristalsis with $\geq 20\%$ panesophageal pressurization	Median IRP elevated (supine and/or upright) & 100% failed peristalsis with $\geq 20\%$ panesophageal pressurization
Type III Achalasia	Median IRP elevated & 100% failed peristalsis with $\geq 20\%$ swallows with spasm	Median IRP elevated (supine and/or upright), 100% absent peristalsis & $\geq 20\%$ swallows with spasm
EGJ outflow obstruction	Median IRP elevated and not meeting criteria for achalasia type I-III	Supine and upright median IRP elevated, supine intrabolus pressure elevated, and presence of normal peristalsis, with symptoms of dysphagia and/or non-cardiac chest pain, and at least one confirmatory non-HRM supportive test
Disorders of peristalsis		
Absent contractility	Normal median IRP and 100% failed peristalsis	Normal median IRP and 100% failed peristalsis
Distal esophageal spasm	Normal median IRP and $\geq 20\%$ swallows with spasm	Normal median IRP and $\geq 20\%$ swallows with spasm along with symptoms of dysphagia and/or non-cardiac chest pain
Hypercontractile esophagus	Normal median IRP and $\geq 20\%$ hypercontractile swallows (Referred to as Jackhammer esophagus)	Normal median IRP and $\geq 20\%$ hypercontractile swallows with symptoms of dysphagia and/or non-cardiac chest pain
Ineffective esophageal motility	$\geq 50\%$ ineffective swallows	$>70\%$ ineffective and/or fragmented swallows, or $\geq 50\%$ failed swallows

Third, the standardized manometric protocol should ideally include supine and upright positions as well as additional manometric maneuvers such as the multiple rapid swallows and rapid drink challenge. Solid test swallows, postprandial testing, and pharmacologic provocation can also be considered for particular conditions. Finally, the definition of IEM is more stringent and now encompasses fragmented peristalsis. As such, CCv4.0 no longer distinguishes between major versus minor motility disorders but simply separates disorders of EGJ outflow from disorders of peristalsis.

The CC originally brought to light the prognostic importance of achalasia subtypes. Along these lines, CCv4.0 introduces the relevance of distinct phenotypes within EGJOO and hypercontractile esophagus. We anticipate further evolution of this classification as evidence accumulates. Similarly, it is possible that impedance measurements will be incorporated in future iterations of Chicago Classification. Although our initial intention was to incorporate high-resolution manometry with impedance within CCv4.0, this technology is not widely available across motility labs and there is currently a lack of consistent data to guide inclusion. Another area of active research is the diagnostic and prognostic role of esophageal HRM prior to and following foregut interventions (eg, antireflux interventions, myotomy, bariatric procedures). Finally, CCv4.0 is by no means the final version of the CC. With future modeling analytics, artificial intelligence, and outcomes research, the interpretation of HRM will continue to evolve improving both diagnostic and therapeutic guidance.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

RY, JEP, MRF, AJB, PJK: Literature review, Drafting of manuscript, Critical revision of manuscript, Final approval of manuscript to be published. Writing Assistance: None.

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