Vaccine 41 (2023) 2605–2614

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Anaphylaxis: Revision of the Brighton collaboration case definition

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ARTICLE INFO

Article history:
Received 16 October 2022
Accepted 14 November 2022
Available online 24 November 2022

Keywords:
Anaphylaxis
Adverse event following immunization
COVID-19 immunization
Guidelines
Case definition
Vaccine safety

ABSTRACT

The Brighton Collaboration (BC) has formulated a number of case definitions which have primarily been applied to adverse events of special interest in the context of vaccine safety surveillance. This is a revision of the 2007 BC case definition for anaphylaxis. Recently, the BC definition has been widely used for evaluating reports of suspected anaphylaxis following COVID-19 vaccination. This has led to debate about the performance of the BC definition in comparison with those from the US National Institute of Allergy and Infectious Disease/Food Allergy Anaphylaxis Network (NIAID/FAAN) and the World Allergy Organization (WAO). BC convened an expert working group to revise the case definition based on their usual process of literature review and expert consensus. This manuscript presents the outcome of this process and proposes a revised case definition for anaphylaxis. Major and minor criteria have been re-evaluated with an emphasis on the reporting of observable clinical signs, rather than subjective symptoms, and a clearer approach to the ascertainment of levels of certainty is provided. The BC case definition has also been aligned with other contemporary and international case definitions for anaphylaxis.

1. Preamble

In 2007 the Brighton Collaboration (BC) published a case definition for anaphylaxis along with guidelines for data collection, analysis and presentation of immunization safety data [1]. It has been one of the most frequently cited BC case definitions for classifying adverse events following immunization (AEFIs) reported to pharmacovigilance reporting systems [2]. Recently the BC case definition for anaphylaxis has been widely applied to AEFI reports of suspected anaphylaxis following immunization with COVID-19 vaccines [3-8]. This has stimulated debate about the ability of the BC case definition to differentiate anaphylaxis from non-allergic events and from allergic but non-anaphylactic events. This in turn led to a comparison of different case definitions for anaphylaxis, including those proposed by the US National Institute of Allergy and Infectious Disease/Food Allergy Anaphylaxis Network (NIAID/FAAN) and the World Allergy Organization (WAO) [9-11]. The 2007 BCE Working Group referenced the 2006 NIAID/FANN consensus definition but noted concern that it did not allow for different levels of evidence and made assumptions about 'known allergens for the patient' which rendered it less suitable for a vaccination setting. The WAO case definition was published several

Abbreviations: AEFI, adverse events following immunization; BC, Brighton Collaboration; COVID-19, coronavirus disease; CARPA, complement activation related pseudo allergy; CDC, Centres for Disease Control; FAAN, Food Allergy Anaphylaxis Network; FcεRI, Fc epsilon receptor I; IgE, immunoglobulin E; ILO, inducible laryngeal obstruction; LOC, level of certainty; MCT, mast cell tryptase; mRNA, messenger ribonucleic acid; MRGPRX2, Mas-related G protein-coupled receptor X2; NIAID, National Institute of Allergy and Infectious Disease; VCD, vocal cord dysfunction; WAO, World Allergy Organization; WG, working group.

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https://doi.org/10.1016/j.vaccine.2022.11.027
0264-410X/

years after the BC case definition. It was always the intention of the BC to subject case definitions to cyclical review and revision every 3 to 5 years [12]. The anaphylaxis case definition has not been updated yet, and an update is now needed given the issues arising during COVID-19 vaccine deployment [13-17]. Accordingly, the purpose of this paper is to present the revised BC anaphylaxis case definition, based on current knowledge. It is intended for use in scientific and epidemiologic research relating to the safety of vaccines, as well as for determination of anaphylaxis rates in unvaccinated populations. The main objective of this case definition is to enable data comparability across trials and surveillance systems and, in turn, facilitate data interpretation and promote scientific understanding of anaphylaxis. The case definition is not intended to assign causality or to guide clinical management.

2. Introduction

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise of airways, breathing or circulation; in around 10 % of cases, anaphylaxis can occur without typical skin features being present. Anaphylaxis results from widespread activation and degranulation of effector cells (including mast cells and probably basophils), resulting in the release of multiple mediators which include vasoactive substances, cytokines, proteases, lipids, chemokines, interleukins, hormones and neurotransmitters. The primary target organs for these mediators are the skin/mucosa, respiratory, cardiovascular and gastrointestinal systems [18]. An immunoglobulin E (IgE)-dependent, type 1 hypersensitivity reaction is the most common mechanism of anaphylaxis that results in mast cell degranulation through the allergen crosslinking of the high affinity Fc epsilon receptor I (FcεRI)-bound allergen-specific IgE on the cell surface. The IgE-independent mechanisms of mast cell and basophil degranulation are less well understood, for example, through the Mas-related G protein-coupled receptor X2 (MRGPRX2) [19]. Complement activation-related pseudo allergy (CARPA) is another mechanism, first described in drug allergy, where activation of complement triggers mast cell degranulation [20]. Anaphylaxis is a clinical diagnosis, which can be confirmed by the objective finding of raised serum mast cell tryptase (MCT) levels [21]. However, MCT is infrequently measured, even in high income countries with adequate resources. In addition, MCT may not be elevated in some presentations of anaphylaxis for reasons which are poorly understood (e.g., food allergy) [21].

For the majority of anaphylaxis presentations, an allergen trigger can be identified (typically, exposure to a food, insect venom, drug or vaccine) and occasionally anaphylaxis can also be triggered by physical factors such as exercise or requires multiple co-factors (non-steroidal anti-inflammatory drugs, alcohol, fever) [22]. In some cases, no obvious trigger can be identified despite extensive investigation. These cases are referred to as idiopathic anaphylaxis, accounting for 30 % to 60 % of cases of anaphylaxis in adults and up to 10 % of cases in children [23]. The frequency of idiopathic anaphylaxis presentations is likely to depend on the clinical resources and expertise available to identify a trigger and, as reported by the European Anaphylactic Registry, in highly specialistic settings this accounts for 6.5 % of presentations [22]. In addition, in recent years this diagnosis has decreased due to the recognition of novel clinical entities (α-gal anaphylaxis) [24]. Anaphylaxis can also be a feature of systemic mastocytosis or mast cell activation syndrome [25].

Anaphylaxis to vaccines is rare, despite the billions of vaccine doses that are administered globally. Reported rates of anaphylaxis as an AEFI are between 1:100,000 and 1:1,000,000 vaccine doses administered, which meets the definition for a very rare event [26]. This ten-fold or more difference in reporting rates results from variation in the specific vaccine or vaccines evaluated, methods used for case ascertainment (passive versus active surveillance), reporting bias, case definitions applied, and denominator used to calculate rates (vaccines distributed or number of vaccine doses actually administered or number of people vaccinated) [27]. AEFI reports can be challenging to interpret due to incomplete documentation of symptoms and signs and, in the case of hypersensitivity reactions, modification of the clinical presentation due to patient management with adrenaline (epinephrine). Standardization of case definitions is critical for comparing the rates of anaphylaxis across different vaccines or the same vaccine across different populations, both from clinical trials and post-licensure surveillance studies in high and low resourced countries [28]. However, having a standard case definition may not ensure a uniform approach to data collection and analysis, and thus operational guidelines are also required, and these can be found in the anaphylaxis companion guide (https://zenodo.org/search?page=1&size=%2020&q=SPEAC).

Recently the BC case definition for anaphylaxis has been widely used to assess reports of immediate adverse events following immunization with COVID-19 vaccines [3-8]. The application of this case definition for anaphylaxis has stimulated debate about its ability to differentiate anaphylaxis from non-allergic events, and allergic but non-anaphylactic events. This has led to comparisons of different case definitions for anaphylaxis, including the clinical criteria proposed by the NIAID/FAAN and the WAO [13,15,17]. Classification of an AEFI as anaphylaxis, when it is not anaphylaxis, and vice versa, can have significant implications for the individual vaccine recipient – an important issue when multiple doses of the same vaccine are required. In addition, erroneous classification can result in significant over-estimates of anaphylaxis rates, undermining public confidence in the safety of a particular vaccine [14].

3. Methods for the revision of the Brighton Collaboration case definition for anaphylaxis

The BC anaphylaxis working group (WG) was formed in June 2021 by invited expressions of interest. The final WG consisting of 10 members: six allergists (paediatric and/or adult) with an interest in vaccine allergy (MSG, MG, JMK, PJT, BYHT, MW) and four vaccine safety public health experts (SK, AA, KAT, BL). The WG included participants from United States of America (USA) (2), Canada (2), United Kingdom (UK) (1), Germany (1), India (1), Singapore (1), Sri Lanka (1) and Australia (1). A total of 12 virtual meetings, commencing in June 2021, were held. Prior to making changes to the existing case definition the WG discussed the strengths and weaknesses of the case definition and defined the objectives of formulating a revised case definition. The 2007 version was used as the starting point for discussion, which focused on each major and minor criterion and formulation of the different levels of diagnostic certainty (Level 1 highest to Level 3 lowest). The WG members were asked to independently classify 15 AEFI reports of suspected anaphylaxis using the penultimate case definition. These classifications were analysed for consistency and used to refine the new case definition, which will be referred to as BC anaphylaxis - version 2 (BC-V2) and the original 2007 version will be referred to as BC anaphylaxis - version 1 (BC-V1).

3.1. Rationale for selected decisions about changing the case definition of anaphylaxis

Prior to revision of the BC-V1, the WG discussed the specific issues, summarised below, that needed to be addressed.

3.2. Classification of AEFI reports as anaphylaxis – Comparison of BC-V1, NIAID/FAAN and WAO case definitions.

The WG was aware of the debate concerning the performance of the BC-V1 when compared with the NIAID/FAAN and WAO clinical criteria for classifying suspected anaphylaxis after immunization with COVID-19 vaccines. Some authors have suggested that using BC-V1 resulted in an overestimate of cases [13-16] while others disagree [17]. In addition, using the BC-V1 there was double counting of lip swelling as both a major dermatological criterion and a major respiratory criterion leading to a Level 1 classification. In one prospective active surveillance study, 16 anaphylaxis cases were identified in 64,900 employees vaccinated with a messenger ribonucleic acid (mRNA) COVID-19 vaccine using a review of immunization and clinical details [29]. Using the BC-V1 definition and the NIAID/FAAN clinical criteria an anaphylaxis rate of 216 and 140 per million vaccine doses, respectively, can be calculated. This is much higher than the Centers for Disease Control (CDC) estimates of 2.5 to 4.7 per million doses from the Vaccine Adverse Event Report System using passive surveillance [30]. The authors postulate that the source, i.e., extent of detail and accuracy of information available, rather than the specific criteria, is the major contributor to differences in reported anaphylaxis rates [17,29]. Case reports of suspected anaphylaxis following mRNA vaccines first published by the CDC COVID-19 task force were reevaluated in another study [13]. Of the 31 cases judged by CDC reviewers to meet the BC case definition (Level 1, n = 16, Level 2, n = 14, Level 3, n = 1) only 20 met the definition when assessed by allergists (all of whom were experts in anaphylaxis). In addition, only 7 and 14 (of the 31 cases) met the NIAID/FAAN and WAO criteria for anaphylaxis, respectively.

In considering these issues, the WG concluded that there is no 'gold standard' case definition for anaphylaxis. The purpose of the BC case definition differs from that of the NIAID/FAAN or WAO clinical criteria. The latter are used prospectively by front-line clinicians to facilitate diagnosis and treatment of anaphylaxis, due to any trigger, or retrospectively by specialist allergists to aid longer-term preventative management. In contrast, the BC case definition is meant to be applicable to a wide variety of settings, from pre-licensure controlled clinical trials to post-licensure AEFI reporting, where the assessment is usually post-hoc and often based on a bare minimum of clinical information. This process is facilitated by the definition of several levels of certainty. In comparing the BC V-1 criteria with the NIAID/FAAN and WAO criteria, the WG noted that the inclusion of subjective symptoms in BC-V1, particularly with respect to respiratory symptoms, could explain why many AEFI reports following immunization with COVID-19 vaccines might have been misclassified as anaphylaxis. For this reason, the WG closely reviewed the use of subjective symptoms in the revised definition, with the aim of improving the specificity of the definition. The WG further noted a significant area of ambiguity due to lip angioedema having been counted both as a major respiratory criterion (representing part of upper airway tract swelling) and as a major dermatological criterion (as part of angioedema) criterion resulting in a Level 1 BC classification. This is problematic because the opinion of the experts in the WG was that lip swelling was not usually reflective of upper airway mucosal involvement and should only be regarded as a skin criterion (i.e., angioedema) – something entirely consistent with NIAID/FAAN and WAO clinical criteria.

The revised WAO 2020 clinical criteria noted how some cases of anaphylaxis may present initially with sudden hypotension or respiratory tract obstruction (wheeze/stridor) in isolation, without multisystem involvement [11]. Skin signs are absent in 10–20 % of presentations of fatal anaphylaxis [11]. The likelihood of this presentation for anaphylaxis following immunization is unknown. Though these single-system presentations meet a case definition in the NIAID/FAAN or WAO criteria, this is strictly in the context of exposure to a known or highly probable allergen for a given patient. For immunization this context would necessarily imply that a person with a previously known and pre-existing allergy to a given vaccine is reimmunized with the same vaccine, which is an unlikely scenario. In addition, vasovagal events following vaccination are not uncommon and present with single-organ system involvement. The same is true of vocal cord dysfunction (VCD), also known as inducible laryngeal obstruction (ILO), presenting with stridor. For these reasons, after consideration, the WG decided not to include single system involvement in the updated BC case definition for anaphylaxis in the absence of an accompanying increase in mast cell tryptase which is a biomarker of anaphylaxis (inferring mast cell degranulation). It is recommended that cases with a single system cardiovascular or respiratory presentation have their MCT level assayed within four hours of the onset of symptoms and that the patient is reviewed by a specialist allergy (if feasible) to ascertain if NIAID/FAAN or WAO clinical criteria are met. Until this review occurs these cases may be unclassifiable. In fatal cases of single system presentation, a post-mortem (if feasible) is critical as this may show findings consistent with anaphylaxis (usually upper airway edema) or demonstrate an alternate and coincidental cause.

3.2.1. Mimics of anaphylaxis and the BCCD

The BC-V1 was formulated at a time when vaccines were infrequently administered globally to adolescents and adults. The implementation of widespread, urgent COVID-19 immunization campaigns in older age groups has highlighted the variety of presentations of immediate adverse events that can mimic anaphylaxis. Such events are consistent with an immunization anxiety-related response, also referred to as immunization stress-related response, and include: vasovagal syncope with collapse and loss of consciousness; VCD or ILO with stridor and dyspnoea; acute stress reactions with dyspnoea, light-headedness and a sensation of throat closure; and autonomic skin reactions with skin flushing due to vasodilatation [31,32]. Such events might explain the observation that most individuals with reported anaphylaxis (Level 1 to 3 BC V-1) following immunization with a COVID-19 vaccine have tolerated a further dose of the same vaccine [33,34]. For example, ten individuals with respiratory symptoms, i.e., sensation of throat closure, tachypnoea, vocal hoarseness, stridor/wheeze following immunization with a COVID-19 vaccine, all of whom were assumed to have had anaphylaxis, were examined is a case series. Five of the nine individuals who were rechallenged with the same vaccine had VCD documented on laryngoscopy and none had anaphylaxis [34]. The WG discussed how a revised case definition might differentiate anaphylaxis from both non-allergic mimicries and non-anaphylaxis events that are nevertheless allergic. The WG concluded that where possible, subjective symptoms should be excluded from the revised case definition.

3.2.2. Inclusion of gastrointestinal symptoms as a major criterion in BC-V2

Since the publication of the BC-V1 in 2007, several specialist allergy societies and groups have included significant gastrointestinal signs and symptoms in their case definition for anaphylaxis [9-11]. The reason for this change is that, in the context of an injected allergen, gastrointestinal symptoms and signs were noted to be part of systemic mast cell degranulation and to be associated with severe episodes of anaphylaxis [35]. The WG considered it important that BC-V2 was consistent with contemporary case definitions of anaphylaxis and have, therefore, included objective gastrointestinal signs (new onset diarrhea and vomiting in close temporal proximity to vaccination) as major criteria.

4. The Brighton Collaboration case definition V2

The Brighton Collaboration anaphylaxis case definition V2 is shown in Table 1 and Fig. 1.

4.1. Similarities between the BC-V1 and BC-V2 definitions

The terminology used to describe anaphylaxis (including events previously described as anaphylactoid, a term which has been superseded by non-IgE-mediated anaphylaxis) and the caveat that there is not intent for the case definition to guide clinical diagnosis and acute management were unchanged in BC-V2. These points are all discussed in detail in the BC-V1 publication and will not be repeated here [1]. It is also important to reiterate that neither treatment nor response to treatment (usually adrenaline administration) is considered diagnostic of anaphylaxis, and therefore is not included in the case definition. However, this should not diminish the importance of administering intramuscular adrenaline (epinephrine) whenever anaphylaxis is suspected, and the importance of documenting all symptoms and signs prior to (and after) administering adrenaline. Administration of adrenaline (or response to adrenaline) is therefore not included as a criterion in the case definition.

4.2. Differences between the BC-V1 and BC-V2 anaphylaxis definitions

The differences between BC-V1 and BC-V2 are summarized in Table 2 and a description and the rationale for the changes are presented below.

4.2.1. Sudden onset and rapid progression of symptoms and signs

For BC-V2, the term 'sudden onset' has been removed as a mandatory requirement to fulfil any level of diagnostic certainty. The WG considered that the term 'rapid progression' was more specific for anaphylaxis and has been retained in BC-V2. However, 'rapid progression' has been defined to highlight the concept of a concurrent multisystem presentation or a sequential organ system progression, occurring over a short period of time (within 1 h of onset of the first symptoms or signs). BC-V1 did not specify a particular time interval as 'using an arbitrarily restrictive set point might bias future data collection unnecessarily', but the WG considered this could contribute to a case definition that was less specific for anaphylaxis. BC-V2 also clarifies that rapid progression is not the same as time from vaccination to onset of the first symptom or sign, which is not required as a criterion to fulfil the case definition. Still, time to onset is an important consideration for assessing causality, that is, whether the adverse event under consideration was due to vaccination [36].

4.2.2. Skin and mucosal criteria

Urticaria and angioedema have been retained as major skin criteria, because in this context they are likely to be specific for mast cell degranulation. The requirement for these skin changes to be generalized has been clarified. For BC-V2, the descriptor 'at a location other than the vaccine administration site' has been added. Localized urticaria or angioedema that are contiguous with the injection site (even if extensive) are poorly predictive of vaccine allergy, including anaphylaxis. Local skin changes at the injection site may be caused by irritation or inflammation independent of an allergic reaction. The Working Group thought that erythema (without itch) was poorly specific for mast cell degranulation, and therefore the descriptors of generalized (widespread) erythema of the skin with itch as a sign that is more indicative of mast cell degranulation were included. It was recognized that patchy erythema, particularly in adolescents and adults, is commonly a part of an acute stress response. Generalized erythema without skin itch has been maintained as a minor skin criteria in BC-V2, but generalized prickle sensation and generalized itch without rash have been removed. This reflects the aim of formulating a case definition based on observable objective signs rather than reported subjective symptoms. The combination of red and itchy eyes indicating involvement of the mucosal surface of the eyes has been retained, but with the specific caveat that this should be new onset (that is not precede vaccination) and should be bilateral.

4.2.3. Respiratory

The major respiratory signs of wheeze and stridor have been retained in BC-V2 with the caveat of one or both being documented by a healthcare professional. There is a similar caveat for upper airway tract swelling which is now referred to as 'angioedema of the mucosa of the upper airway - swelling of the tongue, pharynx, uvula and/or larynx'. Lip swelling has been removed as a sign of upper airway tract swelling in BC-V2. Indicators of respiratory distress remain unchanged except for the addition of 'measured hypoxia with oxygen saturation < 90 %' to make the criterion more objective. The addition was made because in some AEFI reports it was noted that reduced oxygen saturation was reported without reporting of clinically observable signs (e.g., cyanosis). The minor subjective symptoms, i.e., reported breathing difficulties, sensation of throat closure and hoarse voice, have been removed from BC-V2. Hoarse voice was thought to be influenced by subjective reporting and that any significant upper airway tract swelling would be observable as pharyngeal (or laryngeal) swelling with or without stridor. Minor respiratory symptoms, i.e., cough, sneezing or runny nose, have been retained, but it has been specified that they should be new onset and persistent. The reason for new onset was to highlight that these signs also occur in individuals with allergic rhinitis, a common condition, that may precede vaccination.

4.2.4. Cardiovascular

Measured hypotension is retained as a major cardiovascular criterion in BC-V2, with reference to the age-appropriate ranges for hypotension [37,38]. The reporting of 'compensated shock' i.e., normal blood pressure with clinical signs of peripheral compensation, was thought to be unlikely in the context of an AEFI report and hence this has been removed. Loss of consciousness is a sign of hypotension, but to differentiate anaphylaxis from vasovagal syncope the caveat 'other than brief, self-resolving loss of consciousness typical of a vasovagal reaction' has been added. All minor cardiovascular criteria have been removed from BC-V2, as these criteria are seldom reported and are more in line with evaluation for clinical diagnosis and management.

4.2.5. Gastrointestinal

The gastrointestinal signs included in BC-V1 as minor criteria have been modified to include only objective symptoms, specifically, new onset vomiting or diarrhea and they are now considered as major criteria in BC-V2. The inclusion of these symptoms is restricted to the context of parenterally-administered vaccines (as opposed to orally-administered vaccines) which is consistent with other anaphylaxis definitions [9,11]. Subjective symptoms, including abdominal pain and nausea, have been removed. There are no minor gastrointestinal criteria included in BC-V2.

4.2.6. Laboratory

An increase in mast cell tryptase (MCT) has been retained, but is now a major criterion in BC-V2 whereas it was a minor criterion in BC-V1. An increase in MCT is now defined as *either* above the upper limit for the laboratory or an increase of at least 20 % from the baseline tryptase level plus 2 ng/ml, i.e., [(1.2-fold increase over the baseline tryptase level) plus 2 ng/ml], as measured either

Table 1
Brighton Collaboration Case Definition for Anaphylaxis – V2.

Anaphylaxis presents acutely and leads to a marked change in an individual's previous stable condition and is characterised by the following:

For all levels of diagnostic certainty
Rapid progression of symptoms and signs which typically affects multiple body systems (skin/mucosa/respiratory/cardiovascular/gastrointestinal) at the same time or sequentially but occurring over a short period of time (within 1 h, from the onset of the first symptom and/or sign) (1)
AND
Major and/or minor symptoms and/or signs involving the following systems:

Systems	Major	Minor
Skin and/or conjunctival mucosa	**Urticaria (hives)** o at a location other than the vaccine administration site **Angioedema of the skin (swelling)** o at a location other than the vaccine administration site **Generalised (widespread) erythema (redness)** of the skin **with itch**	Bilateral **red and/or itchy eyes** o new onset (2) **Generalised (widespread) erythema (redness)** of the skin without itch
Respiratory	**Expiratory wheeze** o documented by healthcare professional which could be with/out stethoscope **Inspiratory stridor** o documented by healthcare professional which could be with/out stethoscope **Angioedema of the mucosa of the upper airway - swelling of the tongue, pharynx, uvula and/or larynx** o unequivocally documented by a healthcare professional - this does ***not*** include isolated lip swelling. ≥ **2 indicators of respiratory distress**: o Tachypnoea o Cyanosis o Measured hypoxia with oxygen saturations < 90% (3) o Grunting o Chest wall retractions o Increased use of accessory respiratory muscles	**Cough and/or sneezing and/or runny nose** o new onset (2) and persistent (4)
Cardiovascular	**Measured hypotension** (5) **Loss of consciousness** o other than the brief, self-resolving loss of consciousness typical of a vasovagal reaction	
Gastrointestinal	New onset **vomiting** (2,6,7) New onset **diarrhoea** (2,7)	
Laboratory	Elevated mast cell tryptase (8)	

Logic to level of certainty for anaphylaxis
Level 1, 2, 3 must meet the criterion for rapid progression AND use the pattern of MAJOR and MINOR criteria met for skin, respiratory, cardiac, gastrointestinal systems and laboratory result from the table above to determine the highest level of diagnostic certainty (with level 1 > level 2 > level 3) (9,10)

Level 1	MAJOR skin/mucosal AND ≥ 1 MAJOR system involvement including respiratory and/or cardiac and/or gastrointestinal and/or laboratory
Level 2	≥2 MAJOR system involvement including respiratory and/or cardiac and/or gastrointestinal and/or laboratory • Excludes skin/mucosal involvement and must be from different systems (10)
Level 3	Only 1 MAJOR system (skin or respiratory or cardiac or gastrointestinal or laboratory) AND at ≥ 1 MINOR from a different system • Minor criteria from respiratory and/or skin (11)
Level 4	Insufficient information provided to meet any level of certainty. • This may include reports which document anaphylaxis without a description of any signs and/or symptoms (12)
Level 5	Sufficient information provided for review and determined not to meet case definition at any level of certainty (13).

Notes

1. ***Rapid progression*** *does NOT define the time from vaccination to the onset of the first symptom and/or sign. Rather rapid progression specifically refers to the time from the onset of a sign in one system to a sign in at least one other system. Although time from vaccination to first sign is part of subsequent causality assessment, it is not to be considered in case definition. The causality assessment methods can be found at; https://www.who.int/publications/i/item/9789241516990*
2. ***New onset*** *implies that the symptom or sign was not present prior to immunisation. In AEFI reports this is often <u>not</u> stated but could be implied. If a report documents that this was present prior to immunisation, then this cannot be used as a criterion.*
3. ***Oxygen saturations*** *measured by an oximeter can be inaccurate and should if possible be verified on an oximetry trace*
4. ***Persistent*** *(for cough/sneezing/runny nose) implies that these symptoms occur recurrently and/or last for 5 min or longer*
5. *Children 10 years of age and younger: systolic BP less than (70 mm Hg + [2 x age in years]) and children 11 years of age and older and adults: decrease of >30% from that person's baseline systolic BP* ***or*** *less than <90 mm Hg* or a diastolic BP < 60 mm Hg [36,37].
6. *Only following administration of an* ***injected / intranasal vaccine*** *and this does not apply to an orally administered vaccine*
7. *In infants (< 12 months of age) a single non-forceful episode of* ***vomiting*** *(or spilling/reflux) may occur in the context of a painful injection and this should not be regarded as a major criteria. In addition, a single episode of diarrhoea in this age group should not be regarded as a major criterion.*
8. ***Mast Cell Tryptase levels -*** *Greater than upper normal limit for laboratory doing test or > (1.2 X baseline mast cell tryptase) + 2 ng/L [38]. If feasible a second post-event level should be measured and shown to be within the normal range*
9. ***Atypically anaphylaxis*** *may present as only sudden hypotension or respiratory tract obstruction (wheeze/stridor). These cases do fulfil alternate case definitions for anaphylaxis (WAO and NIAID), however this is in the context of exposure to a known or highly probable allergen for a particular patient. Such cases should have an allergy/causality review and after review may be classified as vaccine anaphylaxis.*
10. ***If two or more symptoms and/or signs present in the same system****, count system only once. Examples: urticaria and angioedema count as only one major skin, wheeze and tongue swelling count as only one major respiratory, hypotension and loss of consciousness count as only one cardiovascular, and vomiting and diarrhoea count as only one gastrointestinal.*
11. ***MAJOR and/or MINOR criteria must be from different systems*** *– count system only once: i.e., one respiratory major and one respiratory minor do not fulfil this criterion.*
12. ***Level 4*** *may or may not be anaphylaxis but the information available is not adequate to meet level 1, 2 or 3 of certainty.. The response should be to request additional details (if possible which may enable meeting the case definition. AEFI reports may often be incomplete*
13. ***Level 5 (Not a case of anaphylaxis) -*** *Sufficient information provided for review and the case is determined not to meet case definition at any level of certainty (1–3) and an alternate diagnosis / definition is evident. Such examples, may include clear presentations of other cardiorespiratory events such as myocardial infarction, pulmonary embolism or stress related events (such as vaso-vagal syncope), vocal cord dysfunction or skin manifestations (urticaria) without symptoms or signs of anaphylaxis. Cases that failed to meet the rapid progression criteria would be included here.*

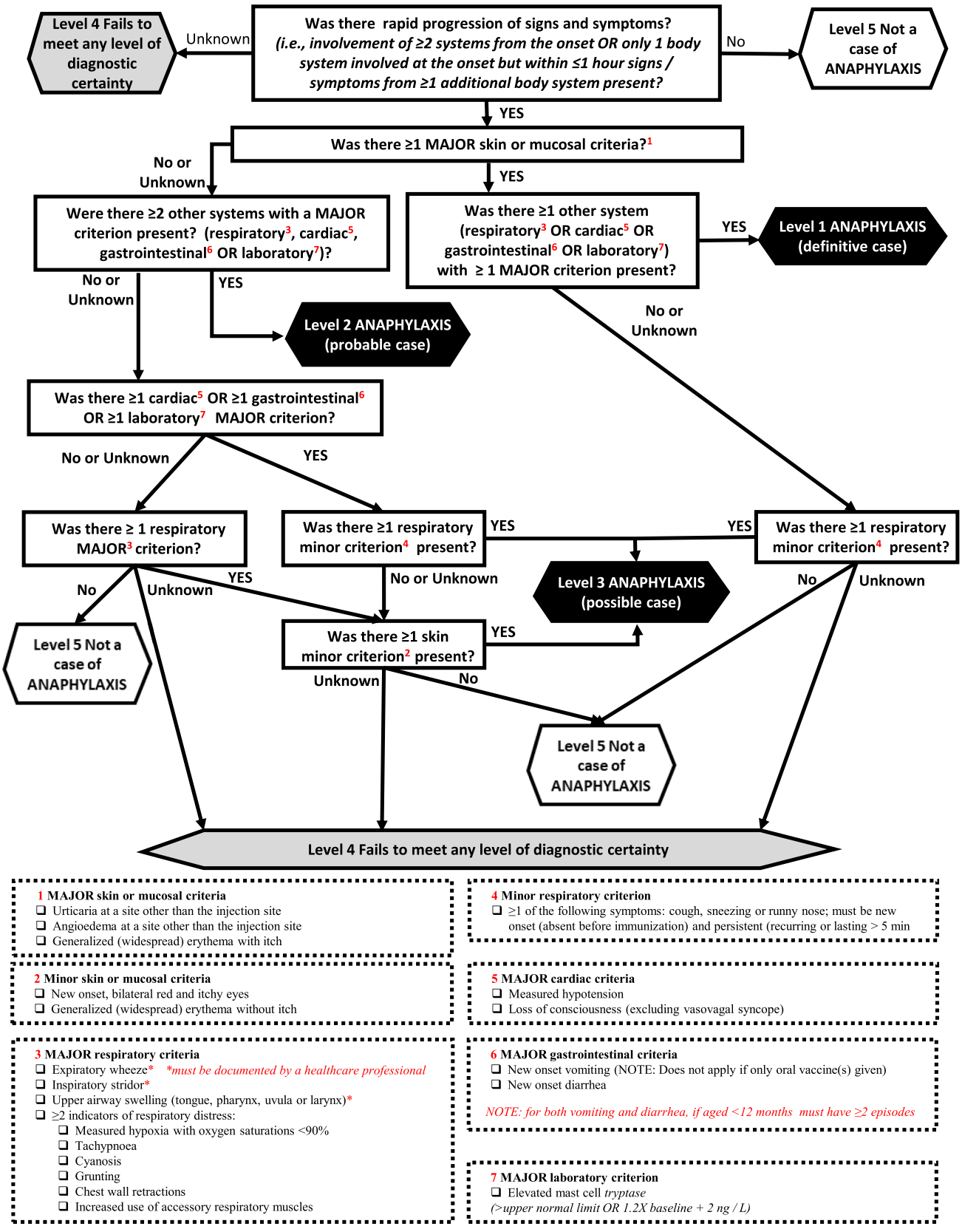

Fig. 1. The Brighton Collaboration anaphylaxis case definition V2 algorithm.

before or after the event [39]. An elevated MCT level may occur in a number of non-anaphylactic conditions (such as hematological malignancy, chronic kidney disease and familial hyper-tryptasaemia), and thus, a second sample taken non-proximate to the event to demonstrate a return to normal of the MCT is indicated (if feasible) [40].

Table 2
Differences between V1 and V2 Brighton Collaboration case definition for anaphylaxis.

General: For all levels of diagnostic certainty			
	BC-V1 **Anaphylaxis is a clinical syndrome characterized by** • sudden onset AND • rapid progression of signs and symptoms AND • involving multiple (≥2) organ systems, as follows	**BC-V2** **Anaphylaxis presents acutely and leads to a marked change in an individual's previous stable condition and is characterized by the following:** **Rapid progression of symptoms and signs** which typically affects multiple body systems (skin/mucosa / respiratory / cardiovascular / gastrointestinal) at the same time or sequentially but occurring over a short period of time (within 1 h of onset of the first symptoms or signs).	**Comments** *Sudden onset* has been removed in BC-V2 and a clearer description of *rapid progression* has been provided and multi-system involvement is defined more clearly**.** Both V1 and V2 require rapid progression for all levels of diagnostic certainty.
Major or minor signs of symptoms involving the following systems:			
Skin and/or mucosal criteria			
	BC-V1	**BC-V2**	**Comments**
Major	Generalized urticaria (hives) or Generalized erythema Angioedema, localized or generalized Generalized pruritus with skin rash	**Urticaria (hives)** o at a location other the vaccine administration site**Angioedema of the skin (swelling)** o at a location other the vaccine administration site**Generalised (widespread) erythema (redness)** of the skin **with itch**	Removal of *generalised* as a descriptor for urticaria and angioedema. Urticarial and angioedema at injection site are excluded.
Minor	Generalized pruritus without skin rash Generalized prickle sensation Localized injection site urticarial Red and itchy eyes	**Red and/or itchy eyes** o bilateral and new onset**Generalised (widespread) erythema (redness)** of the skin without itch	Removal of *generalized pruritus without skin rash, generalized prickle sensation, localized injection site urticarial*, as minor criteria. Inclusion of *new onset* for red and/or itchy eyes.
Respiratory			
	BC-V1	**BC-V2**	**Comments**
Major	Bilateral wheeze (bronchospasm) StridorUpper airway swelling (lip, tongue, throat, uvula, or larynx) Respiratory distress—2 or more of the following: o tachypnoea o increased use of accessory respiratory muscles (sterno-cleidomastoid, intercostal) o recession o cyanosis o grunting	**Expiratory wheeze** o documented by healthcare professional which could be with/out stethoscope**Inspiratory stridor** o documented by healthcare professional which could be with/out stethoscope**Angioedema of the mucosa of the upper airway - swelling of the tongue, pharynx, uvula and/or larynx** o unequivocally documented by a healthcare professional - this does ***not*** include isolated lip swelling.≥ **2 indicators of respiratory distress**: o tachypnoea o cyanosis o measured hypoxia with oxygen saturations < 90% o grunting o chest wall retractions o increased use of accessory respiratory muscles	Inclusion of wheeze, stridor, upper airway swelling documented, by a healthcare professional. Removal of lip swelling as a sign of upper airway angioedema. Inclusion of measured hypoxia with oxygen saturations < 90%.
Minor	Persistent dry cough Hoarse voice Difficulty breathing without wheeze or stridor Sensation of throat closure Sneezing, rhinorrhea	**Cough and/or sneezing and/or runny nose** o new onset and persistent	The minor symptoms (reported difficulty breathing, sensation of throat closure) and signs (hoarse voice) have been removed.Minor respiratory symptoms (cough and/ or sneezing and/or runny nose) have been retained but it has been specified this should be *new onset and persistent*
Cardiovascular			
	BC-V1	**BC-V2**	**Comments**
Major	Measured hypotension Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: o tachycardia o capillary refill time > 3 s o reduced central pulse volume o decreased level of consciousness or o loss of consciousness	**Measured hypotension** **Loss of consciousness** o other than the brief, self-resolving loss of consciousness typical of a vasovagal reaction	The clinical features of uncompensated shock (other than hypotension or loss of consciousness) have been removed as major criteria, to simplify the criteria. Loss of consciousness has been inserted as a major criterion of hypotension. To differentiate vaso-vagal syncope from anaphylaxis the caveat '*other than the brief, self-resolving loss of consciousness typical of a vasovagal reaction*' has been inserted.
Minor	Reduced peripheral circulation as indicated by the combination of at least 2 of the following: o tachycardia o a capillary refill time of > 3 s without hypotension o a decreased level of consciousness	**None**	All minor cardiovascular criteria have been removed.

(*continued on next page*)

Table 2 (*continued*)

	Gastrointestinal		
	BC-V1	**BC-V2**	**Comments**
Major	None	New onset **vomiting** New onset **diarrhea**	Diarrhea and vomiting have been included as major criteria
Minor	Diarrhea Abdominal pain Nausea Vomiting	**None**	Minor gastrointestinal criteria have been removed
	Laboratory		
	BC-V1	**BC-V2**	**Comments**
Major	None	Elevated mast cell tryptase	Mast cell tryptase has been included as a major criterion and defined as either: o upper normal limit for laboratory doing test; or o (1.2 × baseline tryptase) + 2 ng/L
Minor	Elevated mast cell tryptase	None	
Level of certainty	**Logic to level of certainty for anaphylaxis**		
Levels 1, 2, 3	Must meet the criteria for **rapid progression**		
Use the pattern of MAJOR and MINOR criteria met for skin, respiratory, cardiac and gastrointestinal systems and laboratory result from the table above to determine the highest level of diagnostic certainty (with level 1 > level 2 > level 3)			
	BC-V1	**BC-V2**	
Level 1	≥1 major dermatological **AND** ≥1 major cardiovascular **AND/OR** ≥ 1 major respiratory criterion	MAJOR skin/mucosal AND ≥ 1 MAJOR system involvement including respiratory and/or cardiac and/or gastrointestinal and/or laboratory	
Level 2	≥1 major cardiovascular AND ≥ 1 major respiratory criterion **OR** ≥1 major cardiovascular OR respiratory criterion **AND** ≥1 minor criterion involving ≥ 1 different system (other than cardiovascular or respiratory systems) **OR** (≥1 major dermatologic) **AND** (≥1 minor cardiovascular **AND/OR** minor respiratory criterion)	≥2 MAJOR system involvement including respiratory and/or cardiac and/or gastrointestinal and/or laboratory – excludes skin/mucosal involvement and must be from different systems	
Level 3	≥1 minor cardiovascular OR respiratory criterion AND ≥1 minor criterion from each of ≥ 2 different systems/categories	≥ 1 MAJOR system involvement including respiratory, cardiac, gastrointestinal or laboratory **AND** ≥ 1 MINOR system involvement from skin/mucosal or respiratory and must be from different systems.	
Level 4	Reported anaphylaxis with insufficient evidence to meet the case definition	Insufficient information provided for review to meet any level of certainty. This may include reports which document anaphylaxis without a description of any signs and/or symptoms.	
Level 5	Not stated	Sufficient information provided for review and determined not to meet case definition at any level of certainty.	

4.2.7. Levels of certainty

A level of certainty (LOC), 1–3, can only be reached if at least one major criterion is present for BC-V2, unlike BC-V1 where a LOC 2 or 3 could be reached with minor criteria only, provided they were from different systems. The LOC 1 criteria remain unchanged for BC-V2 with the exception of including major gastrointestinal signs and laboratory criteria (i.e., raised MCT, which was previously a minor criterion). In BC-V2, the LOC 2 criteria have been simplified and now include only major criteria, which must be from at least two different organ systems, excluding a major dermatological criterion. If there is a major dermatological criterion and a major criterion from another system, this will meet a LOC 1. LOC 3 can be met by having only one major criterion from any of the four systems or raised MCT and one minor criterion from a different organ system (minor criteria defined for skin and respiratory systems only).

The BC-V2 has retained LOC 4 and 5 and these two classifications are met when the case definition for anaphylaxis (Level 1–3) have not been met. LOC 4, as noted in BC-V1, refers to a case of 'reported anaphylaxis with insufficient evidence to meet the case definition'. This may include reports which document anaphylaxis without a description of any signs or symptoms. LOC 5 is met when the AEFI is definitely 'not a case of anaphylaxis'. This is to be applied when **s**ufficient information has been provided for review and an alternate diagnosis is clearly present. LOC 5 would also apply to; events that do not meet the rapid progression criteria; non-allergic events such as myocardial infarction, pulmonary embolism or stress-related events (including vasovagal syncope or VCD/ILO); and possible allergic events that do not meet the anaphylaxis diagnostic criteria, such as urticaria without airway and or cardiovascular involvement.

5. Discussion

The BC has played an important global role in vaccine pharmacovigilance, by providing tools and resources for the collection and analysis of vaccine safety information including standardised case definitions for AEFIs [41]. These case definitions can also be applied to situations where there is no exposure to vaccine, such as deter-

mination of background incidence, for control groups in studies designed to assess causality and for non-vaccine safety studies, such as assessing presentations of anaphylaxis in a hospital emergency department [41].

The mass global COVID-19 vaccination campaigns rapidly generated a number of vaccine safety signals, which required a public health response. Reports of suspected anaphylaxis after the Pfizer BNT162b2 SARS-CoV-2 mRNA vaccine occurred within days of the start of the vaccination campaign in the UK and USA in December 2019. These reports of anaphylaxis received extensive coverage in the press and social media following communications from governmental regulatory authorities [3,42]. These and subsequent similar events focused attention on the specific criteria used in the BC for anaphylaxis, how case definitions were applied to AEFI reports (often incorrectly), and how this classification was then used to calculate rates of anaphylaxis for comparison and risk assessment.

The BC-V2 has addressed the issues of defining a more specific case definition of anaphylaxis to differentiate non-allergic and allergic but non-anaphylactic events. This now aligns better with definitions used by the allergy specialist community, particularly the NIAID/FAAN and WAO 2020 clinical criteria. However, regardless of the case definition used, incomplete documentation of symptoms and signs of an AEFI, particularly in passive reporting systems, remains a major barrier to assignment, irrespective of the case definition used. This needs to be addressed through education of vaccine providers, to ensure comprehensive documentation of the symptoms and signs that may indicate anaphylaxis [43]. In particular, with the need to administer booster doses, often using the same vaccine, it is important that case assignment of anaphylaxis and other AEFIs is improved so that individuals are not contraindicated from receiving subsequent doses based on erroneous classification of initial AEFI. Urticaria with or without angioedema, post-vaccination and usually delayed with no other symptoms, can occur due to non-reproducible mast cell degranulation and does not preclude repeat exposure to the same vaccine. It is not unexpected that different case definitions applied to the same AEFI reports will result in a different classification; however, without a diagnostic 'gold standard' it is difficult to judge the accuracy of individual case definitions. Ideally, the alternative standard that should be applied to an individual AEFI report of anaphylaxis is the assessment of a clinical review, preferably by at least two independent allergists, when possible, though globally this is not always feasible. Consistency between different reviewers when the case definition is applied to the same reports is arguably more important for a surveillance case definition. In one study of anaphylaxis presentations to an emergency department, the BC-V1 was shown to be superior to the NIAID/FAAN criteria in terms of inter-rater variability between reviewers (kappa = 0.771 vs 0.312, respectively) [43,44].When feasible, reports from individuals who have experienced an adverse event that is classified as anaphylaxis should be reviewed by a specialist to confirm the diagnosis and to consider re-vaccination with the same or alternate vaccine brands, if indicated, and under appropriate medical supervision.

6. Future challenges and suggested research

Although the WG undertook an assessment of consistency in applying the BC-V2 to a set of cases, further evaluation in a global context is required. The BC-V2 case definitions should be used for AEFI surveillance. Existing and novel methods of education, including e-training and e-tools, should be developed to inform vaccine providers what symptoms and signs should be recorded after an immediate adverse event to help differentiate anaphylaxis from non-anaphylaxis events. In addition, the companion guide provides further information, templates and rapid assessment tools and tables (https://zenodo.org/search?page=1&size=%2020&q=SPEAC). There should be continued evaluation of the use of anaphylaxis case definitions against individual clinical allergy assessment and diagnosis to improve the accuracy of these tools.

Supplementary material: Guidelines for data collection and analysis and companion guide

The guidelines for data collection, analysis and presentation that were published with the BC Anaphylaxis V1 (2007) still apply to BC V2. In addition, a companion guide for BC V-1 was published in 2021 and this has been updated for BC V-2 (https://zenodo.org/search?page=1&size=%2020&q=SPEAC).

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors are grateful for the support and very helpful comments provided by the Brighton Collaboration Steering Committee, as well as other experts consulted as part of the process. The authors are also grateful to Margaret Haugh for writing and editorial support.

Matthew Greenhawt reports personal fees from Aquestive, DBV Technologies, Sanofi/Regeneron, Nutricia, Novartis, Acquestive, Allergy Therapeutics, AstraZeneca, ALK-Abello, Prota, ImSci, MedLearningGroup, RMEI Medical Education; stipend for service as the senior associate editor for the Annals of Allergy, Asthma, and Immunology; and is member of the Joint Taskforce on Allergy Practice Parameters guidelines committee. Paul J Turner reports grants from UK Medical Research Council, NIHR/Imperial BRC and JM Charitable Foundation; personal fees from UK Food Standards Agency, Aimmune Therapeutics, Allergenis, Aquestive Therapeutics and Novartis.

Funding

This work was supported by the Coalition for Epidemic Preparedness Innovations (CEPI) under a service order entitled Safety Platform for Emergency vACcines (SPEAC) Project with the Brighton Collaboration, a program of the Task Force for Global Health, Decatur, GA.

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