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Diagnostic Utility of Two Case Definitions for Anaphylaxis

A Comparison Using a Retrospective Case Notes Analysis in the UK

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Abstract

Background: Anaphylaxis is a clinical diagnosis with no gold-standard test. Recent case definitions have attempted to provide objective criteria for diagnosis.
Objective: The aim of this study was to compare the diagnostic concordance of the Brighton Collaboration case definition (the 'Brighton' case definition) to the consensus case definition from the Second Symposium on the Definition and Management of Anaphylaxis (the 'Symposium' definition).
Method: The study setting was a hospital-based emergency department in the UK. We identified cases of anaphylaxis by physicians' discharge diagnoses over a 2-year period from 2005 to 2006, and used randomly selected cases of allergic reaction, asthma and urticaria as a control group. Data was extracted by clinicians (who were unaware of the content of either case definition), and the two case definitions were applied by Boolean operators in a Microsoft® Excel spreadsheet. Concordance between the case definitions was measured using Cohen's kappa (κ) statistic.
Results: We reviewed 128 sets of notes, with 47 cases of anaphylaxis. Brighton and Symposium definitions had sensitivities of 0.681 and 0.671, respectively, and specificities of 0.790 and 0.704, respectively. A discordant result was found in 36/128 cases (28.1%; $\kappa = 0.414$ [95% CI 0.253, 0.574]), which represents a moderate level of agreement between case definitions.
Conclusions: The Brighton case definition has a similar diagnostic concordance to the Symposium case definition. It does not seem to over- or underestimate cases and is sufficiently unique that the identification of an allergic trigger does not have to form part of the case definition. This will be important in the recognition of anaphylaxis resulting from the administration of drug and vaccines, where causality should be examined separately from case ascertainment.

Background

Anaphylaxis is an acute onset, potentially fatal, systemic allergic reaction. It can occur following the administration of drugs and vaccines, making case ascertainment important in pharmacovigilance. Anaphylaxis is distinguished by the involvement of the respiratory tract or cardiovascular system as part of a multisystemic hypersensitivity reaction, often with severe bronchoconstriction as a cardinal feature.[1] There is no gold-standard test and the diagnosis relies upon careful assessment of clinical symptoms and signs, with supporting evidence from the laboratory and cutaneous testing.[2]

Two groups have recently published case definitions for the diagnosis of anaphylaxis.[3,4] Both case definitions are based on expert group consensus using an international panel and are likely to be widely applicable. They also require a rapid onset of symptoms involving more than one organ system. However, both of these models are defined very differently and will capture a different set of cases (tables I, II and III). The Second Symposium on the Definition and Management of Anaphylaxis case definition (described in this study as the 'Symposium' case definition) was designed to clarify clinical diagnosis and provide a standard for epidemiological and pathophysiological research.[3] In contrast, the Brighton Collaboration case definition (described in this study as the 'Brighton' case definition) was designed for ascertaining cases of anaphylaxis occurring as an adverse event following immunization.[4]

Immediate exposure to an allergen prior to the onset of symptoms often alerts the clinician to the diagnosis of anaphylaxis. The Brighton case definition (tables II and III) does not require a causal allergen to define a case. Removal of allergen exposure from the case definition may considerably affect the diagnostic ability of the test. Yet this is important for application to drug and vaccine safety, where the adverse event should be defined separately from any assessment of causality.[5] The Symposium case definition requires a likely or known trigger for two of its three diagnostic pathways but not for the case definition described in pathway 1 (table I). Both of these clinical case definitions have not yet been formally validated. The aim of this study was to compare the diagnostic ability of Brighton and Symposium case definitions by a retrospective case notes review.

Table I. Case definition for the Second Symposium on the Definition and Management of Anaphylaxis[3]

The Symposium case is fulfilled if any one of the following three pathways of criteria is met.
Pathway 1
Acute onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue or both (e.g. generalized hives, pruritus or flushing, swollen lips, tongue, uvula) and at least one of the following: • respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxaemia) • reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
Pathway 2
Two or more of the following, which occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours): • involvement of the skin-mucosal tissue (e.g. generalized hives, itch-flush, swollen lips, tongue, uvula) • respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia) • reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence) • persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
Pathway 3
Reduced BP after exposure to *known allergen for that patient* (minutes to several hours): • infants and children: low systolic BP (age specific) or >30% decrease in systolic BP • adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline

Table II. Case definition for the Brighton Collaboration definition for anaphylaxis as an adverse event following immunization[4]

The sudden onset and rapid progression of symptoms involving more than two organ systems as follows:[a]
Level 1 of diagnostic certainty
≥1 major dermatological AND >1 major cardiovascular or major respiratory symptom
Level 2 of diagnostic certainty
≥1 major cardiovascular AND ≥1 major respiratory criterion OR ≥1 major cardiovascular OR respiratory criterion AND ≥1 minor criterion involving ≥1 different system/category (other than cardiovascular or respiratory systems) OR ≥1 major dermatological AND ≥1 minor cardiovascular AND/OR respiratory criterion
Level 3 of diagnostic certainty
≥1 minor cardiovascular OR respiratory criterion AND ≥1 minor criterion from each of two or more different systems
a Major and minor criteria are outlined in table III.

Methods

We performed a case notes review of all cases of anaphylaxis attending the emergency departments of the Bristol Royal Infirmary and Bristol Royal Hospital for Children, Bristol, UK. We searched discharge diagnostic text from all admissions over a 2-year period from 2005 to 2006. This clinical categorization was used in the absence of a 'gold standard'. Cases of anaphylaxis were defined as those with a discharge diagnosis of 'anaphylaxis', 'anaphylactoid' and 'anaphylactic reaction'. We compared these cases to a randomly selected control group with a discharge diagnosis of 'allergic reaction', 'allergy', 'allergic', 'allergic rash', 'urticaria', 'asthma', 'exacerbation of asthma' and 'asthma attack'. There were a large number of cases presenting with asthma and a sample was selected using random number tables generated through uniform distributions in Minitab software (Version 15.0, Minitab Inc., State College, PA, USA). Non-identifiable demographics and clinical information relating to a diagnosis of anaphylaxis were recorded using a reporting website (Bristol Online Surveys, University of Bristol, Bristol, UK) and downloaded for analysis using Microsoft® Excel and Minitab software. Each symptom was recorded as present, absent or not recorded. Age-related normal values for heart and respiratory rates and blood pressure were taken from the Advanced Life Support Group, Manchester, UK.[6] Cases were excluded if notes were missing or there was miscoding of discharge diagnosis, e.g. trauma. A further random sample of approximately one-fifth of the cases was entered by a second clinician to establish the reproducibility of data entry. A diagnosis of anaphylaxis was then made according to both the Brighton and Symposium case definitions.[3,4] Case definitions were applied by combining diagnostic symptoms and signs using Boolean operators in an Excel spreadsheet. The

Table III. Symptoms and signs contributing to the Brighton Collaboration case definition[4]

Organ system	Major	Minor
The Brighton Collaboration diagnostic criteria are as follows:		
Dermatological and mucosal	Generalized urticaria (hives) Erythema Angioedema	Generalized pruritus without skin rash Localized injection site urticaria Red and itchy eyes Sneezing Rhinorroea
Cardiovascular	Hypotension based on a measurement Clinical diagnosis of uncompensated shock, as indicated by the combination of at least three of the following: • tachycardia • capillary refill time >3 seconds • reduced central pulse volume • decreased level or loss of consciousness	Reduced peripheral circulation, as indicated by the combination of at least two of the following: • tachycardia • capillary refill time of >3 seconds without hypotension • decreased level of consciousness
Respiratory	Bronchospasm/bilateral wheeze Stridor Obvious upper airway swelling (tongue, throat, uvula or larynx) Respiratory distress by two or more of the following: • tachypnoea • excessive use of accessory muscles • recession • cyanosis • grunting	Persistent dry cough Hoarse voice Difficulty breathing without wheeze or stridor Sensation of throat closure
Abdominal	None	Diarrhoea Abdominal pain Nausea Vomiting
Laboratory	None	Serum mast cell tryptase above normal limit

Table IV. Clinical detail of cases and controls

Parameter	Anaphylaxis	Allergic reaction	Asthma	Urticaria
Discharge diagnoses (n)	75	34	34	34
Excluded cases (n)	2	7	0	4
Missing notes (n)	26	0	6	4
No. of patients	**47**	**27**	**28**	**26**
Male [n (%)]	27 (57.4)	14 (51.8)	16 (57.1)	10 (38.5)
Age in years [median (range)]	35 (0.9–80)	25 (0.5–57)	7.5 (2–63)	3 (0.3–69)
Past medical history (n)				
Anaphylaxis	17	4	0	0
Food allergy	16	6	4	1
Eczema	4	1	8	2
Urticaria	1	3	1	1
Asthma	16	8	26	2
Rhinitis	4	3	6	1
Likely cause of current reaction (n)				
Previous reaction to this allergen	10	2	0	1
Nuts and seeds	10	3	4	0
Other food	4	2	0	1
Insect venom	4	0	0	2
Drugs	9	1	0	0
Other	5	9	2	5
Upper respiratory tract infection	0	0	6	2
Not identified	15	12	16	16
Onset[a]				
Within 5 minutes	13/24	7/10	1/1	0/3
Within 2 hours	23/24	10/10	1/1	2/3
Symptoms worse after 2 hours	4/15	7/20	13/22	9/21
Treatment [n (%)]				
Intramuscular adrenaline (epinephrine)	26 (55.5)	5 (18.5)	0	0
Nebulized adrenaline	3 (6.4)	0	0	0
Nebulized salbutamol	12 (25.5)	1 (3.7)	16 (57.1)	0
Intravenous fluid bolus	10 (21.3)	0	1 (3.6)	0
Intravenous chlorphenamine	32 (68.1)	7 (25.9)	0	0
Oral chlorphenamine	9 (19.2)	18 (66.7)	0	18 (69.2)
Intravenous corticosteroids	33 (70.2)	8 (29.6)	2 (7.1)	0
Oral corticosteroids	7 (14.9)	7 (25.9)	9 (32.1)	4 (15.4)
Admission to hospital	40 (88.9)	12 (52.2)	7 (28.0)	0

a Onset denominator is the number of recorded responses.

presence or absence of symptoms was the only point at which clinical reasoning was required, as the criteria for meeting the case definitions were then decided using spreadsheet formulae. Coding clinicians (SD, OJ, RF, HM) were trained in data entry but were not aware of how the clinical presentation would impact upon case ascertainment. Specificity and sensitivity were calculated with positive and negative likelihood ratios (LRs) for each definition. Cohen's kappa (κ) was used as a measure of inter-rater agreement between case definitions. The relevance of the κ statistic was applied using a standard interpretation.[7] Ninety-five percent confidence intervals for proportions were calculated according to the efficient-score method.[8] This study did not use patient

identifiable information, and the Frenchay Research Ethics Committee, Bristol, UK, approved the study.

Results

We reviewed 128 sets of notes, of which 47 were cases of anaphylaxis, 27 were allergic reactions, 28 were asthma and 26 were urticaria. Patient demographics, clinical details and treatments are outlined in table IV. Thirty-six percent (17/47) of the subjects with a discharge diagnosis of anaphylaxis had a prior history of anaphylaxis and 34% (16/47) had known food allergy. Fifty-five percent (26/47) of this group received intramuscular adrenaline (epinephrine) and 21% (10/47) received intravenous fluid boluses. Eighteen percent (5/27) of cases of allergic reaction were administered intramuscular adrenaline either at home or in hospital, indicating that they might have been miscoded cases of anaphylaxis.

The diagnostic ability of the case definitions is outlined in table V in comparison with our 'gold standard' of physician diagnosis. No cases in this sample met the Brighton case definition level 3 diagnostic certainty, although all cases meeting level 1 and 2 also met level 3 criteria. No cases met the case definition for the Symposium case definition pathway 3. The specificity, sensitivity and positive and negative LRs were calculated for the case definitions; these are shown in table VI and are compared visually by receiver operator characteristic curve (figure 1).

A concordant result was found in 92/128 cases (71.9%) yielding a 'moderate' level of agreement between case definitions, expressed as $\kappa = 0.414$ (95% CI 0.253, 0.574). Of the 49 cases that met the Brighton definition, 16 cases met Brighton criteria alone (32.6%). Similarly, 20/53 (37.7%) cases met the Symposium definition alone. The 36/128 (28.1%) discordant cases were spread throughout each of the four diagnostic groups: 19/47 cases of anaphylaxis (52.8% of discordant cases), 6/27 (16.7%) allergic reactions, 7/28 (19.4%) cases of asthma and 4/26 (11.1%) cases of urticaria. A known or likely allergic trigger was present in all of the discordant Symposium cases compared to 4/16 Brighton discordant cases. The presence of an allergic trigger decreased concordance between case definitions (odds ratio 0.385; 95% CI 0.172, 0.861). No other symptoms, signs or treatments, including the administration of adrenaline, affected the concordance between definitions.

We recalculated the diagnostic ability of the Symposium definition using pathway 1 (no trigger required) as the sole diagnostic criterion, where the sensitivity was 0.404 (95% CI 0.276, 0.547), specificity 0.901 (95% CI 0.817, 0.949), positive LR 4.093 (95% CI 1.946, 8.611) and negative LR 0.661 (95% CI 0.517, 0.846). When compared with all three Brighton case definition levels, a concordant result was found in 100/128 cases with a 'moderate' level of agreement between definitions as $\kappa = 0.494$ (95% CI 0.328, 0.660).

Reproducibility of Results

We reviewed the reproducibility of coding and data entry. A random sample of 22 sets of notes was chosen for second entry by a second member of the research team. Case notes were independently

Table V. Frequency of cases diagnosed in the sample [n (%)]

Case definition	Anaphylaxis (n = 47)	Allergic reaction (n = 27)	Asthma (n = 28)	Urticaria (n = 26)
Brighton	**32 (68.1)**	**12 (44.4)**	**4 (14.3)**	**1 (3.8)**
Level 1 diagnostic certainty	24 (5.1)	10 (37.0)		1 (3.8)
Level 2 diagnostic certainty	8 (17.0)	2 (7.4)	4 (14.3)	
Level 3 diagnostic certainty	0	0	0	0
Symposium	**29 (61.7)**	**14 (51.9)**	**5 (17.9)**	**5 (19.2)**
Pathway 1	19 (40.4)	6 (22.2)	1 (3.6)	1 (3.8)
Pathway 2	10 (21.3)	8 (29.6)	4 (14.3)	4 (15.4)
Pathway 3	0	0	0	0

Table VI. Diagnostic concordance (and 95% CI) of the Brighton and Symposium case definitions

Parameter	Brighton	Symposium
Sensitivity	0.681 (0.527, 0.805)	0.671 (0.464, 0.751)
Specificity	0.790 (0.683, 0.870)	0.704 (0.590, 0.797)
Positive LR	3.244 (2.036, 5.168)	2.262 (1.503, 3.405)
Negative LR	0.404 (0.262, 0.622)	0.526 (0.358, 0.774)

LR = likelihood ratio.

scrutinized and entered using the same data collection method as used in primary data entry. The Brighton case definition had 'substantial' agreement between first and second data entry with $\kappa = 0.771$ (95% CI 0.470, 1.000), in contrast to the Symposium definition where $\kappa = 0.312$ (95% CI 0, 0.755) yielding a 'fair' level of agreement between entries.

Some of the cases of allergic reaction may have been miscoded cases of anaphylaxis (five had received intramuscular adrenaline). We therefore repeated the analysis excluding subjects with allergic reactions. Under these circumstances, Brighton had a sensitivity of 0.681 (95% CI 0.538, 0.796), specificity of 0.907 (95% CI 0.801, 0.956), positive LR of 7.353 (95% CI 3.12, 17.34) and negative LR of 0.352 (95% CI 0.230, 0.539). This compared to the Symposium pathway 1, which showed a sensitivity of 0.404 (95% CI 0.273, 0.547), specificity of 0.963 (95% CI 0.875, 0.990), positive LR of 10.91 (95% CI 2.68, 44.42) and negative LR of 0.619 (95% CI 0.486, 0.787). There was a 'moderate' level of agreement between these case definitions with $\kappa = 0.484$ (95% CI 0.309, 0.658).

Discussion

This is the first study to assess the diagnostic concordance of the Brighton and Symposium case definitions for anaphylaxis. Our results show that the Brighton case definition is at least as accurate as that of the Symposium. The Brighton symptoms of anaphylaxis are accurate enough to secure the diagnosis without reference to the cause of the event. This will be important for use in the surveillance of the safety of drugs and vaccines where causality should be examined separately from the case definition. The Symposium pathway 1, which also does not require a cause, compared well to Brighton with a moderate level of agreement between definitions, and was more specific but less sensitive than Brighton. The inclusion of an allergic trigger contributed to the majority of observed discordance between the definitions. Cases identified with the Symposium case definition may be overestimated by the presence of an allergen, but without a gold-standard test, it is impossible to say which definition is the more accurate.

Studies of anaphylaxis are hampered by the lack of a gold standard.[9-11] We used physicians' discharge diagnosis as the gold standard for this study. In our centre, discharge diagnosis does not bear any financial implications for patients or insurance companies, and is used to summarize clinical information for primary-care physicians. Our comparison of different case definitions has recently been suggested as a possible solution in the absence of a gold standard.[12] Others have used an 'alloyed gold standard' of consensus diagnosis by a panel of clinicians.[11]

It is probable that some cases of anaphylaxis were miscoded as an allergic reaction. In our study, 18.5% of allergic reactions received intramuscular adrenaline, which may well have modulated an anaphylactic reaction. Anaphylaxis has

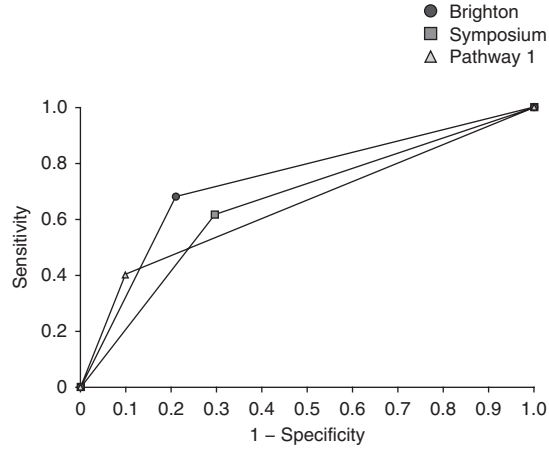

Fig. 1. Receiver operator characteristic (ROC) curve comparing anaphylaxis case definitions. A ROC curve summarizing the diagnostic concordance of the Brighton case definition, Symposium case definition and pathway 1. Pathway 1 refers to the first diagnostic pathway of the Symposium definition and does not require a causal trigger.

been shown to be under diagnosed in emergency department records, reflecting confusion over its classification amongst physicians.[12,13] Specificity improved for both Brighton and Symposium definitions on removal of the allergic reaction group from the analysis, as both definitions identified cases in this group. The interpretation of our results is unchanged by removal of allergic reactions from the analysis, which suggests that misdiagnosis and the lack of a predefined gold standard are non-contributory to the findings of our study. However, the absence of predefined criteria for the gold standard makes it impossible to conclude that one definition is better than the other.

There are several other methodological issues in this study. Firstly, the retrospective interpretation of medical notes requires clinical judgment during data extraction, and it was important to assess the reproducibility of these methods, as case ascertainment was automated following this initial step. We have shown that, unlike the Symposium case definition, Brighton retained substantial reproducibility with second data entry. This is important for its use in the passive reporting systems used in postmarketing surveillance of drugs and vaccines, where clinical data is always retrospective and frequently incomplete. Secondly, there were no cases that met Brighton level 3 or Symposium pathway 3 criteria. Brighton level 3 diagnostic certainty is suggested to be the most sensitive Brighton definition. In our study, it did not add to case ascertainment, as all cases that met its criteria also met the level 2 definition. Its relevance in the case definition is yet to be established and it may be too sensitive to be of value. The Symposium case definition pathway 3 relates to hypotension from a known allergen and did not identify any cases in this emergency department-based dataset. This pathway is more suited to identifying cases of anaphylaxis to radiological contrast media or anaesthetic agents where hypotension is often prominent.[14] Thirdly, there were more missing notes in the anaphylaxis group than for other diagnoses. This is probably because there had been a recent departmental audit on anaphylaxis and, as a consequence, many of the notes had been removed from medical records. We do not think that this would have unduly biased our results.

This study considered unselected cases from an emergency department, where only 9 (19%) cases of anaphylaxis were related to drugs. Further studies using cases of anaphylaxis to drugs and vaccines will confirm the utility of these case definitions in pharmacovigilance. Any modification of these case definitions should consider the impact that any changes may have on their diagnostic ability.

Conclusion

In summary, in a test sample of real cases of anaphylaxis presenting to an emergency department, Symposium and Brighton definitions have similar diagnostic concordance. Brighton is sufficiently unique that an allergic trigger does not have to form part of the case definition. This will be important for use in safety reporting of anaphylaxis relating to drugs and vaccines where causality should be examined separately from case ascertainment.

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