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The diagnostic criteria of pityriasis rosea and Gianotti-Crosti syndrome – a protocol to establish diagnostic criteria of skin diseases

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ABSTRACT We established and validated diagnostic criteria for pityriasis rosea and Gianotti-Crosti syndrome. In this paper, we compare and contrast both diagnostic criteria to formulate a protocol in establishing diagnostic criteria for other dermatological diseases.
The diagnostic criteria are similar in employing clear dividing lines and conjunctions ('and/or') to assure high reliability. Both sets of criteria should be applicable for all ethnic groups. Spontaneous remission is not included, so diagnosis is not delayed while waiting for disease remission. Laboratory investigations are not enlisted, so that the criteria can be used in medical care systems in different parts of the world.
The diagnostic criteria are different in that pathognomonic clinical manifestations exist for pityriasis rosea, such as the herald patch and the orientation of lesions along the lines of skin cleavages. These features, however, score low for sensitivity. These specific manifestations are not seen in Gianotti-Crosti syndrome. Such differences led to different categorisation of clinical features. Atypical variants are more common for pityriasis rosea. The diagnostic criteria for pityriasis rosea therefore do not include a list of differential diagnoses, while diagnostic criteria for Gianotti-Crosti syndrome do.
Using this comparison, we constructed a protocol to establish diagnostic criteria for other skin diseases. We advocate the need to justify the establishment of diagnostic criteria, that multiple diagnostic criteria for the same disease should be avoided, that diagnostic criteria should be compatible with the disease classification if applicable, and that the scope should be well-delineated with regard to clinical variants. We outline the need for validation studies to assess the criteria-related validity, test-retest intra-clinician reliability, and inter-clinician reliability.
We emphasise that the establishment of diagnostic criteria should not be a generic process. We also highlight limitations of diagnostic criteria, and emphasise that no diagnostic criteria can replace the bedside experience of clinicians.

KEYWORDS acyclovir, azithromycin, hepatitis B virus, human herpesvirus 7, paraviral exanthems, viral exanthems

DECLARATION OF INTERESTS No conflict of interest declared

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BACKGROUND

Diagnostic criteria are frequently used in dermatology. There are many skin diseases with well-established diagnostic criteria, particularly those with an autoimmune pathogenesis and with systemic involvement. Utilising diagnostic criteria might enhance the validity, inter-rater reliability, and intra-rater reliability of diagnoses. Investigators have pointed out the need for diagnostic criteria in autoimmune vesiculobullous diseases such as bullous pemphigoid, for which atypical variants could well be more common than classical bullous eruptions.

The paraviral exanthems, a relatively new concept,[1] are a group of diseases with numerous atypical variants. We have previously proposed and validated, in different ethnic groups, sets of diagnostic criteria for pityriasis rosea (PR)[2,3] (Figures 1a and 1b) and Gianotti-Crosti Syndrome (GCS)[4,5] (Figures 2a and 2b), which are the two most common paraviral exanthems (see Tables 1 and 2, respectively).

The pros and cons of the diagnostic criteria have been assessed in detail[6] and are summarised in Table 3. In brief, most clinical studies, including clinical trials on these exanthems, adopted different inclusion criteria, and the results cannot be readily meta-analysed. This is

TABLE 1 A patient is diagnosed with pityriasis rosea if:

• On at least one occasion or clinical encounter, he/she has all the **essential clinical features** and at least one of the **optional clinical features** • On all occasions or clinical encounters related to the rash, he/she does not have any of the exclusional clinical features
The **essential clinical features** are: • Discrete circular or oval lesions • Scaling on most lesions • Peripheral collarette scaling with central clearance on at least two lesions
The **optional clinical features** are: • Truncal and proximal limb distribution, with less than 10% of lesions distal to mid-upper-arm and mid-thigh • Orientation of most lesions along skin cleavage lines • A herald patch (not necessarily the largest) appearing at least two days before eruption of other lesions, from history of the patient or from clinical observation
The **exclusional clinical features** are: • Multiple small vesicles at the centre of two or more lesions • Two or more lesions on palmar or plantar skin surfaces • Clinical or serological evidence of secondary syphilis

TABLE 2 A patient is diagnosed with Gianotti-Crosti syndrome (GCS) if:

• On at least one occasion or clinical encounter, he/she exhibits all the **positive clinical features** • On all occasions or clinical encounters related to the rash, he/she does not exhibit any of the **negative clinical features** • None of the **differential diagnoses** is considered to be more likely than GCS on clinical judgment • If lesional biopsy is performed, the findings are consistent with GCS
The **positive clinical features** are: • Monomorphous, flat-topped, pink-brown papules or papulovesicles 1–10 mm in diameter • At least three of the following four sites involved – (i) cheeks, (ii) buttocks, (iii) extensor surfaces of forearms, and (iv) extensor surfaces of legs • Being symmetrical • Lasting for at least ten days
The **negative clinical features** are: • Extensive truncal lesions • Scaly lesions
The **differential diagnoses** are: acrodermatitis enteropathica, erythema infectiosum, erythema multiforme, hand-foot-and-mouth disease, Henoch-Schönlein purpura, Kawasaki disease, lichen planus, papular urticaria, papular-purpuric gloves and socks syndrome, and scabies.

demonstrated in our Cochrane report on the treatment of PR.[7] Of the three clinical trials we ultimately included, one[8] explicitly included all subjects with classical and atypical PR, a second[9] explicitly included only patients with typical PR while excluding all patients with PR variants, and the third[10] did not mention whether patients with atypical PR were included or not.

These studies evaluated the efficacy of three different treatment modalities, rendering meta-analysis inapplicable. However, if all three studies evaluated the same treatment, meta-analysis would still be impossible owing to the three patient pools being heterogeneous. Furthermore, even if all three studies explicitly excluded all patients with atypical features, meta-analysis would still be inapplicable unless and until typical rashes and atypical rashes are well-defined.

Diagnostic criteria would serve this purpose. With validated diagnostic criteria, recruited participants would be more homogeneous, rendering systematic reviews and meta-analyses much more feasible. The power of findings from these studies would then be substantially greater.[6]

Moreover, primary care physicians have been reported to significantly underdiagnose PR. Validated diagnostic criteria might assist these medical practitioners as well as specialist trainees in dermatology when they confront patients with marginal clinical manifestations of PR, GCS, and their differential diagnoses. However, if administered improperly, diagnostic criteria can hinder the independent clinical judgement of clinicians and instil a potential overreliance on such criteria by physicians.

Since our diagnostic criteria were published, the diagnostic criteria for PR have been adopted as recruitment criteria in our clinical and laboratory-based studies[11-14] as well as in at least three clinical studies by investigators not associated with us.[15-17] The diagnostic criteria for GCS have been adopted in our virological studies.[12-14,18] Both diagnostic criteria are also depicted in major textbooks.[19-21] Further validation studies in other ethnic groups are desirable.

AIMS

Our aims in this paper were to compare and contrast the diagnostic criteria for PR and GCS to illustrate the rationale behind the establishment of these diagnostic criteria, and to formulate a protocol for the establishment of diagnostic criteria for other dermatological diseases.

SIMILARITIES

The factual comparisons of the diagnostic criteria are summarised in Table 4. We hereby discuss the most important similarities.

Clear-cut dividing lines

The dividing lines of both diagnostic criteria are clear-cut. We defined the number of occasions and the occurrence of clinical features. The latter was in the form of essential clinical features and exclusional clinical features for PR, and positive clinical features and negative clinical features for GCS. The clear-cut dividing lines

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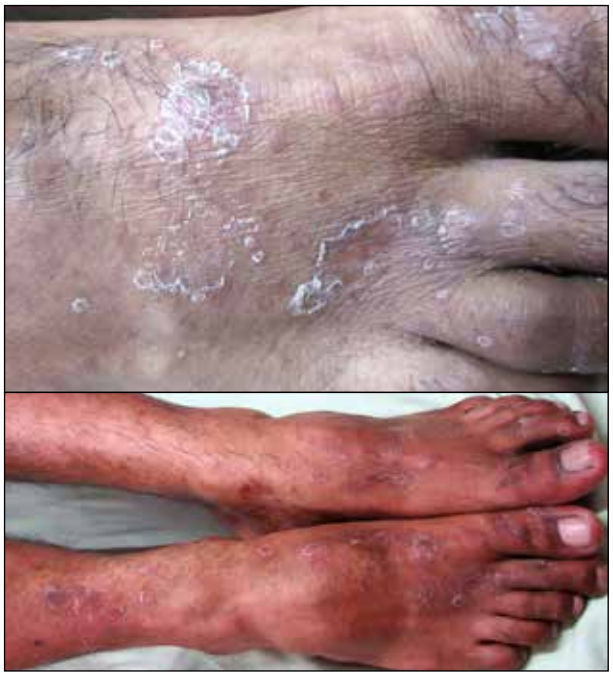

FIGURE 1 (A) Collarette scaling in a patient with pityriasis rosea. Fine fragments of scales are seen, attached only at the periphery. This reflects a tendency of peeling from the centre towards the edge. In the diagnostic criteria of pityriasis rosea, peripheral collarette scaling with central clearance on at least two lesions is an essential clinical feature. This patient fulfils this essential clinical feature. (B) Lesions on the dorsa of feet in a patient with pityriasis rosea. In the diagnostic criteria of pityriasis rosea, truncal and proximal limb distribution, with less than 10% of lesions distal to mid-upper-arm and mid-thigh is an optional clinical feature. This patient has an atypical distal distribution of lesions, and does not fulfil this optional clinical feature.

assure that a diagnosis of PR or GCS is either substantiated or refuted, therefore optimising intra- and inter-rater reliabilities.

Adopting conjunctions and disjunctions

When tallying fulfilled or unfulfilled clinical features, we incorporated conjunctions (AND/OR). These constructs, in combination with the clear-cut dividing lines mentioned in the previous section, secure high intra- and inter-rater reliabilities.

Assurance of applicability for all ethnic groups

The clinical manifestations of paraviral exanthems, and a number of other skin diseases, vary in different ethnic groups. For PR, a rosea or erythematous picture is seldom seen in dark-skinned patients. The term 'pityriasis rosea' might thus not be applicable to these patients. Dark-skinned patients have been reported to have more severe and extensive rashes, and are more likely to have face and scalp involvement.[22] For these reasons, the diagnostic criteria for PR do not include the term 'rosea', and do not describe face and scalp involvement.

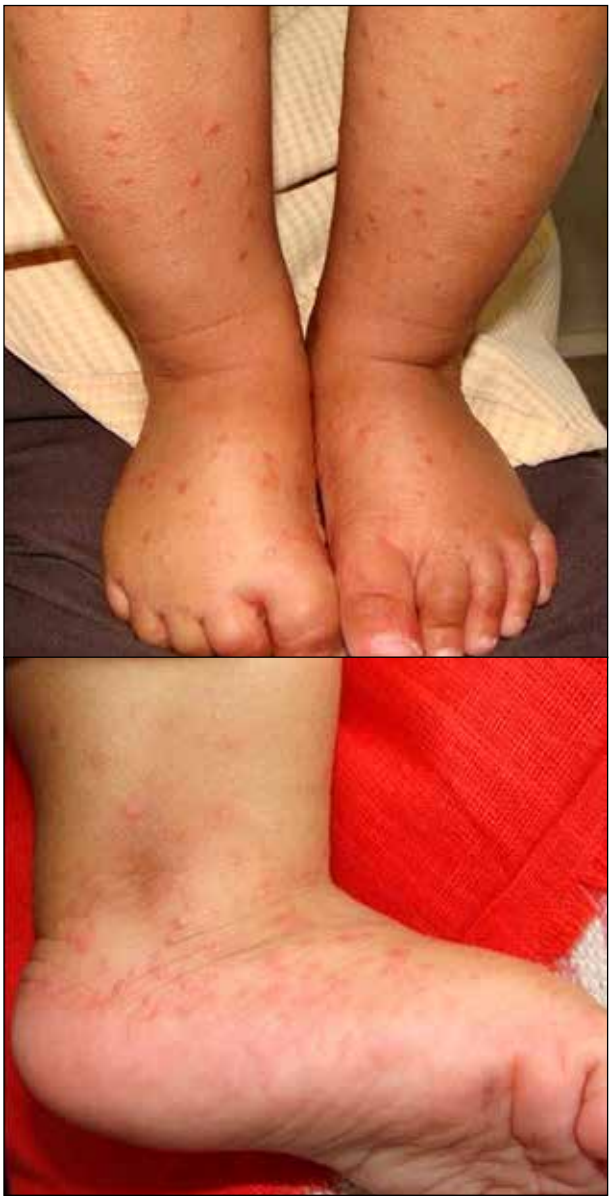

FIGURE 2 (A) Monomorphous erythematous papules on the legs and feet of a boy aged 1 year 6 months with Gianotti-Crosti syndrome. In the diagnostic criteria, monomorphous, flat-topped, pink-brown papules or papulovesicles 1–10 mm in diameter are a positive clinical feature. (B) Similar lesions on the left foot. The soles are not involved, which is typical for this disease. Another clinical positive feature is at least three of the following four sites are involved: (i) cheeks, (ii) buttocks, (iii) extensor surfaces of forearms, and (iv) extensor surfaces of legs. If similar lesions are noted on at least two other sites, this positive clinical feature would be fulfilled.

To the best of our knowledge, no difference in the clinical manifestations has yet been reported for GCS in different ethnic groups. We believe that the diagnostic criteria are applicable for all ethnic groups, pending further validation studies on children from other ethnic groups.

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TABLE 3 Advantages/disadvantages of diagnostic criteria

Advantages of diagnostic criteria

- Clear portraits of positive and negative clinical features, allowing patients to be given either a yes or a no for the diagnosis
- Particularly helpful in diseases with high occurrence or large number of atypical variants
- Particularly helpful for diseases with different clinical manifestations in different ethnic populations
- Renders high homogeneity for the diagnosed patients, thus enabling meta-analyses and systematic reviews to be performed. Such a consideration is particularly pertinent for uncommon or rare diseases, as individual investigational reports might suffer from a lack of power in the findings. The combined results can be much more powerful
- Publication bias exists, with higher chances of publication for clinical studies reporting positive findings. Diagnostic criteria can take unpublished data into account if the drafters of such criteria have access to unpublished study reports
- Of educational value for medical students, trainees, non-consultants in the specialty concerned, and paramedical professionals

Disadvantages of diagnostic criteria

- Might hinder independent clinical judgement of clinicians, with a potential for intruding on professional autonomy
- Might oversimplify clinical manifestations, instill internal incongruities, and overlap with diagnostic criteria of differential diagnoses.
- Necessitates time and human resources for validation and re-validation studies, preferably in different ethnic groups
- Necessitates time and human resources to keep criteria updated regularly to incorporate new clinical information found in investigational reports
- Might not be agreed on by all experts in the field concerned, thus leading to the possibility of multiple diagnostic criteria which would hinder the diagnoses of individual patients as well as recruitment into clinical studies and clinical trials
- Might be abused by medical administrators or health maintenance organisations to cut costs in further managing the patients

Spontaneous remission

Both PR and GCS remit spontaneously without active intervention. Spontaneous remission is a cornerstone in the retrospective diagnosis of any viral or paraviral exanthems. However, we purposely omitted spontaneous rash resolution in the diagnostic criteria, as this can only be ascertained retrospectively after the disease has run its course. Otherwise, the diagnosis cannot be made in the earliest phases of these eruptions, leading to delays in clinical photography and collecting samples from multiple body sites for polymerase chain reaction to detect viral DNA and for other investigations.

Furthermore, in our proposed classification for PR,[23] patients with a prolonged clinical course may still be diagnosed with PR retrospectively if spontaneous remission is seen later than six or 12 weeks after rash onset. For GCS, we have reported that rash duration can be as long as six months. We therefore deliberated whether to omit spontaneous rash remission in two to 12 weeks as an essential clinical feature for PR or as a positive clinical feature for GCS.

No reference to laboratory investigations

Case presentations in different institutions and in different parts of the world could necessitate different repertoires of laboratory investigations. For example, if a clinician would like to exclude dermatophyte infection in a patient suspected to have PR, they might proceed to submit lesional scrapings for potassium hydroxide smear and fungal culture. Another clinician might prefer differentiation on clinical grounds only.

There also exist different opinions on whether serological investigations to exclude secondary syphilis should be performed for all patients with a provisional diagnosis of PR. Moreover, PR can co-exist with secondary syphilis.

We therefore decided not to include mandatory investigations in the two diagnostic criteria, and leave these to the discretion of the clinician.

DIFFERENCES

Effects of historical progression on the diagnostic criteria for the exanthems

A progression in our understanding over time has had significant effects on the diagnostic criteria for both PR and GCS. For PR, the macular variety was described by Camille Melchoir Gibert in 1860, with the annular variety subsequently described by Pierre-Antoine-Earnest Bazin in 1862. Since then, the characteristic clinical features such as the herald patch (first described by Louis-Anne-Jean Brocq in 1887) and the peripheral collarette scaling configuration (first described by Alfred Blaschko in 1899) were recognised. The PR rashes as described around 1900 (such as those reported by Weiss in 1903[24]) are similar to those described by modern investigators.

To explore this issue, we searched databases and retrieved the literature over the most recent decades. As Robert Willan (1757–1812), who quoted the first few pityriasis diseases, was a medical graduate of Edinburgh, we also asked the librarians of the Royal College of Physicians of Edinburgh and Royal College of Physicians and Surgeons of Glasgow to retrieve early articles describing PR,[24] and confirmed that the diagnostic entity of PR had been quite uniform over the past century.

The course of sequential discoveries has not been so smooth for GCS. The first report of GCS by Ferdinando Gianotti in 1955[25] was treated sceptically by his colleagues. With the joint publications by Agostino Crosti and Ferdinando Gianotti in 1957, the status of GCS being a newly discovered eruption likely to be related to viral infections was firmly established. The aetiological role of hepatitis B virus (HBV) infection was widely accepted in the 1970s.

However, children with GCS not accounted for by HBV infection soon surfaced.[26] Concomitant HBV and Epstein-Barr virus infections have also been reported in a child with GCS.[27] Gianotti and Crosti were initially convinced that the clinical manifestations for GCS rashes caused by HBV infection and those caused by other viral infections could be distinguished clinically. As a result, the former would be termed Gianotti-Crosti disease, while the latter would be termed Gianotti-Crosti syndrome.

By the early 1990s, it had become clear that these two rashes could not be differentiated clinically. Some investigators also believed that GCS was a bona fide syndrome with multiple causes, and should not be termed a disease – regardless of whether an underlying infection was identifiable. Some investigators thus recommended coining 'Gianotti-Crosti syndrome' for all eruptions related or unrelated to HBV infection. This convention is still followed.

We therefore cast doubt on whether early patients with GCS in the 1950s are clinically akin to those children presenting with GCS today. To safeguard the validity of the diagnostic criteria for current and future utilisation, we considered whether to formulate positive and negative clinical features from the more recent medical literature (mainly 1996–2000) only while compiling the diagnostic criteria.

Highly specific but insensitive clinical features

Pityriasis rosea claims several manifestations which are almost pathognomonic of this rash, such as the herald patch and the orientation of individual lesions along relaxed skin tension lines. In clinical practice, if we encounter a generalised skin eruption and the patient reports a herald patch, the rash is highly likely to be PR. For another patient with lesions aligned along the skin creases, PR is also highly likely as such orientation is exemplified by only one other disease, namely Kaposi's sarcoma.

Our first study[2] substantiated that these two clinical features carried high specificities (96.6% for herald patch; 98.3% for the rash orientation) but relatively low sensitivities (27.8% for herald patch; 77.8% for the rash orientation).

These manifestations of PR could not be simply assigned as positive clinical features such as those for the diagnostic criteria of GCS. The absence of a herald patch would exclude a diagnosis of PR, which we know from the literature and our clinical experience to be untrue. To make the best effective use of these specific but insensitive manifestations, we thus created a category of optional clinical features.[2,3]

For the remaining four positive clinical features (discrete circular or oval lesions, scaling on most lesions, peripheral collarette scaling with central clearance on at least two lesions, and relatively truncal and proximal limb distribution), the first three were 100% sensitive, and were thus qualified to be essential clinical features. The sensitivity of a relatively truncal and proximal limb distribution was 83.3%. This would be incompatible with the category of essential clinical features. Relatively truncal and proximal limb distribution of lesions therefore joined the herald patch and the characteristic orientation as optional clinical features.[2,3]

For GCS, however, such highly characteristic and almost pathognomonic clinical features are not to be found. All the positive clinical features are shared by some of the differential diagnoses of GCS. We decided not to incorporate a category of optional clinical features, and enlisted positive clinical and negative clinical features instead.[4,5]

Atypical clinical manifestations

We have reviewed the numerous clinical variations of PR, in terms of atypical rash morphology, distribution of lesions, size of lesions, number of lesions, sites of lesions, and severities of symptoms.[23,28] Each of these atypical features could generate a list of differential diagnoses. Based on atypical rash morphology, we could produce separate lists of differential diagnoses for macular, vesiculo-bullous, purpuric and haemorrhagic, urticarial, and follicular PR.[23,28] Together with other atypical parameters, the number of differential diagnoses is vast. Inserting a long list of differential diagnoses would render the diagnostic criteria much less usable in practice. We therefore opted not to incorporate such a list for the diagnostic criteria of PR.[2,3] For GCS, we have also reported atypical variants;[29,30] however, the number and variability of these variants is much smaller than that seen in PR. The list of differential diagnoses is also much shorter, and we therefore included these in the diagnostic criteria of GCS.[4,5]

THE ADVANTAGES AND DISADVANTAGES OF DIAGNOSTIC CRITERIA

We summarise the advantages and disadvantages of diagnostic criteria in Table 3. A particular example of problems that could arise from the misuse of diagnostic criteria is found for another set of diagnostic criteria for

GCS,[19] which listed general signs and symptoms – malaise, low-grade fever, diarrhoea, lymphadenopathy (cervical, axillary and inguinal), hepatomegaly, splenomegaly, or both, as part of the diagnostic criteria. We agree that systemic symptoms are a characteristic of paraviral exanthems such as GCS. However, it is unclear from these diagnostic criteria whether general signs and symptoms are mandatory for a diagnosis of GCS. Moreover, if a patient manifests some but not all of the general signs and symptoms as listed, one clinician might tick this box as being fulfilled, while another might tick the box as being unfulfilled.

As the occurrence and severities of systemic manifestations in GCS are highly variable, we did not incorporate these into our diagnostic criteria (Table 2). We listed how to count the positive and negative clinical features. If one clinician applies our diagnostic criteria to a patient and comes to the conclusion that the patient does have GCS, it is highly probable that another clinician will come to the same conclusion while applying the diagnostic criteria. In other words, our diagnostic criteria has high intra-rater and inter-rater reliability.

A PROTOCOL TO ESTABLISH DIAGNOSTIC CRITERIA FOR OTHER SKIN DISEASES

Based on our experience, we devised a protocol to establish diagnostic criteria for other dermatological diseases (Appendix 1, available with the online version of this paper). Other investigators have used a similar approach to establish diagnostic criteria for skin diseases such as necrotising fasciitis.

The first step is to evaluate whether diagnostic criteria for a skin disease should be established. We start by envisaging scenarios in which diagnostic criteria would be desirable. The next step would be to evaluate whether diagnostic criteria are already in place, otherwise the existence of multiple diagnostic criteria for one disease would make combining results from multiple clinical studies difficult.[6]

It has been proposed that diagnostic criteria exist on a continuum with classification criteria. This is indeed the case for PR, as the diagnostic criteria[2,3] are fully compatible with our proposed clinical classification.[23] Therefore, if classification criteria are already in place for a skin disease, the possibility of rendering the diagnostic criteria fully compatible with the classification criteria should be explored. The scope of the disease should then be delineated, such as the inclusion or exclusion of atypical rashes and drug-induced rashes. For the literature search, the historical backgrounds should be attended to as the definition, nature and, most importantly, the aetiology of the disease might have evolved with the passage of time. A decision then has to be made on the inclusion of laboratory investigations. For our diagnostic criteria of PR and GCS we did not incorporate investigations. We advocate that investigators might consider the wide range of medical care systems with differing resources before the inclusion of laboratory investigations in the diagnostic criteria. The next step, the categorisation of clinical features, should not be a generic process. We listed possible strategies for this step. The final layout of the diagnostic criteria should then be designed, with appropriate use of conjunctions ('and/or'). The dividing line between confirmation and rejection of the diagnosis should ideally be evidence-based. Experts in the field might be consulted during this step to evaluate the face validity and content validity of the diagnostic criteria.

Sometimes, the diagnostic criteria need to be flexible, leaving a degree of autonomy to clinicians engaging with individual patients. For example, it has been reported that 14% of children with Kawasaki disease were treated with intravenous immunoglobulin despite not completely fulfilling the diagnostic criteria for this disease. We therefore fully recommend that for some diseases, flexibility statements could be incorporated into the diagnostic criteria.

Validation studies evaluate the criteria-related validity, test-retest intra-clinician reliability, and inter-clinician reliability. The numbers of patients for these studies on diagnostic criteria in skin diseases have been as small as three,[28] to as large as 3,000. Ideally, validation studies should be applied to a large number of patients with the disease and a comparable number of control subjects with differential diagnoses of the disease. These studies should also be repeated for different ethnic groups and in different geographic locations. Our diagnostic criteria for PR and GCS, for example, were each validated in two ethnic groups.[2-5]

A GLOBAL ORGANISATION FOR THE DEVELOPMENT OF DIAGNOSTIC CRITERIA

Is the establishment of a global organisation for diagnostic criteria feasible, given that diagnostic criteria development should not be generic, and multiple diagnostic criteria for one disease should be avoided? Many clinical diagnoses need to take into account the context of individual patients and their living environments. A global approach might lead to rigid adherence to algorithms, and such might be too restrictive for the process of clinical decision making in some countries and regions.

We thus suggest that the leading academic institutions and professional organisations could establish a global working group to develop consensus statements highlighting how to develop and validate diagnostic criteria. The working group could also conduct international workshops periodically and publish workshop summary reports with the continuous refine-

ment of consensus statements on the establishment, validation, and utilisation of diagnostic criteria for skin and other diseases.

CONCLUSIONS

The establishment of diagnostic criteria is not a generic process. Each set of diagnostic criteria should be established and validated through clinical studies with high scientific rigour, and tailor-made to reflect the peculiarities of the disease addressed. The diagnostic criteria should aim to strike a balance between validity, reliability, and applicability so as to facilitate rather than to hinder the diagnostic process.

Apart from patient recruitment in clinical studies and clinical trials, these diagnostic criteria are also useful for less experienced clinicians and for patients with borderline clinical features. For many other skin diseases, especially for diseases with known aetiologies and diseases with less atypical variants, diagnostic criteria may not be necessary.

We elected to establish and validate diagnostic criteria for PR and GCS for specific reasons, namely unclear aetiology, the abundance of atypical variants, the absence of confirmatory diagnostic investigations, and the potential for unifying the recruitment spectra for clinical studies. All diagnostic criteria have inherent limitations, such as oversimplification of clinical manifestations, internal inconsistencies, overlap with diagnostic criteria of differential diagnoses, inadequate validation and re-validation studies, potential of overreliance by physicians, and the potential for abuse by medical administrators and health maintenance organisations. Diagnostic criteria, for skin or other diseases, can impair the independent professional integrity of physicians if inappropriately utilised. Therefore, we emphasise that diagnostic criteria should not replace the first and foremost attributes of a clinician, namely diagnostic acumen and bedside experience.

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TABLE 4 Factual comparisons of the diagnostic criteria for pityriasis rosea and Gianotti-Crosti syndrome

	Diagnostic criteria for pityriasis rosea	**Diagnostic criteria for Gianotti-Crosti syndrome**
Clear-cut dividing line	Present	Present
Use of conjunctions and disjunctions	Yes	Yes
Applicability for all ethnic groups	Intended, but pending further validation studies	Intended, but pending further validation studies
Consistency of clinical manifestations over the time span	Yes	Probably yes, with some doubts
Literature search	Assisted by librarians at the Scottish Royal Colleges of Physicians	Searched by the first author
Number of references	118 articles reviewed with the earliest one being published in 1903. Particular attention given to 17 articles from 1956 to 2000	17 articles reviewed, from 1996 to 2000
Highly specific but insensitive clinical features	Yes	No
Categories of clinical features	Essential clinical features, optional clinical features, and exclusional clinical features	Positive clinical features and negative clinical features only
Spontaneous remission of the eruption	Not stated	Not stated
Differential diagnoses	Not explicitly listed. The exclusional clinical features suggest nummular dermatitis and secondary syphilis	Clearly listed, with acrodermatitis enteropathica, erythema infectiosum, erythema multiforme, hand-foot-and-mouth disease, Henoch-Schönlein purpura, Kawasaki disease, lichen planus, papular urticaria, papular-purpuric gloves and socks syndrome, and scabies

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