

# Hypersensitivity to antipyretics: pathogenesis, diagnosis, and management

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## ABSTRACT

Antipyretics are commonly prescribed drugs and hypersensitivity occurs at rates of 0.01% to 0.3%. Hypersensitivity can be due to immune mechanisms that include type I to IV hypersensitivity. Type I hypersensitivity results from specific immunoglobulin E production following sensitisation on first exposure. Subsequent exposures elicit degranulation of mast cells, culminating in an immediate reaction. Non-type I hypersensitivity is a delayed reaction that involves various effector cells, resulting in maculopapular rash, fixed drug eruptions, drug reaction with eosinophilia and systemic symptoms, and Stevens-Johnson syndrome/toxic epidermal necrolysis. Antipyretics also cause non-immune hypersensitivity via cyclooxygenase inhibition. Apart from hypersensitivity to parent compounds, hypersensitivity to excipient has been reported. Clinical manifestations of antipyretic hypersensitivity involve the skin, mucosa, or multiple organs. Diagnosis of hypersensitivity requires a detailed history taking and knowledge of any underlying disorders. Differential diagnoses include infection, inflammatory conditions, and antipyretics acting as co-factors of other allergens. Investigations include specific immunoglobulin E assays,

lymphocyte transformation test, basophil activation test, and skin prick test. Lack of standardisation and a scarcity of available commercial reagents, however, limit the utility of these tests. A drug provocation test under close supervision remains the gold standard of diagnosis. A trial of the culprit drug or other structurally different antipyretics can be considered. Patients with confirmed hypersensitivity to antipyretics should consider either avoidance or desensitisation. Other theoretical options include subthreshold or low-dose paracetamol, cyclooxygenase-2 inhibitors, pre-medication with antihistamines with or without a leukotriene receptor antagonist, co-administration of prostaglandin E2 analogue, traditional Chinese medicine, or desensitisation if antipyretics are deemed desirable. Safety and efficacy of unconventional treatments warrant future studies.

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## Introduction

Antipyretics (APs) are widely consumed drugs. In 2013, the National Institute for Health and Care Excellence advised that paracetamol and ibuprofen can be prescribed for febrile children in distress.<sup>1</sup> In a national cross-sectional study in France, more than 80% of health care professionals resorted to AP to manage fever in children. Paracetamol was the first-choice AP among 88% of health care professionals while ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), was preferred by 11%.<sup>2</sup> Diclofenac sodium and mefenamic acid have also been advocated as APs for children.<sup>3,4</sup> What makes use of APs truly ubiquitous is their non-prescription, over-the-counter availability. Widespread consumption often entails an increased chance of adverse drug reaction (ADR). Paracetamol and NSAIDs are two of the most common drugs to cause an allergic or pseudo-allergic reaction, secondary to general anaesthetic agents and beta-lactam antibiotics.<sup>5</sup> Prevalence of NSAID hypersensitivity ranges from 0.1% to 0.3%.<sup>6</sup> Hypersensitivity reactions to ibuprofen

occur at 0.01%.<sup>7</sup> The epidemiology of paracetamol hypersensitivity is unclear. This is understandable since prescription data for over-the-counter drugs are difficult to obtain. Nevertheless between 1982 and 1991, the Spanish Drug Monitoring System estimated the incidence of ADR to paracetamol to be less than 1 per 100 000 inhabitants below the age of 15 years. Among the reported ADRs, 30% were related to skin eruption, urticaria, or itchiness.<sup>8</sup> The real incidence might have been higher, had unreported cases been included. This is a review of the pathogenesis, diagnosis, and management of hypersensitivity to APs.

## Types of hypersensitivity reactions to antipyretics

Hypersensitivity reactions to APs are idiosyncratic responses of the body towards drugs given at a therapeutic dose. Around two thirds of patients with NSAID or paracetamol hypersensitivity are single reactors, while one third are cross-reactors.<sup>9</sup> Reaction may either be to the active ingredient or

## 退燒藥物的過敏：發病機制、診斷和治理

李君宇

醫生處方退燒藥很普遍，所產生的過敏反應比率只有0.01%至0.3%。過敏是由於身體產生過度的免疫反應。過敏可分為I型至IV型。I型過敏反應起初是由過敏原第一次進入人體產生特異性免疫球蛋白E (IgE) 所得。當相同的過敏原再次進入人體時便會引發肥大細胞的脫顆粒現象，最終發展成即時性過敏反應。非I型過敏涉及不同細胞的延遲反應，可導致斑丘疹、固定型藥物疹、藥物疹合併嗜伊紅血症及全身症狀，以及Stevens-Johnson綜合徵或毒性表皮溶解症。退燒藥還會通過環氧合酶抑制的過程引起非免疫過敏反應。過敏的根源可能是藥物的主要成分，但另有病例顯示是由藥物的賦形劑所造成的。對退燒藥過敏的臨床表現牽涉皮膚、粘膜或多個器官。診斷過敏反應須先詳細了解病人的病史和其他潛在疾病。作鑒別診斷時要考慮感染、引致炎症情況和退燒藥是否其他過敏原的輔因子。過敏反應測試包括IgE過敏測試、淋巴細胞轉化試驗、嗜鹼性粒細胞活化試驗和皮膚點刺測試。然而，欠缺標準化的測試過程以及市場上缺乏試劑均限制了這些測試的效用。密切監測下進行藥物激發測試仍是診斷的黃金標準。有懷疑可考慮對該藥或對結構不同的退燒藥進行測試。如病人確診對退燒藥產生過敏反應，應避免服用有關藥物或接受脫敏治療。其他可行方案包括服用低於最低限度劑量或低劑量撲熱息痛、使用環氧合酶-2抑制劑、在用藥前預防性給予抗組胺藥物（不論是否有白三烯素受體拮抗劑）、與前列腺素E2類似物一起服用、使用中藥治療，或使用合適的退燒藥前先作脫敏治療。至於非常規治療的安全性和療效則有待進一步的研究。

to excipients. Hypersensitivity to APs can manifest as an immune-mediated reaction that stems from an immunoglobulin (Ig) E-mediated (immediate) reaction or a non-IgE-mediated (delayed) reaction. Unlike other drugs, hypersensitivity to APs can also be non-immune-mediated.

### Immune-mediated hypersensitivity

#### Type I hypersensitivity

Type I hypersensitivity to APs, or an IgE-mediated reaction, is selective in nature. It presents with single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) or hypersensitivity to NSAIDs with structural similarity but tolerance to NSAIDs from different classes. Ibuprofen and paracetamol are two common causes of SNIUAA.<sup>10</sup> Severity ranges from localised urticaria, mucosal swelling, and angioedema to anaphylaxis. Susceptible patients become sensitised to an AP on first exposure, with the production of drug-specific IgE. Specific IgE molecules become attached to high-affinity IgE receptors on mast cells or basophils. Re-exposure to the same AP or cross-reacting drugs leads to cross-linking of adjacent IgE receptors and subsequent degranulation of vasoactive inflammatory mediators like histamine and tryptase.<sup>11</sup> Patients with SNIUAA against ibuprofen produce IgE against specific

antigen determinants of the drug. Hence they may react to arylpropionic acids with similar chemical structure but tolerate NSAIDs from other groups, such as acetic acids.<sup>7</sup> Similarly, patients with selective hypersensitivity to paracetamol confirmed by IgE tests or oral challenge can tolerate other NSAIDs.<sup>12</sup>

#### Non-type I hypersensitivity

##### Maculopapular eruptions

According to the revised Gell and Coombs classification, maculopapular eruption (MPE) is a type IV-c, T-cell-mediated delayed hypersensitivity reaction.<sup>13</sup> It is said to be the most common delayed drug rash due to an AP. Implicated drugs include ibuprofen, diclofenac, and paracetamol.<sup>14</sup> Such MPE manifests as a morbilliform or scarlatiniform rash that starts on the trunk with subsequent spread to the limbs. Onset of MPE ranges from within 7 to 14 days of first consumption of the drug, but may take only 2 to 3 days in patients with prior sensitisation. The reaction of MPE involves skin-homing T lymphocytes, drug-specific cells that express cutaneous lymphocyte antigen. Around two thirds of the T-cells are CD4+, while one third are CD8+. Having resided in the dermo-epidermal junction, these cells release perforin and granzyme B, two mediators of keratinocyte apoptosis, via their ability to induce pore formation in the cell membrane.<sup>15</sup> Histological changes include intracellular, intercellular and dermal papilla oedema, dislodgment of epidermal basal cells, hydropic degeneration, spongiosis of the lower epidermis, and dyskeratosis and necrosis of keratinocytes. Inflammatory infiltration by T-cells is seen at the dermo-epidermal junction and eosinophils in the perivascular region.<sup>16</sup>

##### Fixed drug eruption

Fixed drug eruption (FDE) is a peculiar type of T-cell-mediated delayed drug hypersensitivity. It starts with solitary, well-circumscribed macules that erupt anywhere on the skin or mucosa, usually over the lips, palms, soles, groins, or glans penis. With time, the lesions evolve into plaques that recur at the same site on re-exposures to the same drug. The interval between drug intake and FDE is around 30 minutes to 8 hours. The eruption resolves spontaneously after cessation of the culprit, leaving hyperpigmentation at the affected site. Pathologically, migration and residence of drug-specific effector-memory CD8+ T-cells in the epidermal side of the dermo-epidermal junction of the affected area account for the recurrence of eruption at the same site. Upon drug re-exposure, quiescent CD8+ cells become activated and secrete interferon- $\gamma$  and cytotoxic granules into the local microenvironment.<sup>17</sup> Paracetamol is one of the most common causes of FDE, as are mefenamic acid, ibuprofen, and aspirin.<sup>18</sup>

### *Drug reaction with eosinophilia and systemic symptoms*

Drug reaction with eosinophilia and systemic symptoms (DRESS) is classified as a type IV-b delayed hypersensitivity reaction with eosinophil involvement. It is characterised by fever, exfoliative dermatitis, lymphadenopathy, haematological abnormalities (hypereosinophilia, atypical lymphocytes), and organ dysfunction. The interval between drug consumption and onset of symptoms is quite prolonged, ranging from 3 weeks to 3 months. The pathophysiology of DRESS involves viral reactivation (eg human herpes type 6) and T-cell activation, two determining factors with a mutual causal relationship.<sup>19</sup> FOXP3+ (forkhead box P3) regulatory T-cells are activated early in the course of DRESS, but are subsequently deactivated and become deficient, culminating in the emergence of autoimmune diseases commonly seen in the aftermath of DRESS. Ibuprofen and paracetamol have rarely been associated with DRESS.<sup>20,21</sup>

### *Stevens-Johnson syndrome/toxic epidermal necrolysis*

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a type IV-c delayed hypersensitivity reaction to infections or drugs including APs. The interval between intake of the culprit drug and SJS/TEN is shorter than that of DRESS, ranging from 1 to 21 days.<sup>22</sup> Skin lesions in SJS/TEN are typically target-like with central necrosis, bullae formation, or purpuric lesions. In SJS, less than 10% of the body surface area is involved, whereas in TEN, more than 30% is involved. Gentle rubbing of 'normal' skin causes separation of the epidermis (Nikolsky sign). Mucosal and eye inflammation is present in 90% and 60% of cases, respectively. Severe cases culminate in corneal scarring, respiratory distress syndrome, pneumonia, and respiratory failure.<sup>23</sup> A caveat in the diagnosis is that the prodromal phase of SJS/TEN may be mistaken as symptoms of a febrile illness, with consequent administration of APs. In the event that SJS/TEN occur secondary to other causes, subsequent appearance of skin and mucosal lesions may impart the wrong impression of AP as the causative agent. In SJS/TEN, CD4 T-cells accumulate in the dermis while CD8 T-cells predominate in the epidermis. T-cell infiltration causes massive apoptosis of the keratinocytes via the toxic action of perforin, granzyme, and Fas/Fas ligand interaction.<sup>24</sup> Of note, SJS/TEN due to NSAIDs is exceedingly rare. The incidence for ibuprofen was 0.013 per 1 000 000 as opposed to 0.032 per 1 000 000 for oxicams.<sup>25</sup> Compared with controls, the relative risk of paracetamol and ibuprofen for SJS/TEN in children ranges from 5 to 11.<sup>26</sup> It is also noteworthy that APs are often prescribed together with antibiotics to treat

infection, with the latter two factors (antibiotics and infection) potentially related to SJS/TEN.<sup>27</sup>

### *Acute generalised exanthematous pustulosis*

Acute generalised exanthematous pustulosis (AGEP) is a rare type IV-d drug hypersensitivity with sterile subcorneal pustule formation. Onset of pustules occurs around 1 day after drug intake. Most patients present with fever. Non-follicular small pustules with an erythematous base start on the face or intertriginous area and subsequently become generalised. The pustules, which are itchy or burning, persist for 4 to 30 days before desquamation.<sup>28</sup> Histological characteristics include papillary oedema, perivascular infiltration by neutrophils, and drug-specific T-cells and epidermal keratinocyte necrosis. Interleukin-8, a neutrophil chemoattractant, is expressed by drug-specific T-cells. Presence of human leukocyte antigens (HLAs)-DR within the inflammatory infiltrate suggests the role of a major histocompatibility complex in causing this peculiar type of drug eruption.<sup>29</sup> Among NSAIDs, only the oxicams are significantly associated with AGEP, with a multivariate odds ratio of 8.4. Paracetamol is not considered at an increased risk of causing AGEP.<sup>30</sup>

### *Organ-specific delayed hypersensitivity*

Of note, NSAIDs can cause an allergic inflammatory response in different organs. Cases of NSAID-induced hepatitis, pneumonitis, nephritis, and aseptic meningitis have been reported.<sup>6</sup>

### **Non-immune-mediated hypersensitivity: cyclooxygenase inhibition**

Three types of non-immune drug hypersensitivity to NSAIDs have been described: NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), and NSAID-induced urticaria/angioedema (NIUA). In NERD, patients usually have asthma, rhinosinusitis, and/or nasal polyps. Aspirin or other NSAIDs may precipitate nasal congestion, rhinorrhoea, bronchial obstruction, or dyspnoea within 30 to 180 minutes of ingestion. Urticaria, angioedema, and flushing of the upper thorax may occur. Patients with NECD usually have underlying chronic spontaneous urticaria. Aspirin or NSAIDs may cause flare-up of urticaria and angioedema in 12% to 30% of patients with chronic spontaneous urticaria. On the other hand, NIUA occurs primarily in patients without underlying disease. Immediate reactions that occur less than 15 minutes following consumption and late reactions that occur after several hours have been described.<sup>10</sup>

Non-immune hypersensitivity to NSAIDs is the result of cyclooxygenase (COX) inhibition, a

pharmacological property common to all NSAIDs that accounts for their propensity to cause cross-reactivity. Three COXs—COX-1, COX-2, and COX-3—have been identified, and NSAIDs like ibuprofen inhibit all three COXs. On the contrary, paracetamol is a weak inhibitor of COX-1 and COX-2, especially at a low dose, and preferentially inhibits COX-3.<sup>31</sup> In susceptible patients, inhibition of COX leads to overproduction of pro-inflammatory cysteinyl leukotrienes by mast cells and eosinophils but depletion of the homeostatic and anti-inflammatory prostaglandin E<sub>2</sub> (PGE<sub>2</sub>).<sup>31</sup> Imbalance of leukotrienes and prostaglandins culminates in inflammation in the skin, nasal cavities, sinuses, and airway mucosa.<sup>32</sup> Accumulation of leukotrienes in the skin results in urticaria and angioedema characterised by dermal oedema, and lymphatic dilation involving perivascular or interstitial cellular infiltration.<sup>33</sup>

Recent genetic studies have further elucidated the pathogenesis of NSAID hypersensitivity due to COX inhibition, explaining why it only occurs in some patients. Candidate genes are responsible for various enzymes, receptors, or mediators involved in dysregulation of arachidonic acid metabolism, initiation of immune response, dysfunction of epithelial cells, biochemical signalling, effector function in inflammatory cells, and aspirin metabolism.<sup>34</sup> Studies revealed that HLAs are associated with NSAID hypersensitivity, for instance, subjects with HLA DPB1\*0301 are at a higher risk of developing NERD.<sup>35</sup> Aside from genes, methylation profiles of DNA have been associated with NERD, underscoring the role of epigenetics.<sup>36</sup>

### Hypersensitivity to excipients

Discussion of hypersensitivity to APs is incomplete without mentioning the role of excipients that act as vehicles of drugs. It was thought that an excipient, being ostensibly inert, should not cause ADR. Recent reports of excipient hypersensitivity, however, have cast doubt on that.<sup>37</sup> Common paracetamol preparations come in the form of tablets, syrup, and suppositories. As with other drugs, excipients in paracetamol contain preservatives, colouring, sugar, and ethanol. Parabens and benzoates, two potential allergens, are preservatives widely used in various paracetamol preparations.

Different excipients are added to produce different formulations. For instance, one type of paracetamol syrup contains propylene glycol, methyl hydroxybenzoate, propyl hydroxybenzoate, xanthan gum, sorbitol solution 70%, sucrose, mango flavouring, and purified water.<sup>38</sup> There are currently more than 90 registered manufacturers of generic paracetamol in Hong Kong, producing a stunning inventory of more than 900 paracetamol-containing formulations in the drug registry of the

Department of Health.<sup>39</sup> Patients hypersensitive to the excipient of one product (eg paracetamol tablet) may tolerate another form (eg paracetamol syrup) or the same form of another brand. Unfortunately, pharmaceutical companies may not disclose excipient components of a drug in their entirety. This makes thorough comparison between different products difficult.

## Diagnosis of hypersensitivity to antipyretics

### History and clinical scoring system

Prudent management of hypersensitivity to APs starts with an attempt to confirm or exclude the diagnosis. As APs are usually prescribed for fever on an as-required basis, clinicians should concentrate on actual consumption rather than prescription. Reactions that appear within 1 to 2 hours of AP consumption constitute immediate hypersensitivity, while reactions that appear several hours or beyond are considered delayed hypersensitivity. Although symptoms usually subside within 24 to 48 hours, some may persist for up to 1 to 2 weeks.<sup>40</sup>

The number of previous exposures to an AP should be noted. The same drug tolerated on many occasions is unlikely to be the culprit. An AP tolerated only once before may trigger an IgE-mediated reaction the second time it is given to a susceptible patient. An AP given for the first time can still trigger a reaction via T-cell activation or COX inhibition. Previous exposure may not be apparent in case of poor recall or if the AP is given in the context of polypharmacy. With details of the past and present drug treatment, clinicians should estimate the probability of AP hypersensitivity before attaching the label. A validated scoring system can help classify patients as definite, probable, possible, or doubtful cases of ADR.<sup>41</sup> The next step is to differentiate between single-reactors and cross-reactors by thorough history taking and collation of data from various sources, including written and electronic drug records.

Care is needed for proper drug identification, as APs may have many trade names. Clinicians can refer to the Drug Database of the Department of Health for a comprehensive list of registered drugs from different pharmaceutical companies.<sup>39</sup> Over-the-counter drugs should be carefully studied in history taking. Patients should be encouraged to submit any remaining drugs to hand for identification. Clinicians should try to differentiate between hypersensitivity to the active ingredients versus excipients. Patients who react to different preparations of the same drug are likely hypersensitive to the active ingredient, while those who react only to some preparations may be suffering from hypersensitivity to excipient(s).

A clinical history is valuable in predicting

hypersensitivity to APs: 17% of children with such hypersensitivity have a positive family history. Such children are more than 5 times likely to have NSAID hypersensitivity compared with controls.<sup>9</sup> Emergence of an ADR within an hour of administration and a history of hypersensitivity to multiple NSAIDs are two other stronger predictors of challenge-proven NSAID hypersensitivity.<sup>42</sup>

Clinicians should then differentiate between various clinical manifestations. Urticarial rash and angioedema are found in type I hypersensitivity and reactions due to COX inhibition; whereas MPE is erythematous, non-itchy, and flat lesions that blanch on pressure (Fig 1). Isolated discoid lesions recurring at the same site are indicative of FDE (Fig 2). Presence of 'red-flag signs' signifies more sinister diseases. Mucosal inflammation and ulcerations associating with unremitting fever, intense skin pain, and Nikolsky sign should raise concern about possible development of SJS/TEN. Widespread MPE associating with persistent fever, peripheral eosinophilia, liver impairment but absence of mucosal inflammation is suggestive of DRESS. In NERD, patients typically have underlying chronic rhinosinusitis, nasal polyps, and asthma complicated by NSAID intolerance. Patients with NECD may have chronic spontaneous urticaria.<sup>10</sup>

Differential diagnoses of hypersensitivity to APs include hypersensitivity to concomitant drugs and diseases with skin or mucosal manifestations, eg viral infections, chronic urticaria, or Kawasaki disease. On the other hand, SJS is related to infection such as mycoplasma in 25% of affected children.<sup>27</sup> As mentioned, AP may be given for fever control after the onset of other symptoms. The febrile illness that requires AP can also cause skin or mucosal symptoms. One should also consider the possibility that the AP is a co-factor of other allergens. A co-factor may not cause allergy per se, but may lower the threshold for allergic reaction to another allergen. Common co-factors include exercise, infection, menstruation, stress, alcohol, angiotensin-converting enzyme inhibitors, and NSAID. Possible mechanisms of co-factors include tight junction dysregulation, increased gastrointestinal absorption of allergens, and COX inhibition. The prevalence of co-factor-dependent anaphylaxis related to NSAID ranges from 1.2% to 4.7%.<sup>43</sup>

Workup for hypersensitivity to APs should be carried out 4 to 6 weeks after complete resolution of symptoms.<sup>44</sup> A battery of in-vitro and in-vivo tests can confirm or exclude hypersensitivity to APs and ascertain safe alternative drugs.

### In-vivo tests

Aside from diagnosis of allergy to an aeroallergen in patients with NERD, the skin prick test for AP is probably useful only in the context of IgE-mediated



FIG 1. Maculopapular rash due to sensitivity to non-steroidal anti-inflammatory drugs  
Reproduced with permission from Dr YW Kwan



FIG 2. Fixed drug eruption due to ibuprofen  
Reproduced with permission from Dr YW Kwan

SNIUAA. A negative skin prick test, however, does not exclude hypersensitivity to APs as many reactions are non-IgE-mediated. Moreover, with the passage of time, even individuals with IgE-mediated hypersensitivity may lose skin test positivity. An intradermal test and atopic patch test may be

helpful in diagnosing NSAID-induced delayed hypersensitivity. These tests are generally specific but not sensitive for diagnosis. Lack of standardisation and a scarcity of available commercial reagents limit their utility. Except for diagnosis of IgE-mediated hypersensitivity to APs, skin tests seem to have little diagnostic value.<sup>10</sup>

A drug provocation test (DPT), which works independently of the underlying mechanism, remains the gold standard for diagnosis of hypersensitivity to APs and establishment of cross-reactivity. As usual formulations are used, DPT is more feasible than skin tests for AP. In a Turkish paediatric study, only five (14%) of 36 children with a history of single NSAID hypersensitivity reacted positively to a DPT using the culprit drug. For 18 children with an alleged history of multiple NSAID hypersensitivity, DPT was positive in eight (44%). Among patients with NSAID hypersensitivity, 50% also reacted to paracetamol.<sup>9</sup> Conversely, only 25% of patients with paracetamol hypersensitivity develop cross-intolerance to NSAID.<sup>12</sup> The negative predictive value of DPT in children reaches 100% for NSAIDs, so patients who pass a DPT can be safely given the NSAID in future.<sup>45</sup> A DPT is generally not recommended during pregnancy, intercurrent illness, or in patients with co-morbidities such as cardiac, hepatic or renal disease, or uncontrolled asthma. Contra-indications to DPT include a history of SJS/TEN, DRESS, AGEP, systemic vasculitis, drug-induced autoimmune diseases, and severe anaphylaxis.<sup>46</sup>

A typical protocol for DPT starts with 1/50 to 1/20 of a single maximum dose of an AP, followed by four to five incremental doses given at regular intervals (eg 60 minutes) until the single maximum dose is reached.<sup>9</sup> Patients who pass a DPT on day 1 can be given a 2-day course on day 2 to ensure full tolerance to the test drug. In case symptoms or signs of ADR appear, DPT should be aborted and anti-allergic treatment immediately given. The threshold cumulative dose can then be determined. For paracetamol, this ranges from 75 mg to 325 mg.<sup>47</sup> The same procedure can be repeated at least 1 week later, using another AP from a structurally unrelated class to determine cross-reactivity.<sup>48</sup> For instance, patients who fail a DPT for ibuprofen, an arylpropionic acid, can undergo a subsequent DPT for diclofenac, an acetic acid. A DPT should be carried out in the hospital setting with resuscitation facilities available and supervised by clinicians experienced in managing drug hypersensitivity and anaphylactic reaction.

### In-vitro tests

Most in-vitro tests to date have not been validated or standardised. Aside from research purposes they are not routinely recommended for clinical use.

### Serum specific immunoglobulin E test

Demonstration of specific IgE (sIgE) against a NSAID in the serum theoretically aids diagnosis of SNIUAA. Serum sIgE against paracetamol has been demonstrated by some researchers.<sup>49</sup> Compared with skin prick test, however, serum sIgE against NSAID is less useful. Sensitivity and specificity of sIgE are not known.<sup>14</sup>

### Basophil activation test

Detection of CD63 signifies activation of basophils and forms the basis of the basophil activation test. As a diagnostic tool for NIUA, basophil activation test is relatively sensitive but not specific.<sup>50</sup>

### Lymphocyte transformation test

As drug-specific T-lymphocytes are frequently involved in NSAID hypersensitivity, a lymphocyte transformation test (LTT) has been advocated as a diagnostic tool. The test is based on measurement of <sup>3</sup>H-thymidine uptake by dividing T-cells. The NSAIDs considered suitable for LTT include diclofenac, mefenamic acid, and paracetamol. Sensitivity of the LTT ranges from 60% to 70% with specificity of approximately 85%. A positive LTT is useful for diagnosis, but a negative test does not exclude hypersensitivity. Involvement of a stringent protocol and need for expert interpretation means that LTT can be performed only by specialised laboratories.<sup>51</sup>

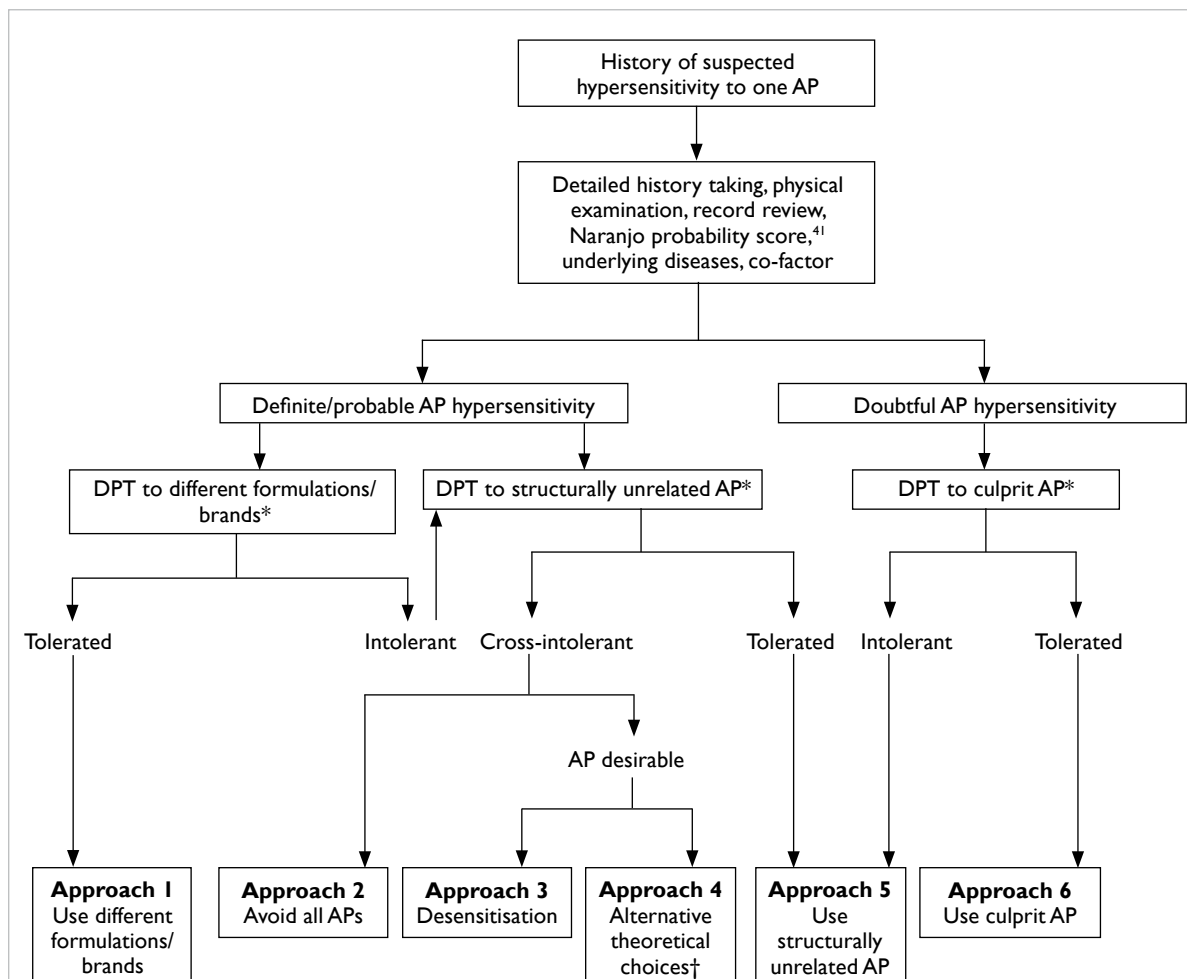
## Management of hypersensitivity to antipyretics

### Acute management

The offending AP should be stopped and antihistamine given. In case of anaphylactic reaction, emergent treatment and resuscitation should be performed. Oxygen, intramuscular adrenaline, and antihistamine should be given. A severe cutaneous adverse reaction should be managed in the intensive care unit. Standard treatment includes intravenous fluids, corticosteroid, intravenous Ig, and other immunosuppressants.<sup>23</sup>

### Follow-up

Management of suspected AP hypersensitivity starts with thorough discussion with patients or caretakers of the pros and cons of the AP as opposed to avoidance. The aims of investigation include confirmation of hypersensitivity and cross-reactivity, differentiation between hypersensitivity to the active ingredient versus excipients, and trial of safe alternatives. Detailed review of drug history is of paramount importance. Above all, DPT is pivotal to achieving the aims of investigation. A combination of drug history and DPT culminates in six alternative approaches to



**FIG 3. Suggested pragmatic management algorithm for hypersensitivity to antipyretics**

Abbreviations: AP = antipyretic; DPT = drug provocation test; DRESS = drug reaction with eosinophilia and systemic symptoms; PGE<sub>2</sub> = prostaglandin E<sub>2</sub>; SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis

\* DPT is contra-indicated in severe reactions like anaphylaxis, SJS/TEN, DRESS, poor lung function, pregnancy

† Alternative theoretical choices: (i) subthreshold/low-dose paracetamol; (ii) type 2 cyclooxygenase inhibitors; (iii) pre-medication with antihistamines ± leukotriene receptor antagonist; (iv) co-administer PGE<sub>2</sub> analogue; and (v) traditional Chinese medicine etc

deal with hypersensitivity to APs (Fig 3).

Patients allergic to excipients in one AP may tolerate a different brand or different formulation of the same drug (approach 1). Detailed comparison of constituents may reveal the excipient in question. In case of doubt, DPT can be performed on the alternative brand or formulation to confirm tolerance. In case the patient reacts to different formulations and brands of the same AP, a trial of AP with unrelated structure can be considered (approach 5). A common example is to try ibuprofen in patients with paracetamol hypersensitivity. As mentioned before, three quarters of patients with paracetamol hypersensitivity tolerate NSAIDs. Patients hypersensitive to ibuprofen, an arylpropionic acid, can consider DPT using paracetamol or an acetic acid such as diclofenac.

Patients with cross-intolerance to paracetamol and NSAIDs pose a management dilemma. Avoidance of all APs seems logical (approach 2), especially if the feverish patient is not 'distressed'. Nonetheless whether a patient is in distress or not is a matter of subjective judgement. For cultural reasons, it is exceedingly difficult to persuade Hong Kong parents not to give APs to a child with a high fever. In case fever control is deemed desirable by either parents or physicians, viable solutions should be sought. Desensitisation (approach 3) is another viable option. A standard desensitisation protocol has been established for aspirin.<sup>52</sup> Desensitisation is applicable to patients having NERD or NIUA.<sup>10</sup> It is contra-indicated in patients with a history of severe, life-threatening drug reactions such as SJS/TENS or DRESS. Nonetheless desensitisation should only be

carried out in medical facilities with resuscitation equipment and expertise in drug allergy. Alternative theoretical choices (approach 4) include subthreshold or low-dose paracetamol,<sup>47,53</sup> COX-2 inhibitors,<sup>54</sup> pre-medication with antihistamines with or without leukotriene receptor antagonist,<sup>55</sup> co-administration of a PGE<sub>2</sub> analogue,<sup>56</sup> and traditional Chinese medicine.<sup>57</sup> Future studies are needed to define the safety and efficacy of these unconventional treatments.

Patients with a mild or doubtful reaction to an AP can consider a DPT, the gold standard to diagnose or exclude hypersensitivity to the culprit drug. Patients who react to the culprit AP during DPT can either try a structurally unrelated AP (approach 5) or try a different brand/formulation (approach 1). Finally, patients who pass the DPT can be given the culprit drug in future (approach 6), as the test has a very high negative predictive value.<sup>10</sup>

### Conclusion

It is arguable that APs may not be indicated in the first place and should be avoided in patients with hypersensitivity. Although APs should not be prescribed simply for the sake of ‘temperature control’, the need to mitigate patient discomfort should not be disregarded.<sup>58</sup> Patients with illnesses such as heart failure, head injury, or sepsis present special problems. Their limited reserve to withstand the hypermetabolic state associated with febrile episodes puts them at particular risk.<sup>59</sup> For these patients, APs seem beneficial. In case they have hypersensitivity to APs, viable options should be sought. Attempts to predict such hypersensitivity are daunting. Disappointingly, prediction of severe cutaneous adverse reactions to APs is virtually impossible. However, the presence of a positive family history, reaction within 1 hour of consumption, and history of multiple NSAID hypersensitivities may sound an alarm for the increased risk of genuine immediate hypersensitivity to APs. Clinicians need to strike a balance between ‘hypersensitivity phobia’ for the sake of drug safety and liberal use of APs to uphold patients’ rights. Knowledge of the pathogenesis of AP hypersensitivity and meticulous diagnostics are key to judicious management.

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