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### **Diagnosis and treatment of radiocontrast media hypersensitivity**

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Radiocontrast media (RCM) are concentrated solutions of tri-iodinated benzene derivatives for enhancement of radiographic contrast. Adverse reactions associated with RCM administration can either be hypersensitivity reactions, toxic reactions (e.g. generalized pruritus, heat sensation, flushing, nausea), or events unrelated to RCM exposure (e.g. spontaneous urticaria).<sup>1</sup> Hypersensitivity reactions are

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classified into immediate reactions (IHR) occurring within 1 hour after RCM administration, or non-immediate reactions (NIHR) presenting > 1 hour after exposure.<sup>1</sup> IHR present most often with urticaria (including angioedema), but also with anaphylaxis.<sup>2</sup> NIHR typically present with maculopapular exanthem (MPE), but sometimes also with other exanthem variants, such as exanthems with blisters (e.g. toxic epidermal necrolysis), pustules or systemic symptoms.<sup>3</sup> IHR and NIHR occur each in about 0.5-2% of patients receiving RCM.<sup>1</sup> Indirect evidence by histamine release from basophils and mast cells, positive skin and basophil activation tests (BAT) has accumulated that in some patients IHR to RCM may be IgE-mediated, whereas in most patients the mechanism is non-allergic. NIHR are T cell-mediated, although skin tests and lymphocyte transformation tests (LTT) are not uniformly positive. Patients with IHR or NIHR, but not those with mild toxic symptoms only (e.g. generalized pruritus, heat sensation, flushing, nausea), should be investigated for RCM allergy (Fig. 1) to identify a safe alternative RCM.<sup>4,5,6</sup> Cross-reactivity between different RCM are more common in NIHR than in IHR.

Iodine allergy is an exceptional cause of NIHR and can be excluded by patch test.<sup>4</sup> Prophetic allergy testing in those without previous reaction (e.g. "iodine allergy", atopy) is not recommended.<sup>6,7</sup> In IHR, elevated plasma histamine or serum tryptase in comparison with baseline may confirm anaphylaxis. Premedication can suppress non-allergic reactions, whereas its efficacy in allergic reactions remains questionable.<sup>4</sup> Combination of corticosteroids at several time points (eg. 50 mg prednisone 13, 7, and 1 h before application) and H1- antihistamine (eg. 50 mg diphenhydramine 1 h before application) is a protocol most often used.<sup>6</sup>

Figure legend:

**Figure 1. Management of patients with previous radiocontrast medium reaction.**

(1) Patients with history of anaphylaxis, bronchospasm, urticaria and/or angioedema and exanthems to RCM should undergo allergological work-up. Those with severe NIHRs, as bullous exanthems or with systemic symptoms should avoid future RCM application, whereas skin tests can be done. (2) In patients with mild IHR (urticaria +/- angioedema) or NIHR (maculopapular exanthem) and urgent need for RCM-based imaging, a non-culprit RCM may be given after premedication. In patients with anaphylaxis, RCM should be avoided and native CT- or MR-scan performed. If RCM is considered indispensable and a risk-benefit analysis positive, best administer the RCM after pre-medication and in emergency preparedness including anesthesia stand-by. (3) For best sensitivity, skin tests are done 2-6 months after the reaction. Skin prick test and, if negative, intradermal test are performed, in NIHR additionally patch tests. Test concentrations and reading times differ between IHR and NIHR (Tab.1).<sup>2</sup> The culprits of previous reactions

are skin tested. If positive, or if the culprit is unknown, a panel of available RCM is added. Basophil activation test (BAT) and lymphocyte transformation tests (LTT) may optionally be used. If no RCM allergy can be demonstrated by positive skin tests to the tested RCM (nonallergic RCM hypersensitivity), further skin tests were not helpful, thus use a non-culprit RCM, and apply premedication under emergency preparedness. (4) If skin tests are positive to the culprit, RCM allergy is diagnosed and alternative skin-test-negative (+/- BAT- or LTT-negative) alternative RCMs are looked for. (5) Provocation tests confirm tolerability to a skin test-negative RCM, e.g. after very severe reaction, but are often dispensable. Otherwise, a skin test-negative alternative RCM is administered without premedication under emergency preparedness.

**Table 1. Skin test concentrations and reading time points**

| Test             | Concentration <sup>a</sup> | Readings           |                                 |
|------------------|----------------------------|--------------------|---------------------------------|
|                  |                            | Immediate reaction | Non-immediate reaction          |
| Skin prick test  | Undiluted                  | 20 min             | 20 min, 48 h, 72 h <sup>b</sup> |
| Intradermal test | 1/10 diluted <sup>c</sup>  | 20 min             | 20 min, 48 h, 72 h <sup>b</sup> |
| Patch test       | Undiluted                  |                    | 20 min, 48 h, 72 h <sup>b</sup> |

<sup>a</sup> Undiluted radiocontrast media with an iodine concentration of 300-320 mg/ml. In severe reactions, IDT should initially tested with higher dilutions.

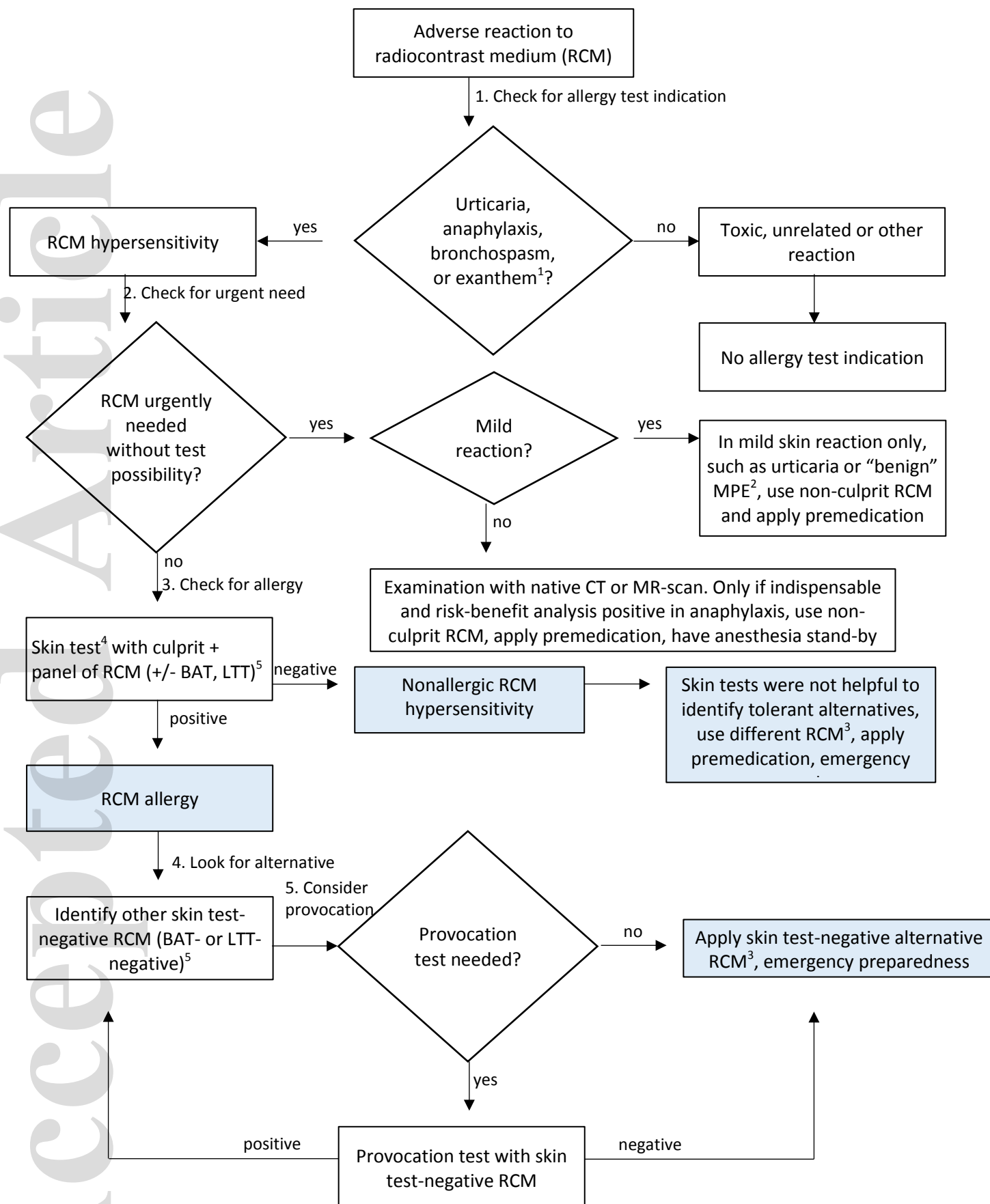
<sup>b</sup> Reading times are standard: if the patient notices a positive reaction (pruritus, erythema) at the skin test site at other time points, additional readings should be performed (e.g. after 24 h or 96 h)

<sup>c</sup> For non-severe non-immediate reactions also undiluted radiocontrast media may be used, if reactions in the 20 min reading are interpreted as possibly irritative

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<sup>1</sup>including exanthem variants, however, after severe bullous exanthems or after reactions with systemic symptoms skin test can be done, but future total RCM avoidance is normally recommended; <sup>2</sup>MPE= maculopapular exanthema; <sup>3</sup>not after severe bullous exanthems or after drug reaction with systemic symptoms: here RCM avoidance; <sup>4</sup>see Table 1; <sup>5</sup>BAT= basophil activation test, and LTT= lymphocyte transformation test may be helpful in some cases