

Heparin-induced skin lesions

More common than suspected

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Keywords

Heparin, skin, allergy, delayed-type hypersensitivity

Summary

Cutaneous reactions to subcutaneous heparin injections have been described first in 1952. These reactions may be caused by several mechanisms such as immediate or delayed-type hypersensitivity responses, or by life-threatening immune-mediated heparin-induced thrombocytopenia (HIT). In contrast to bleeding, induction of osteoporosis and hair loss, no data on the incidence and causes of heparin-induced skin lesions had been available until recently. In a large prospective epidemiological study, the incidence of heparin-induced skin lesions was as high as 7.5% in medical patients, far exceeding the expected incidence. As heparin-induced skin lesions may be the sole clinical manifestation of immune HIT, rapid and valid diagnosis of heparin-induced skin lesions is of utmost clinical importance. Therefore, we have reviewed all known causes of heparin-induced skin lesions, and propose diagnostic and therapeutic procedures.

Schlüsselwörter

Heparin, Haut, Allergie, allergische Reaktionen Typ IV

Zusammenfassung

Hautreaktionen auf subkutan appliziertes Heparin wurden erstmals 1952 beschrieben. Hierfür kommt eine Reihe von Ursachen in Frage, am häufigsten sind allergische Reaktio-

nen vom Typ IV und Mikrothromben im Rahmen einer Heparin-induzierten Thrombozytopenie vom Typ II (HIT II) beschrieben worden. Im Gegensatz zu weiteren unerwünschten Arzneimittelwirkungen der Heparine, wie Blutungen, Osteoporose oder Haarausfall, lagen bis vor kurzem keine Daten zur Inzidenz und Ursache Heparin-induzierter Hautveränderungen vor. In einer kürzlich abgeschlossenen prospektiven Untersuchung bei internistischen Patienten betrug die Inzidenz Heparin-induzierter Hautveränderungen 7,5%. Da das initiale klinische Bild Heparin-induzierter Hautveränderungen bei einer lebensbedrohlichen HIT II und einer relativ selbstlimitierenden Typ-IV-allergischen Reaktion ähnlich sind, ist die Differenzierung zwischen beiden Erkrankungen von hoher klinischer Relevanz. Daher stellen wir hier alle bekannten Ursachen Heparin-induzierter Hautveränderungen vor und diagnostische sowie therapeutische Maßnahmen zur Diskussion. **Heparin-induzierte Hypersensitivitätsreaktion (HIHS):** Dieser Begriff bezeichnet Heparin-induzierte Hautveränderungen im Sinne einer kutanen Typ-IV-Reaktion. Erstes klinisches Zeichen ist Juckreiz im Bereich der Injektionsstellen. Im weiteren Verlauf entwickeln sich dort typische Erytheme und Plaques. In seltenen Fällen kann es zur generalisierten Ausbreitung der Veränderungen kommen. Die Inzidenz der HIHS wird in der Regel unterschätzt. Weibliches Geschlecht und Adipositas gelten als prädisponierende Faktoren. Ebenso bergen langkettige Heparinpräparationen ein höheres Risiko der HIHS. Die Diagnose wird klinisch gestellt – eine ergänzende Histologie ist sinnvoll. Eine allergologische Testung bei HIHS wird nur im Ausnahmefall empfohlen. **Immunmediier-**

te Heparin-induzierte Thrombozytopenie (HIT II): Eine schwerwiegende Komplikation der Heparinexposition stellt die immunologische Form der Heparin-induzierten Thrombozytopenie (HIT Typ II oder HIT II) dar, die durch Antikörperbildung hauptsächlich gegen den Komplex aus PF4/Heparin verursacht wird. Die Inzidenz der HIT II wird je nach Patientenkollektiv mit etwa 0,5–5% angegeben, wobei unter niedermolekularen Heparinen wesentlich seltener eine HIT II auftritt als unter unfraktioniertem Heparin. Besonders gefährdet sind Patienten nach kardiochirurgischen Operationen oder größeren orthopädischen Eingriffen. Unter einer HIT II kommt es aufgrund der Thrombozytenaktivierung trotz der sich entwickelnden Thrombozytopenie paradoxerweise zu einer massiven Thromboembolieeigung, so dass die Heparinexposition sofort beendet und auf eine alternative Antikoagulation umgestellt werden muss. Hautveränderungen im Rahmen einer HIT II sind Folge von Verschlüssen der Arteriolen und Venolen. Sie beginnen als blasse Erytheme, die rasch in eine Nekrose übergehen. **Heparin-induzierte Soforttypreaktion:** Sehr selten treten typische allergische Reaktionen vom Soforttyp im Zusammenhang mit Heparinen auf. Es handelt sich dabei um Urtikaria, Angioödem, Bronchospasmus und schwere Anaphylaxie. **Heparin-induzierte bullöse hämorrhagische Dermato:** Bislang wurden 6 Patienten beschrieben, bei welchen es 5–21 Tage nach Einleitung der Heparintherapie zum Auftreten von subcornealen hämorrhagischen Blasen ohne Bezug zum Injektionsort kam. **Recall-Urtikaria auf Heparin:** In früheren Injektionsstellen kann es unter Heparin-gabe zu urtikariellen Veränderungen kommen. Für dieses spezifische Gedächtnis spielen Mastzellen eine Rolle. **Heparin-induzierte Hautnekrosen unklarer Genese:** In einem Fall wurden Heparin-induzierte Hautnekrosen ohne die typischen Zeichen einer HIT II beschrieben. Der Pathomechanismus blieb unklar. **He-**

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Heparin-induzierte Hautveränderungen sind häufiger als vermutet

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parin-induzierte Pustulose: Ein Fallbericht liegt vor, der eine heparininduzierte generalisierte Pustulose beschreibt, die sich durch Provokationstestungen reproduzieren ließ. **Schlussfolgerung:** Heparin-induzierte unerwünschte Nebenwirkungen am Hautorgan sind häufiger als allgemein angenommen. Regelmäßige Untersuchungen der Haut unter Heparintherapie werden daher empfohlen. Alternative Präparate (z. B. Fondaparinux) stehen bei Patienten mit dem Risiko eine HIHS oder HIT zu entwickeln zur Verfügung.

Heparin* was discovered in 1916, when it was accidentally isolated as an anticoagulant from dog liver. Chemically heparin is a complex mixture of molecules differing not only in their chain length, but also in the fine structure of their monosaccharide units. Shortly later, heparin was introduced in clinical practice in the late 1930's (19, 32). In 1947, the World Health Organization defined the 1st International Standard of heparin. With the introduction of prefilled syringes 20 years later, standardized heparin dosages were administered for the first time.

More than 50 years after its discovery, the mode of action was identified (13): Binding of heparin to antithrombin (AT) induces a conformational change and thus an acceleration of the AT-mediated inactivation of a number of coagulation enzymes (4). The discovery of the separability of anti-FXa and anti-thrombin-activity of heparin was accounted a chance to optimize the heparin therapy, as the anti-FXa activity retained the anticoagulatory activity, but was associated with a reduced risk of bleeding (7). LMWH are presently produced by chemical or enzymatic degradation of UFH. As a consequence, the different manufacturing methods lead to diverse molecular weights and chemical changes (3). Hence, each LMWH represents an individual substance with a characteristic biochemical and pharmacological profile.

A major drawback of all the heparins is that they have to be isolated from animal material, so that any risk of contamination with pathogens such as prions or porcine viruses cannot be absolutely excluded. Unfortunately, this has recently been an issue of concern due to the presence of oversulfated chondroitin sulfates in heparin (35). In addition, there is a growing shortage of resources to produce heparin (20). Based on these considerations, a synthetic compound with a high affinity to AT was developed (10). After its successful testing in several clinical studies (9, 21, 38), the pentasaccharide fondaparinux has been approved by the FDA in December 2001 and by the EMEA in March 2002 for the prevention and therapy of thrombosis and pulmonary embolism in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgery (30). Fondaparinux has also been applied successfully for additional indications, such as myocardial infarction, prevention of thrombosis in medical patients, and high-risk abdominal surgery (1, 17, 57). Overall, due to their potent anticoagulatory activity, short half-life and good safety profile, heparins and fondaparinux have a broad range of clinical applications (22, 29, 63).

Adverse events, such as bleeding, osteoporosis, hair loss and immune and non-immune heparin-induced thrombocytopenia (HIT) are well characterized (34, 51, 67). However, cutaneous adverse events, presenting as heparin-induced skin lesions have been noted as early as in 1952 (53). Until recently, most authors considered heparin-induced skin lesions as "under-reported" (48), but no data on the incidence of heparin-induced skin lesions had been available.

Recently, a prospective study identified the incidence and causes of heparin-induced skin lesions (56). This study showed that 7.5% of the medical patients treated with heparin develop heparin-induced skin lesions. As heparin-induced skin lesions may be the sole indicator for an underlying, life-threatening immune-mediated HIT (71), we here review the causes of heparin-induced skin lesions and summarize the current diagnostic algorithms and therapeutic recommendations.

Heparin-induced skin lesions: many faces and several causes

Despite some overlap in the clinical presentation, heparin-induced skin lesions are a symptom which has been shown to be the result of at least seven different disease entities (► Tab. 1):

- heparin-induced delayed-type hypersensitivity,
- immune-mediated heparin-induced thrombocytopenia (HIT),
- immediate hypersensitivity,
- recall urticaria,
- bullous haemorrhagic dermatosis,
- skin necrosis or
- pustulosis.

To distinguish between the causes of heparin-induced skin lesions is of immense clinical significance, as some of these conditions, such as immune-mediated HIT, are life-threatening conditions.

Heparin-induced hypersensitivity

For reasons of practicability, we propose the term heparin-induced hypersensitivity (HIHS) for cutaneous type IV allergic reactions induced by heparin. The first symptom of HIHS is itching located at the heparin injection sites. Concurrently or with a small delay erythemas and/or plaques develop. Scaling, as well as papules can be observed in some cases. Mostly, the skin lesions are restricted to the injection sites. In few cases, generalization occurs, especially, when the anticoagulatory treatment with the causative heparin preparation is continued (► Fig. 1). Until lately, most authors reported, that the incidence of HIHS is "underestimated" (12, 31, 48, 55, 56). A recent prospective investigation strongly supports this notion: In a cohort of medical patients treated with subcutaneously administered heparin, 7.5% presented with heparin-induced skin lesions. Detailed determination of the underlying causes identified a type IV allergic reaction in all cases (56). Therefore, HIHS has to be considered a common adverse event of s.c. heparin therapy. How-

* In this manuscript the term „heparin“ refers to both unfractionated heparin (UFH) and low molecular weight heparins (LMWH) if not specified otherwise.

ever, certain patients seem more prone to develop HIHS, and the ability to induce type IV allergic reactions depends on the heparin preparation utilized (►Tab. 2). Regarding patient-related risk factors, obesity and female sex predispose to HIHS. In addition, long duration of heparin, but not a history of previous heparin therapy, is associated with a higher risk to develop HIHS (56). Regarding drug-related risk factors, molecular weight has been implied to determine the ability of different heparin preparations to induce a type IV allergic reaction (46). This concept has been recently challenged (25); i. e. no correlation of increasing molecular weight with a higher degree of type IV responses was found in a cohort of patients with HIHS. A significantly higher rate of HIHS in nadroparin versus enoxaparin treated medical patients (56) supports the later notion, as both LMWH have a comparable molecular weight. Other proposed risk factors such as older age and pregnancy could not be confirmed by regression analysis in a large cohort of s.c. heparin treated patients.

In our opinion, the diagnosis of HIHS should be based on the history, clinical presentation and on a lesional skin biopsy. Taking these into account, diagnosis of HIHS, as well as exclusion of other, possibly life-threatening causes, such as HIT, can be accomplished within 1–3 days after development of heparin-induced skin lesions. Itching located at the injection sites, accompanied by the typical skin lesions (►Fig. 1) is suggestive of HIHS. Despite unspecific findings, i. e. (perivascular) lymphocyte and eosinophil infiltration, histology can support the clinical suspicion while in conjunction with appropriate laboratory tests allows to exclude other causes of heparin-induced skin lesions. In addition, it still remains uncertain, if histology alone can sufficiently diagnose HIT-associated skin lesions by detection of intradermal microthromboses. In the future, a recently established lymphocyte proliferation assay (42) may also contribute to the diagnosis, and possibly identify applicable alternative anticoagulants. We recommend to refrain from allergologic testing in the case of suspected HIHS, since

Tab. 1
Incidence of heparin-induced skin lesions

heparin-induced skin lesion	incidence
delayed-type hypersensitivity (HIHS)	up to 7.5%
immune HIT (incidence of skin lesions)	several case reports
immediate-type hypersensitivity	several case reports
bullous haemorrhagic dermatosis	6 reported patients
recall urticaria	2 reported patients
skin necrosis with unknown cause	case report
pustulosis	case report

- the sensitivity of all tests is too low with the exception of subcutaneous provocation (*Schindewolf et al, submitted*),
- it might induce novel delayed-type allergic reactions,
- they are contraindicated if HIT is not excluded, and
- they are not available when clinical decisions have to be made.

Yet, provocation tests might be useful to determine possible alternative anticoagulants. Future work in the field will aim to

- clarify the high incidence of HIHS in other patient cohorts,
- identify the precise drug-related risk factors, and
- establish rapid and reliable diagnostic algorithms.

Immune-mediated, heparin-induced thrombocytopenia

Immune thrombocytopenia type II (HIT II) is a rare immunological-mediated ad-

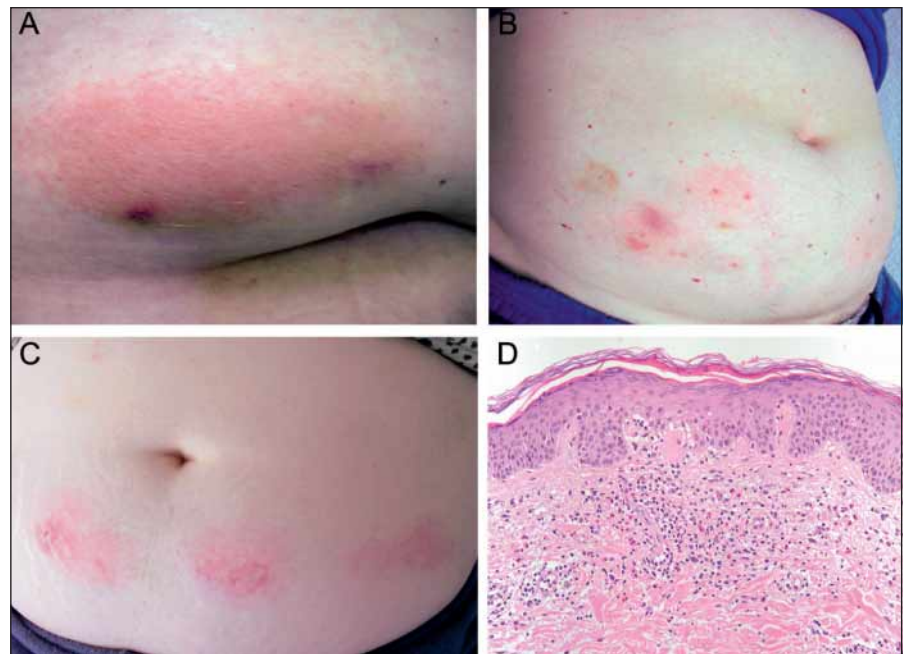


Fig. 1 Clinical and histological presentation of heparin-induced hypersensitivity (HIHS); induction of HIHS at the heparin injection sites: In the majority of cases, they are also confined to this location. In several cases, widespread and/or generalized lesions occur. According to our experience, generalization occurs in 5–10% of cases. However, this has not been systematically addressed.

a–c) patients with localized HIHS; **d)** Histology is unspecific, showing a mostly perivascular lymphocyte infiltration. In most cases eosinophils are also present in higher numbers, whereas changes within the epidermis (e. g. spongiosis) are commonly not observed.

risk factors	patient related (ref.)	heparin related (ref.)
confirmed	obesity, i.e. BMI >25 kg/m ² (56)	nadroparin > enoxaparin (56)
	female sex (56)	
	long duration of heparin therapy (56)	
putative	pregnancy (48)	increasing molecular weight (25, 46, 47)
	older age (48)	

verse reaction caused by unfractionated (UFH) or low-molecular weight heparins (LMWH) that form a complex with the positively charged tetrameric protein platelet factor 4 (PF4), secreted from platelet's α -granules. The binding reaction of heparin with PF4 leads to conformational changes with appearance of antigenic epitopes that may trigger antibody formation (40, 60). Platelet-activation with release of more PF4 than results from binding and cross-linking of antibody-PF4/heparin-complexes with Fc γ RIIa-receptors on platelets (6). This leads to platelet aggregation, generation of prothrombotic platelet-derived microparticles, activation of blood coagulation pathways and, subsequently, a thrombin burst and thrombus formation. PF4 may also bind to endothelial negatively charged polysaccharides i.e. heparan sulfates, and the resulting complex may then be targeted by the HIT-antibodies which causes vascular damages (64). The incidence of HIT with UFH is 10 times

higher than with LMWH (50) which reflects that the binding to PF4 is a function of the polysaccharides chain length and degree of sulfation (24). The incidence of HIT also depends on the type of the heparin-exposed patient population (postsurgical >medical>obstetric). The incidence ranges from 0.5–5% in patients receiving UFH with 5% in orthopedic surgery patients and 0.5% in medical patients (66).

Clinically, HIT is characterized by at least one of the following:

- Thrombocytopenia that occurs in >95% of the patients (69) and typically shows a drop in platelet count of 30–50%. Nevertheless thrombocytopenic platelet counts are not always reached in all those patients with initially elevated baseline platelet counts (26).
- Venous and/or arterial thromboembolism may develop at almost any vascular region, and may complicate the clinical course of HIT and, thus, account for the high mortality of up to 30% (23).

Tab. 2
Patient- and heparin-related risk factors for HIS

- Acute systemic reactions, i.e. fever, chills, tachycardia, hypertension, dyspnea amongst others (66). They are not typical of IgE-mediated immediate anaphylaxis (see next paragraph) and account for approximately 5% of patients identified with HIT (66).
- Skin lesions due to intradermal microvascular thromboses. They start as erythematous lesions that may turn into cutaneous necroses. They may appear at or distant from the sites of heparin injection. Their incidence in patients with HIT is described with 10–20% in literature (66) and they are considered an unusual clinical sequelae of HIT. They may even appear in the absence of thrombocytopenia and are strongly associated with the formation of HIT-IgG-antibodies (71).

Two case series have implied the appearance of skin lesions under therapy with unfractionated heparin to be strongly associated with HIT in 22–50% (27, 65). This seems not to be valid for non-necrotizing skin lesions under therapy with LMWH where an association of skin lesions with HIT in only approx. 1% could be shown; the vast majority of skin lesions were due to a delayed-type hypersensitivity reaction (Schindewolf et al, submitted). Diagnosis of HIT is based on the combination of well-established clinical pre-test probability scores for HIT (41) and laboratory testing using complementary washed platelet activation assays i.e. serotonin release assay (SRA), heparin-induced platelet aggregation assay (HIPA), platelet aggregation test (PAT), and solid phase PF4/Heparin enzyme immunoassays (EIA).



Fig. 2
Heparin-induced skin lesions caused by HIT: In this patient multiple necrotic lesions developed under heparin therapy. Upon diagnosis of HIT, the patient presented with multiple ulcerations on the arms, partially covered by necrotic tissue. In addition, erythema is noted around the ulcerations.

Heparin-induced immediate hypersensitivity

Heparin-induced immediate-type reactions such as generalized urticaria, angioedema, allergic rhino-conjunctivitis, bronchospasm, hypotension and severe anaphylaxis are very rare in the literature (14, 28, 62). Nevertheless, severe type-I-allergic reactions have occurred in the past in more than 900 cases with fatal outcomes in more than 80 patients in the U.S. (35) – these were however due to contamination with

oversulfated chondroitin sulfates, which were shown to directly activate the complement system and induce the generation of C3a/C5a anaphylatoxins *in vitro*, and to activate kallikrein *in vivo* as a mediator of hypotensive anaphylactoid responses via bradykinin, a potent vasoactive peptide mediator. It remains uncertain, if heparins alone exhibit a greater anaphylactical potential since anti-inflammatory properties have been described (44). Nevertheless, these anaphylactical reactions must be distinguished from possible acute systemic reactions which may rarely occur in the context of HIT after intravenous UFH application (68).

Because of its synthetic origin and its clear pharmacological definition as compared to heparins, we do not expect any such contamination-induced systemic immediate-type allergic reactions with fondaparinux as described with heparins. In support of this assumption, we can report on our own clinical experiences with a female pregnant patient with previous severe systemic type-I-allergic reactions to various heparins without any complications during fondaparinux therapy throughout her whole pregnancy. However, when allergologic testing is performed, immediate reading in prick tests are usually false positive (Schindewolf et al, submitted).

Heparin-induced bullous haemorrhagic dermatosis

Induction of bullous haemorrhagic blisters has been noted in a total of 6 patients so far. Clinically, patients present with haemorrhagic blisters, and histology shows intraepidermal or subcorneal blisters filled with red blood cells. In all patients, heparin-induced skin lesions developed distant from the injection sites within 5–21 days after initiation of heparin therapy. Several heparin preparations have been associated with the induction of bullous haemorrhagic blisters, namely enoxaparin, dalteparin, tinzaparin and UFH (11, 52, 61).

Recall urticaria to heparin

Recall urticaria develops in the previously injected area when antigens enter the body

through another route or injection site. Even though clinically well characterized, it's underlying pathomechanisms remain elusive. As mast cells are crucial for immediate hypersensitivity reactions (36), they are the most obvious candidates for mediating this type of localized tissue memory. In total, two patients with recall urticaria to heparin have been described (16, 72). A recently described 42-year-old woman was treated with dalteparin undergoing radioactive iodine therapy. One hour after the first subcutaneous injection at the right lower quadrant, she developed weals at the injection site. In addition, she developed weals on her left lower quadrant where she had been treated with dalteparin previously. Allergologic testig was performed almost 12 months after this episode. While absence of a reaction at the test site was noticed, she developed recall urticaria at former injection sites of dalteparin (72).

Heparin-induced skin necrosis with unknown cause

In addition to immune HIT, heparin-induced skin necrosis may also be caused by different, so far uncharacterized pathomechanisms. This heparin-induced skin necrosis has been described in one patient treated with the LMWH enoxaparin. This 89-year-old African-American female developed large, multiple, painful lesions associated with enoxaparin therapy. Laboratory investigations for HIT, disseminated intravascular coagulation, protein C- and protein S-deficiency, antithrombin III, and homocysteine deficiency were all negative (58). Ruling out of the above listed differentials is of utmost importance, as heparin-induced skin necrosis may be the only clinical presentation of immune HIT, which has been described in the absence of thrombocytopenia (71).

Heparin-induced pustulosis

Komericki and colleagues have described a female patient, whose localized reaction from dalteparin was followed by a generalized rash presenting as acute generalized

exanthematous pustulosis. Subcutaneous provocation testing reproduced the clinical observation, and additionally showed cross-reactions to enoxaparin, certoparin, reviparin, nadroparin, danaparoid, fondaparinux, but not to pentosan polysulfate. This is the first, and so far only described case of heparin-induced pustulosis (37).

Management of heparin-induced skin lesions

If a cutaneous reaction under heparin is observed, immune heparin-induced thrombocytopenia with associated skin lesions needs to be ruled out clinically and by appropriate laboratory investigations for HIT, which include measurement of platelet count, comparison with recent pretreatment baseline values (to detect new-onset thrombocytopenia that begins five or more days after starting heparin) and detection of pathogenic platelet-activating anti-platelet factor 4/heparin (PF4/heparin) antibodies using heparin-dependent platelet activation assays in combination with anti-PF4/heparin immunoassays. Until final diagnosis is established, anticoagulation with heparins must be immediately switched to an alternative non-heparin anticoagulant such as the heparinoid danaparoid, an antithrombin-mediated indirect factor Xa-inhibitor (grade 1b recommendation), or the direct thrombin inhibitors lepirudin or argatroban (both grade 1c), bivalirudin (grade 2c) or the pentasaccharid fondaparinux (grade 2c) (69). For the latter, its use in patients with acute HIT is still under debate (54, 70). Regarding the possible cross-reactivity of danaparoid with heparins, we recommend one of the other possible alternatives. Regarding cost and practicability (i.v. versus s.c. injection), use of fondaparinux, despite not approved for the treatment of HIT, seems a safe and practicable alternative.

The treatment of already existing heparin-induced skin lesions depends on the underlying cause. For skin lesions caused by HIT, appropriate wound care should be applied. Regarding HIHS, short term application of topical class II-III corticosteroids is usually sufficient. If itching is severe, non-sedating antihistaminics are indi-

cated. Type I allergic reactions to heparins have to be treated according to the clinical presentation. In mild cases antihistaminics may be sufficient, however severe cases may require emergency care.

Need for an individualized anticoagulant therapy

In conclusion, adverse cutaneous reactions to heparin are common. In addition, individual heparin preparations have a different capacity to induce those, at least for HIHS and HIT. In our opinion this reflects the fact that despite a similar anticoagulatory profile, the non-anticoagulatory activities, such as induction of adverse events, considerably differs among individual heparin preparations. Therefore, preparations such as fondaparinux seem suited and practicable for patients with risk factors to develop either HIHS or HIT. However, other patients might benefit more from preparations such as dalteparin, nadroparin, UFH or (in the future) semi-synthetic glucan sulfates, as those possess strong anti-metastatic (15, 18, 33, 39, 43, 45, 59) and/or anti-inflammatory activities (2, 5, 49).

Consequently, we propose, that the anticoagulant should be selected based on the pharmacological profile of the distinctive heparin preparations and the individual needs of each patient.

Conflict of interest

E. Lindhoff-Last is member of an advisory board for GlaxoSmithKline.

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