

Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome?

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The term 'baboon syndrome' (BS) was introduced 20 years ago to classify patients in whom a specific skin eruption resembling the red gluteal area of baboons occurred after systemic exposure to contact allergens. Thereafter, similar eruptions have been reported after systemic exposure to beta-lactam antibiotics and other drugs. In addition to the presentation of 2 of our own cases, we have reviewed and characterized the main clinical and histological aspects of published reports of drug-related baboon syndrome (DRBS) and compared the primary clinical signs from such cases to those found in other distinct drug eruptions. Of approximately 100 published baboon syndrome cases, 50 were identified as drug-induced. Of these, 8 were representatives of systemically induced contact dermatitis (SCD), and 42 were examples of drug eruptions elicited by systemic administration of either oral or intravenous drugs. The main clinical findings included a sharply defined symmetrical erythema of the gluteal area and in the flexural or intertriginous folds without any systemic symptoms and signs. 14 of 42 cases were elicited by amoxicillin, 30 of the 42 patients were male, and latency periods were between a few hours and a few days after exposure. DRBS is a rare, prognostically benign and often underdiagnosed drug eruption with distinct clinical features. The term baboon syndrome, however, does not reflect the complete range of symptoms and signs and is ethically and culturally problematic. Moreover, baboon syndrome is historically often equated with a mercury-induced exanthem in patients with previous contact sensitization. Symmetrical drug-related intertriginous and flexural exanthema, or SDRIFE, specifically refers to the distinctive clinical pattern of this drug eruption, and the following diagnostic criteria are proposed: 1) exposure to a systemically administered drug either at the first or repeated dose (excluding contact allergens); 2) sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area; 3) involvement of at least one other intertriginous/flexural localization; 4) symmetry of affected areas; and 5) absence of systemic symptoms and signs.

Key words: allergic contact dermatitis syndrome; baboon syndrome; systemic contact dermatitis.

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The term 'baboon syndrome' (BS) was introduced in 1984 to describe a specific dermatologic response, i.e. erythema of the buttocks and upper inner thighs resembling the red rump of baboons, to systemic or local administration of contact allergens and to certain drugs (1). This reaction was noted in 3 patients previously sensitized by topical contact upon subsequent systemic exposure to the same substance, and mercury, nickel and ampicillin were originally described as causative agents. Therefore, BS was equated by those who first observed this syndrome with one of several clinical variants within the spectrum of systemically induced allergic contact dermatitis (ACD) with a characteristic distribution.

Other systemically induced skin reactions include flare-up of existing eczema or patch test reactions, dyshidrotic reactions or a generalized rash.

Since 1984, about 100 cases have been reported in the literature either as BS or under variant terms, and systemic drugs have been increasingly recognized as causative agents. For most of these drugs, previous skin sensitization or possible cross-sensitization has not been shown.

We report 2 further drug-induced cases with classical baboon pattern skin reactions and propose that systemically induced drug-related baboon syndrome (DRBS) without known previous cutaneous sensitization (Table 1) and systemically induced cases with previous cutaneous

Table 1. Baboon syndrome resulting from systemic drugs (DRBS) in potential symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) cases

Number	Triggering drug	Comedication	Age	Sex	Latency	Patch test	Other tests	Histological pattern	Special remarks	Author (references)
1	Amoxicillin	Nm	35	Female	2d	Nd	Nd	Nd	Previous rash after oral ampicillin in childhood.	Wolf 1992 (9)
2	Amoxicillin	Nm	32	Male	4d	Nd	Nd	Hydropic degeneration of keratinocytes, necrotic keratinocytes, subepidermal separation and superficial perivascular infiltrate with mononuclear cells.	Biopsy taken from an erosive intertriginous lesion. According to authors, histopathology consistent with toxic epidermal necrolysis.	Wolf 1992 (9)
3	Amoxicillin	Nm	52	Male	12 hr	Negative	Prick negative	Spongiosis, superficial perivascular infiltrate with mononuclear cells, edema and extravasation of erythrocytes.	FSME-immunovaccination with first amoxicillin intake. 13 years before generalized exanthem after penicillin-containing antibiotic. 12 years earlier flexural exanthem after amoxicillin-containing antibiotic.	Herfs 1993 (18)
4	Amoxicillin	Nm	60	Female	1d	Positive	Prick negative	Superficial perivascular infiltrate with mononuclear cells.	Similar eruption on the buttocks and major flexures 8 years before—after oral therapy with an unknown antibiotic.	Duve 1994 (19)
5	Amoxicillin	Nm	48	Male	8–12 hr	Positive	Nd	Nd	None	Köhler 1996 (20)
6	Amoxicillin	Nm	37	Male	6 hr	Positive	Nd	Spongiosis, neutrophilic exocytosis, superficial perivascular infiltrate with mononuclear cells and eosinophils, oedema.	Initial periorbital swelling and fever (38°C). Targetoid lesions on palms and soles 3 days later. Penicillin therapy in childhood without adverse effects.	Wakelin 1999 (21)
7	Amoxicillin	Flucloxacillin (Flanamox®); amoxicillin + flucloxacillin	72	Male	2d	Nd	Delayed prick test positive for amoxicillin and Flanamox®, negative for flucloxacillin	Nd	Mild maculopapular rash on trunk in addition to typical baboon type exanthem.	Kick 2000 (22)
8	Amoxicillin	Nm	Nm	Male	2d	Nd	Nd	Nd	none	Loze 2001 (23)
9	Amoxicillin	Diclofenac, acetylsalicylic acid, ibuprofen	57	Male	8–12 hr	Negative	LTT negative for amoxicillin and ibuprofen	Nd	History of previous photo-induced rash after therapy with unknown oral antibiotic.	Strub 2002 (24)
10	Amoxicillin	Nm	28	Male	8d	Negative	Nd	Nd	History of previous penicillin therapy without any adverse effects.	Wolf 2003 (17)
11	Amoxicillin/ clavulanic acid		35	Male	4d	Nd	Nd	Nd	none	Wolf 2003 (17)
12	Amoxicillin (i.v)	Cloxacillin (i.v)	62	Male	1d	Nd	Nd	Superficial perivascular infiltrate with mononuclear cells and eosinophils, oedema.	Few days later, spread of a maculopapular exanthem on trunk and extremities.	Wolf 2003 (17)
13	Amoxicillin	Omeprazole/ clarithromycin	75	Female	8d	Nd	Nd	Nd	No previous history of allergy. Unknown history of previous drug therapy.	Wolf 2003 (17)

Table 1. Continued

Number	Triggering drug	Comedication	Age	Sex	Latency	Patch test	Other tests	Histological pattern	Special remarks	Author (references)
14	Amoxicillin	Oneprazole/ clarithromycine	39	Male	1d	Negative (lesional and non-lesional for all drugs)	Prick and LTT for all drugs negative OPT with 1000 mg amoxicillin positive	Nd	OPT provokes an identical baboon-type exanthem 8 h later.	Our case 1
15	Ampicillin	Sulbactam	53	Male	2d	Negative (lesional and non-lesional for both drugs)	Nd	Nd	No history of previous adverse drug reactions including ampicillin.	Schultz 1996 (25)
16	Pivampicillin	Probenecid	25	Male	1d	Positive	Nd	Nd	Patch test done with ampicillin.	Rasmussen 1985 (26)
17	Ceftriaxone	Ciprofloxacin	64	Male	1d	Nd	Nd	Nd	History of allergy to penicillin. Secondary spread of the exanthem with erythroderma.	Wolf 2003 (17)
18	Cefuroxime	Nm	62	Male	1d	Negative	Nd	Nd	Patch tests done with cefuroxime and cephalixin.	Wolf 2003 (17)
19	Cefuroxime	Nm	78	Female	2d	Nd	Nd	Superficial perivascular infiltrate with mononuclear cells and neutrophils, neutrophilic exocytosis, subcorneal neutrophilic pustules.	None	Our case 2
20	Cephalexin	Nm	48	Female	8d	Nd	Nd	Nd	None	Wolf 2003 (17)
21	Cephalexin	Nm	83	Male	4d	Nd	Nd	Nd	History of previous penicillin allergy not otherwise specified by authors.	Wolf 2003 (17)
22	Clindamycine	Metronidazole, gentamycin, sulfate, cefazolin	28	Female	Nm	Angry back	MCD positive for clindamycin and cefazolin, MIF positive for cefazolin and MCD negative for gentamycin and doxycycline). OPT with clindamycin positive (Latency: few days, provoking an identical eruption)	Superficial perivascular infiltrate with mononuclear cells, hyperkeratosis, acanthosis and elongation of the rete ridges.	Intertriginous rash over 4 months. Initial therapy with clindamycin, gentamycin and cefazolin (start of the rash), then change to doxycycline and metronidazole for several weeks. Various topical treatments for suspected intertrigo for weeks. During evaluation stop of the last systemic drug metronidazole.	Wolf 1993 (27)
23	Erythromycin	Nm	1.5	Male	few hr	Nd	Prick and i/d-test negative. LTT positive	Superficial perivascular dermatitis with lymphocytes	Previous treatment with erythromycin. No history of atopy.	Goossens 1997 (28)
24	Penicillin V	Nm	57	Male	few hr	Positive (for penicillin G.V and Megacillin [®])	Delayed prick test positive for penicillin G.V and MDM (Prick for all negative)	Pustular haemorrhagic drug exanthem	Baboon type exanthem with erosions, petechiae and pustules.	Panhans-Gross 1999 (29)

Table 1. Continued

Number	Triggering drug	Comedication	Age	Sex	Latency	Patch test	Other tests	Histological pattern	Special remarks	Author (references)
25	Roxithromycin	Nm	58	Male	2d	Nd	Nd	Nd	None	Amichai 2002 (30)
26	Allopurinol	Nm	58	Male	1.5 hr	Negative	Delayed i/d-test positive. Prick negative	Superficial perivascular infiltrate with mononuclear cells and eosinophils, exocytosis of erythrocytes, necrotic keratinocytes, oedema	Secondary spread of the exanthem beside typical baboon-like distribution. History of identical rash after previous treatment with allopurinol. Conflicting: Latency, clinics and histology similar to fixed drug eruption!	Montag 1996 (10)
27	Barium sulfate	Nm	79	Female	few hr	Nd	Nd	Nd	Barium-sulfate-containing contrast media.	Wolf 2003 (17)
28	Cimetidine	digitoxin, aminophiline, pentoxifyline, verapamil, troxerutin, pentaerythryl tetranitrate	74	Male	Nm	Negative	Prick negative. OPT positive (200 mg), parenteral provocation test positive with all drugs negative. LTT: negative	Spongiosis, superficial perivascular infiltrate with mononuclear cells	4-month history of baboon-like erythema. Oral medications for several months, cimetidine (31) for 6 months. Withdrawal of all drugs except digitoxin lead to full recovery within 2 days. Skin tests done with all drugs. OPT done with all drugs in one single oral dose.	Helmbold 1998 (31)
29	Daflazacort	Prednicarbate cream	27	Female	few hr	Positive	Patch tests with 12 other corticosteroids negative OPT with prednisone, methylprednisone and dexamethasone negative	Superficial perivascular infiltrate with lymphocytes and eosinophils, apoptotic keratinocytes (consistent with erythema multiforme). Granular IgM deposits at dermoepidermal junction	History of 3 episodes with baboon-like exanthem, with fever, nausea, vomiting, malaise and hypotension after deflazacort.	Garcia-Bravo 2000 (11)
30	Heparin (i.v)	Nm	82	Male	16d	Nd	i/d-test positive for heparin and low molecular heparin (Fraxiparin [®])	Nd	Initially infiltrated erythema at the injection sites and thighs, 9 days later typical baboon-like exanthem. Withdrawal of heparin 6 days before.	Pfeiff 1991 (32)
31	Hydroxyurea	Diigoxin, warfarin and tamoxifen	81	Female	6d	Nd (patient refused)	Nd	Superficial perivascular infiltrate with mononuclear cells	Pruritic rash also on trunk, legs and face. Previous treatment with hydroxyurea with no adverse effects 1 year before. After withdrawal of hydroxyurea resolution of the rash.	Chowdhury 1999 (33)

Table 1. Continued

Number	Triggering drug	Comedication	Age	Sex	Latency	Patch test	Other tests	Histological pattern	Special remarks	Author (references)
32	IVIg (intravenous human immunoglobulins)	Nm	28	Female	1d	Negative (lesional and non-lesional)	Immediate and delayed lesional and non-lesional prick and i/d-tests negative. Parenteral provocation (i.v) induced generalized maculopapular rash with Tegelin [®] , and erythema on the buttocks with Sandoglobulin [®] . LTT and human basophil degranulation test for both drugs negative	Superficial perivascular infiltrate with CD4+ lymphocytes cells, oedema, granular deposits of C1q along dermoepidermal junction, expression of CD62P (p-selectin, GMP 140) observed on keratinocytes mainly along dermoepidermal junction	Recurrent pompholyx following the second series of IVIG. During 10th administration (change from Tegelin [®] to Sandoglobulin [®]) development of typical baboon syndrome.	Barbaud 1999 (34)
33	Mitomycin C (intravesical instillation)	Nm	57	Male	2d	Positive	Nd	Nd	Eruption after 7th intravesical instillation of MMC. 8th therapy induces similar rash after 1 day.	De Groot 1991 (35)
34	Mitomycin C	Nm	81	Male	Nm	Positive	Nd	Nd	Baboon-like erythema after 6th intravesical instillation of mitomycin C.	De Groot 1991 (35)
35	Mitomycin C	Nm	84	Male	Nm	Positive	Nd	Nd	Baboon-like erythema after 6th intravesical instillation of mitomycin C.	De Groot 1991 (35)
36	Naproxene (Naxyn [®])	Nm	60	Male	1d	Negative	Nd	Consistent with the mixed dermal-epidermal type of erythema multiforme	Treatment with the same drug two months earlier without any adverse effects.	Wolf 2003 (17)
37	Nystatin	Nm	47	Male	2d	Positive	Other patch test series including antibiotics, antimycotics and local anaesthetics negative	Spongiosis, superficial perivascular infiltrate with mononuclear cells	Previous topical treatment of the anogenital area with nystatin-containing ointments. Baboon-like erythema follows oral nystatin therapy because of suspected candidiasis. Authors propose systemic induced allergic contact dermatitis after previous skin sensitization.	Leehner 1987 (36)
38	Oxycodone	Percodan [®] containing oxycodone, hydrochloride, oxycodone terephthalate and aspirin	74	Male	2d	Nd	Nd	Nd	Intertriginous baboon-like eruption with erosions and bullae. Reappearance of an identical eruption after oral re-exposition.	Wolf 2003 (17)

Table 1. Continued

Number	Triggering drug	Comedication	Age	Sex	Latency	Patch test	Other tests	Histological pattern	Special remarks	Author (references)
39	Pseudoephedrine	Logradin [®] containing loratadine and pseudoephedrine	73	Female	6 hr	Positive	Nd	Superficial perivascular infiltrate with mononuclear cells and eosinophils, edema, subcorneal and suprabasal pustules	History of an identical eruption after oral therapy with an unknown drug containing ephedrine. Negative patch test with loratadine. Biopsy of pseudoephedrine patch test area shows histological pattern.	Sanchez 2000 (6)
40	Pseudoephedrine	Atiramin [®] containing azatadine and pseudoephedrine	20	Female	3 hr	Positive (lesional and non-lesional)	Prick tests with both drugs and pseudoephedrine negative	Nd	Eruption after the second tablet. Identical eruption 3 months later, after one dose of oral Iniston [®] sirup (tripolidine and pseudoephedrine). Negative patch tests for pseudoephedrine and Atiramin [®] . Authors discuss false-negative patch tests with the latter two substances for technical reasons.	Sanchez-Morillas 2003 (7)
41	Salsalate	Nm	36	Male	14d	Nd	Nd	Consistent with leucocytoclastic vasculitis	Spread of the eruption to the distal extremities within 48 hr No history of allergies.	Gordon 2002 (37)
42	Terbinafin	Nm	26	Male	30 hr	Negative	OPT positive (250 mg, Latency: 20 h) Scratch test negative	Nd	None	Weiss 2001 (38)

d = day; hr = hour; LTT = lymphocyte transformation test; MCD = mast cell degranulation test; MDM = minor determinant mixture; MIF = macrophage migration inhibition test; Nd = not done; Nm = not mentioned; OPT = oral provocation test (oral rechallenge).

sensitization (including cases elicited from absorption of topical substances, e.g. allergic contact dermatitis syndrome (ACDS) 3A and 3B, Table 2) be divided into 2 distinct subgroups.

Materials and Methods

In addition to the presentation of 2 of our own cases, we have reviewed and characterized the main clinical and histological aspects of published Pub Medical reports of DRBS and compared the primary clinical signs from such cases to those found in other distinct drug eruptions, e.g. acute generalized exanthematous pustulosis (AGEP), fixed drug eruption (FDE) and drug rash with eosinophilia and systemic symptoms (DRESS), using key publications and current textbooks.

Case reports

Case no. 1. A 39-year-old man was treated by his primary care physician for suspected *Helicobacter pylori* gastritis with the recommended dosages of amoxicillin, clarithromycin and omeprazole. The next day, he developed a pruritic symmetrical erythema with vesicles and small pustules on both inner thighs, cubital fossae, axillae and the gluteal area (Figs 1–3). This cutaneous drug eruption resembling the red area of the rump of a baboon was presumably a reaction to amoxicillin, and 2 weeks after discontinuing all drugs, the lesions resolved themselves without any further therapy. The patient's history as far as previous exposure to amoxicillin or other beta-lactam antibiotics was not conclusive. Immediate prick and intradermal, and patch tests with all 3 drugs on non-lesional and lesional skin were negative. IgE antibodies to amoxicillin, penicillin G/V and ampicillin were negative. The LTT for all 3 drugs showed no increased stimulation. 3 months after the first visit, re-exposure to amoxicillin was accomplished with one oral dose, resulting in an identical reaction 8 h thereafter. No systemic symptoms were observed, and no laboratory analysis or skin biopsy was performed.

Case no. 2. A 78-year-old woman with a history of chronic asthma and intolerance for acetylsalicylic acid underwent surgery for hallux valgus. Because of arterial hypertension and former pulmonary embolism, she had long been receiving spirinolactone/buticid, torasemide, phenprocoumon and topical anti-asthmatic drugs. On the day of surgery, she received 750 mg cefuroxime intravenously t.i.d. and 2 days later developed a sharp symmetrical erythema with small pustules on the buttocks and erythema alone in a V-shaped pattern on the inner upper thighs, popliteal folds and

submammary areas. Blood tests were normal and systemic signs were absent. A baboon-type drug reaction was diagnosed, and skin biopsy showed a superficial perivascular dermatitis with a dominant involvement of mainly CD3+/CD4+ lymphocytes and some neutrophils. Additionally, subcorneal pustules were present consistent with a pustular variant of a baboon-type drug eruption. The dermatitis spontaneously cleared within 8 days. She denied previous drug eruptions, but she was not certain about previous intake of any antibiotics. The patient did not develop systemic signs and refused further laboratory investigations.

Results

Of approximately 100 cases classified as BS, 50 were found to be drug-induced. Of these, 8 were considered representatives of systemically induced ACD or ACDS (Table 2), and 42 were assessed as examples of drug eruptions elicited by systemic administration of oral or intravenous drugs (Table 1). The main clinical findings included sharp demarcation of a V-shaped erythema in inguinal/genital and gluteal/perianal areas and, in most cases, additional involvement of at least one other flexural or intertriginous fold. In 14 of 42 cases, amoxicillin was the eliciting drug, 30 of the 42 patients were men, and the latency periods were short, between hours and few days. The main histological pattern was non-specific and showed a superficial perivascular mononuclear cell infiltrate with some neutrophils and some eosinophils.

Discussion

In 1983, Nakayama published a report of 15 patients with sharply symmetric erythemas predominantly on major flexural sites that arose in most cases 1 or 2 days after breaking a mercury thermometer. This eruption was labelled mercury exanthem or eczema rubrum (2). A year later, Andersen et al. (1) reported 3 patients with intertriginous and flexural erythemas primarily involving the buttocks after systemic administration or absorption of contact sensitizers such as nickel, mercury and ampicillin. The predominant visual effect was similar to the red rump of the baboon, thus the term 'baboon syndrome' (BS) was introduced. Both of the initial reports mentioned above classified their observations as a form of systemically induced ACD subsequent to previous skin sensitization with identical contact allergens. 10 years later, Menné et al. proposed the term systemic contact dermatitis (SCD) for BS and other types of dermatitis either with or

Table 2. Baboon syndrome resulting from systemic absorption of either systemical or topical applied drugs with previous cutaneous contact with the same molecule (ACDS cases Stage 3A and 3B)

Number	Triggering drug	Comedication	Age	Sex	Latency	Patch test	Other tests	Histological pattern	Latency and special remarks	Author (references)
1	Ampicillin (top.)	Promethazine and thimebumal (for anaesthesia)	63	Male	1d	Positive	Delayed i/d-test with penicillin G positive	Leucocytoclastic vasculitis	Topical application of ampicillin solution during surgery. Authors suggest systemic absorption. Secondary spread of a generalized maculopapular rash.	Andersen 1984 (1)
2	Neomycin (oral)	Metronidazole, nebacetin-forte [®] (neomycin sulfate and bacitracin)	70	Male	1d	Nd	Nd	Nd	History of allergy to cement. Previous topical treatment of chronic ulcer cruris. History of positive patch tests to neomycin, perubalsam, lanolinum, colophonium, carbamix and chromate. Slow resolution of exanthem after withdraw of Nebacetin-forte [®] .	Menné 1984 (39)
3	Aminophylline (i.v., containing ethylenediamine EDA)	Persantine	64	Male	few hours	Positive (for EDA, non-lesional)	Nd	Nd	History of previous topical treatment at exactly these sites with unknown drug (authors postulate EDA containing drug).	Guin 1999 (40)
4	Aminophylline (i.v., containing EDA)	Betamethason i.v.	66	Female	1d	Positive (for EDA)	Nd	Nd	20 years before positive patch test for EDA. Previous topical treatment at intertriginous sites with a medication probably containing EDA.	Isaksson 2002 (41)
5	5-aminosalicylic acid (topical 5-ASA, mesalazine)	Nm	50	Male	few d	Positive (for 5-ASA and enema, nickel sulfate and neomycin, all non-lesional)	Nd	Nd	Tolerance of oral hydroxyzine. History of multiple treatments with various topical drugs in the perianal area. 5-ASA used as foam enemas. Resolution after withdrawal of foam enema. Authors propose systemic absorption of 5-ASA.	Gallo 2002 (42)

Table 2. Continued

Number	Triggering drug	Comedication	Age	Sex	Latency	Patch test	Other tests	Histological pattern	Latency and special remarks	Author (references)
6	Bufexamac (top.)	Nm	48	Female	few d	Positive	Nd	Superficial perivascular infiltrate with mononuclear cells and eosinophils, extravasation of erythrocytes	Topical treatment with bufexamac-containing ointment to the anal region. No further positive patch-test results for all other substances in this bufexamac-containing ointment. Authors propose dermal absorption of bufexamac.	Proske 2003 (43)
7	Cinchocaine (top.)	Cinchocaine within Nupercainal [®] and Scheriproct [®] ointments	54	Male	1d	Positive	Nd	Nd	No history of dental treatment or inhalation of mercury vapour from a broken thermometer. Patch test also positive for both ointments, came mix (benzocaine, tetracaine, cinchocaine), procaine and ammoniated mercuric chloride. Authors propose systemic absorption of cinchocaine.	Marques 1995 (44)
8	Cinchocaine (top.)	Cinchocaine within DoloPosterine N [®] ointment	62	Female	few d	Positive and also for DoloPosterine N [®]	Nd	Nd	Resolution after withdrawal of the ointment. Patch tests for articaine, benzocaine, lidocaine, mepivacaine, prilocaine and tetracaine ointment.	Erdmann 2001 (45)

d = day; h = hour; LTT = lymphocyte transformation test; MCD = mast cell degranulation test; MDM = minor determinant mixture; MIF = macrophage migration inhibition test; Nd = not done; Nm = not mentioned; OPT = oral provocation test (oral rechallenge).



Fig. 1. Sharply demarcated V-shaped erythema in the inguinal/perigenital area.

without previous topical exposure and caused by systemic administration of substances including contact allergens and drugs (3). According to Menné et al. (3), BS was classified as 1 of 5 clinical reaction patterns (in addition to vesicular hand eczema, flexural dermatitis, maculopapular rash and vasculitis-like lesions) within the group of SCD without previous skin sensitization. Recently, Lachapelle (4) proposed the term ACDS to distinguish all clinical types of ACD with previous skin sensitization from other immunologically related CADRs that lacked prior cutaneous sensitization to the allergen. In this classification, BS is again considered an example of ACDS stage 3. Because the term ACDS includes the assumption of previous cutaneous sensitization for all stages, patch testing is the mainstay of aetiological diagnosis for ACDS. Stage 1 comprises circumscribed ACD, Stage 2 includes regional dissemination via lymphatic vessels extending from the cutaneous site of allergen contact, and Stage 3 encompasses haematogenous dissemination of either ACD at a distance (3A) or a systemic reactivation of ACD (3B) equated with systemic reactivation of ACD. In

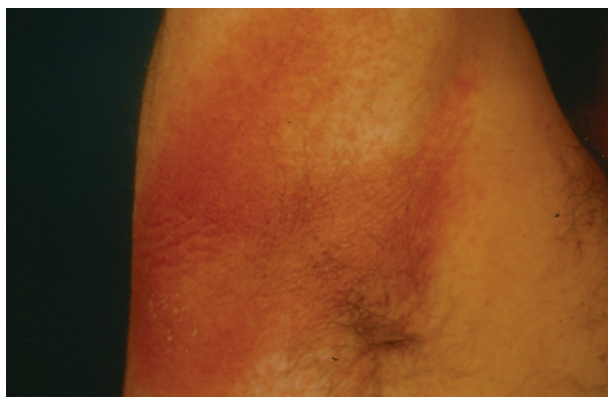


Fig. 2. Sharply demarcated erythema in the axillary fold.

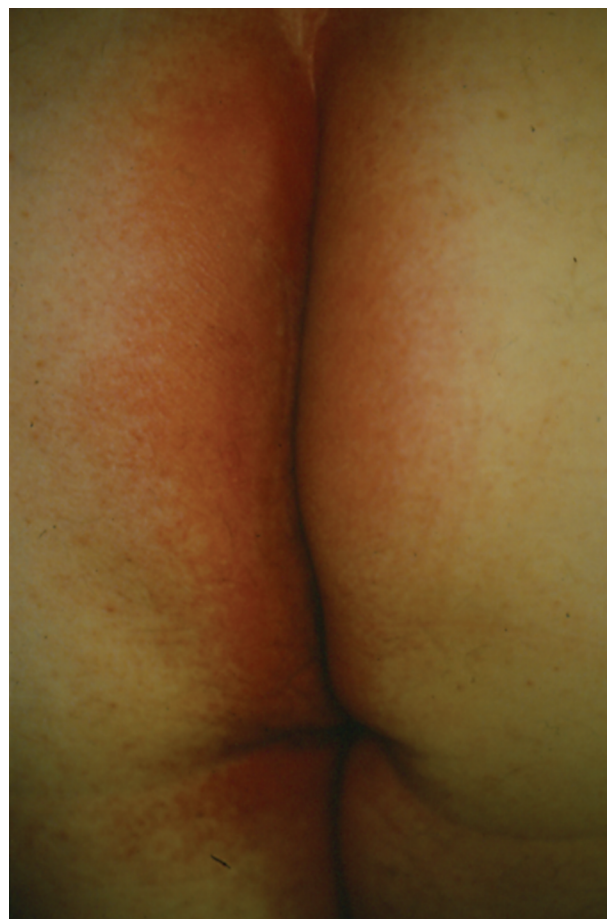


Fig. 3. Sharply demarcated erythema in the gluteal area.

this stage, the elicitation phase is initiated by either an identical allergen, a chemically closely related and cross-reactive molecule or an identical non-allergenic molecule that is transformed into an allergenic molecule. To date, many sometimes confusing terms have been proposed to describe this heterogeneous group of so-called systemically induced contact dermatitis (Table 3).

Thus far, systemic drugs, particularly amoxicillin and β -lactam antibiotics, account for about half of all BS cases (Table 1). Previous cutaneous and systemic sensitization is typically unknown or undocumented. This group of DRBS cases encompasses cutaneous adverse drug reactions with a distinct clinical pattern. In Menné et al.'s (3) classification of SCD, BS would have been considered a member of this first group. Although not currently designated as BS, we also propose to include Shelley's reported cases of 2 pseudoephedrine- and 1 tetrahydrozoline-induced symmetrical non-pigmenting FDEs in the DRBS subgroup, as previously defined by Sanchez and Sanchez-Morillas (5–7).

The second group of systemically induced DRBSs typically follows topical exposure to the

Table 3. Proposed terms for cutaneous eruptions related to or imitating the baboon syndrome

Internal-external contact type hypersensitivity (Ratner 1974) (47)
Mercury exanthem (eczema rubrum) (Nakayama 1983) (2)
Baboon syndrome – systemically induced allergic contact dermatitis (Andersen 1984) (1)
Nonpigmenting fixed drug eruption (Shelley 1987) (5)
Intertriginous drug eruption (Wolf 1992) (9)
Drug-induced intertrigo (Wolf 1993) (27)
Systemic contact dermatitis (Menne 1994) (3)
Parapitic eczema (Happle 1994) (46)
Symmetric pitychotropic and non-pigmenting fixed drug eruption (Helmbold 1998) (31)
Flexural (drug) eruption (Wakelin 1999) (21)

offending molecule via creams or ointments frequently used at perianal sites, often without the occurrence of skin reactions. In these topically sensitized patients, the clinical reaction can be induced by systemic absorption of either systemic or topical substances (Table 2). These cases are all examples of ACDS stage 3A or 3B, as proposed by Lachapelle (4).

DRBS presents with sharply defined V-shaped erythema in inguinal/genital and gluteal/perianal areas, sometimes with tiny papules, pustules and vesicles, and often with exanthem in other flexural areas. Palmae, plantae, facial or mucosal sites are not involved. Blood tests are normal and systemic symptoms are absent. Histology is variable, with a reported predominance of superficial perivascular infiltrates of mononuclear cells. The latency times between drug intake and onset of eruption ranges from hours to a few days. Therefore, DRBS shows homogeneity for clinical distribution, range of primary cutaneous lesions, latency period after systemic absorption and course. In contrast, heterogeneity is observed histologically and in the results of skin tests and *in vitro* investigations. In contrast to maculopapular drug eruptions, there is a surprising predominance of male patients.

The term BS is problematic for several reasons: First, BS is historically equated with the gluteal erythema induced by systemic absorption of mercury and other agents, often after previous cutaneous sensitization with the same substance. Second, based on recent results, it does not reflect the entire range of clinical symptoms and signs of mercury-induced BS (8). Third, according to various investigators, BS incorporates an overbroad

spectrum of diseases, encompassing ACDSs, drug eruptions and a variety of other intertriginous dermatoses such as intertriginous candidiasis. Moreover, the use of such analogies fails to respect ethical and cultural sensitivities. Whether the term should continue in use for cases elicited by contact allergens, e.g. mercury, remains controversial. Because DRBS drug eruptions are rare, distinctive and apparently benign, we propose to establish a new term in line with commonly used and easily remembered abbreviations for specific drug eruptions, e.g. FDE, TEN (toxic epidermal necrolysis), AGEP and DRESS. The acronym SDRIFE, standing for symmetrical drug-related intertriginous and flexural exanthema, seems a reasonable term and has the additional advantage of separating such cases from others represented in the second group (Table 2) to permit recognition as a separate entity within the spectrum of CADR. We propose 5 diagnostic criteria for SDRIFE, as listed in Table 4:

1) exposure to a systemically administered drug either at the first or repeated dose (excluding contact allergens); 2) sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area; 3) involvement of at least one other intertriginous/flexural localization; 4) symmetry of affected areas; and 5) absence of systemic symptoms and signs.

Histopathologically, the main finding in both groups of drug-induced BS is the superficial perivascular infiltrate, primarily composed of mononuclear cells, in some cases including neutrophils and eosinophils. Among other rare findings,

Table 4. Criteria proposed for SDRIFE

Criteria	Description
1	Exposure to a systemically administered drug, first or repeated doses (contact allergens excluded)
2	Sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area
3	Involvement of at least one other intertriginous/flexural fold
4	Symmetry of affected areas
5	Absence of systemic symptoms and signs

Table 5. Comparison and typical clinical features of distinct cutaneous drug eruptions

	AGEP	DRESS	FDE	SDRIFE
Clinical manifestation	Mostly generalized symmetrical pustular exanthem with possible erythroderma and facial involvement, sometimes with purpuriforme acral erythema multiforme like lesions rarely with mucosal involvement	Generalized symmetrical maculo-papular or morbilliform exanthem often with facial involvement and possible erythroderma	Asymmetric distributed solitary or multiple erythematous round-oval patches or plaques commonly with residual pigmentation often in acral, genital and mucosal areas	Symmetrical intertriginous and flexural erythematous exanthem without facial and mucosal involvement, no erythroderma
Systemic symptoms	Fever	Fever	None	None
Organ involvement	Normally none	Hepatitis, lymphadenopathy, nephritis and arthritis	None	None
Laboratory findings	Leucocytosis with elevated neutrophil count, sometimes mild to moderate eosinophilia	Prominent eosinophilia, mononucleosis-like atypical lymphocytosis	Normal	Normal
Latency	Hours to few days	2–6 weeks	1–2 weeks after first exposure, after subsequent exposure regularly within 24 h	Hours to 2 days
Most frequently involved drugs	Beta-lactam antibiotics (penicillins, aminopenicillins, cephalosporines), macrolides, calcium channel blockers (diltiazem) and terbinafine	Aromatic anticonvulsants (e.g. phenytoin, carbamazepine, phenobarbital), lamotrigine (especially when coadministered with valproate), sulfonamides, minocycline and allopurinol	Sulfonamides, NSAIDs (in particular phenazone derivatives), barbiturates, tetracyclines and carbamazepine	Aminopenicillins most often amoxicillin, other beta-lactam antibiotics

AGEP = acute generalized exanthematous pustulosis; DRESS = drug rash with eosinophilia and systemic symptoms; FDE = fixed drug eruption; SDRIFE = symmetrical drug-related intertriginous and flexural exanthema.

vacuolar and hydropic alteration of the basal cell layer with necrotic keratinocytes is mentioned in 3 reports related to amoxicillin, allopurinol and deflazacort, respectively (9–11). These features are usually not seen in SCD, ACDS or common CADR but are typical of bullous drug eruptions, e.g. erythema multiforme, TEN and FDE. From a strict histological perspective, these cases could also be considered as imitators of BS in the course of, for example, FDE or bullous drug eruptions.

Classification of SDRIFE as a separate entity within the spectrum of drug eruptions requires separation from FDE, AGEP and DRESS (Table 5). FDE is clinically distinguishable by its localized, often acral or mucosal, asymmetric, frequently pigmented, round-oval lesions. Histopathological hallmarks include a predominantly lymphocytic inflammation, variable slight parakeratosis, slight focal oedema, rare dyskeratotic cells, vacuolarization along dermoepidermal junction, slight papillary fibrosis and scattered melanophages, especially between venules. Drugs most frequently associated with FDE are sulfonamides, non-steroidal anti-inflammatory drugs, barbiturates, tetracyclines and carbamazepine. The 2 features in common with SDRIFE seem to be the rather short latency period between drug intake and onset of exanthem, and the absence of systemic signs (12).

AGEP has also been recognized as a specific entity that must be differentiated from SDRIFE, particularly in view of the clinical presentation, distribution and histopathology (13). AGEP typically presents with a disseminated erythrodermic eruption with primarily non-follicular pustules associated with high fever and sometimes oedema of the face. Blood neutrophilia and accumulation of neutrophils within the lesions suggest release of neutrophil-activating cytokines by drug-specific T-lymphocytes, e.g. IL-3, IL-8 and G-CSF (14). In the absence of systemic signs, cases with exclusively flexural and intertriginous involvement could be classified as pustular variants of SDRIFE. Except for systemic signs and flexural affection, AGEP and SDRIFE share similar latency times, potential immunologic pathogenesis and causative drugs.

Finally, DRESS has been proposed as a more specific term than 'drug hypersensitivity syndrome', which would be appropriate for most types of drug reactions, including maculo-papular rashes. DRESS clearly differs from SDRIFE in systemic symptoms, cutaneous signs, organ involvement, eosinophilia and responsible drugs, and this difference is even more important in prognosis, because DRESS may be associated with potentially lethal organ involvement such as

fulminant hepatitis (15). We believe that SDRIFE cases represent a distinct subgroup of drug eruptions with very specific involvement sites, presumably elicited by an immunological Type IV mechanism. In our view, there is insufficient evidence to propose additional predisposing factors, such as anatomical structures, e.g. the density of apocrine or eccrine glands (excretion of metabolized drugs), temperature, humidity or the recall phenomenon (16, 17). The precise immunological and pathogenetic mechanisms of SDRIFE have yet to be elucidated, as well as the reason why a drug such as amoxicillin elicits a typical maculo-papular exanthem in some individuals, and urticaria, anaphylaxis, TEN, AGEP or SDRIFE in others.

Conclusion

We propose a new acronym to replace and further refine the overly broad and ethically inappropriate catchword BS and believe SDRIFE is the most appropriate for several reasons. The acronym implies with the 'D' a drug eruption and may help non-specialists to remember the main clinical features, e.g. the symmetrical intertriginous and flexural involvement of an exanthem with the 'S', 'I', 'F' and 'E', respectively. The acronym will further differentiate between other common acronyms for drug eruptions, e.g. AGEP, DRESS and FDE, and distinguish SCD and ACDS as separate entities. SDRIFE, unlike BS, is a neutral term that avoids ethically and culturally offensive comparison with an animal and distinguishes SDRIFE as a relatively benign condition, in contrast to bullous eruptions or DRESS.

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