Bullous Pemphigoid

Anita Dhirad[1], Robert Holik[1] and Maria Kläßbo[2]
[1]*Department for Dermatology and Venereology and Centre for Clinical Research, Central Hospital, SE-651 86 Karlstad, Sweden. E-mail: anita.dhirad@liv.se*

Introduction

Both in Sweden and internationally there is a lack of well accepted diagnostic criteria for bullous pemphigoid (BP) (1). BP is a skin disease where the new registrar often needs guidance from a specialist for investigation, management and treatment. The name *bullous pemphigoid* is a tautology; bullous comes from the Latin word bulla which means blister while pemphigoid is the Greek word for the form of a blister (1).

In Central Europe BP is the most common blistering disease. BP occurs more often with increasing age and more seldom in young people and children. The disease is equally common in both sexes (2). BP is a chronic, autoimmune acquired blistering disease characterized by auto-antibodies (mostly IgG and C3, sometimes IgA, IgM and IgE) against hemidesmosome antigen complex BP180 and BP230 to the basement membrane, resulting in the formation of subepidermal blistering (3–5). Hemidesmosomes are structural proteins that anchor a skin cell to its nearest neighbouring skin cells. BP may have spontaneous exacerbations and remissions. In the US, the prevalence of BP is 6–10 cases/million inhabitants. Varying incidence is reported. For instance in the north-east of Scotland, the incidence is 14 cases/million (5, 6). In 2011, the one-year incidence (number of new patients) for BP was 36 cases/million at the Central Hospital in Karlstad (CSK) and 22 cases/million at Örebro University Hospital (USÖ).

In most cases no trigger of BP is found. Occasionally the following factors have caused the onset of BP: local cutaneous trauma, surgery, exposure to ionizing or UV radiation, vaccination and systemic medications (for example furosemide, spironolactone, diazepam, benzothiadiazide) (3). BP is usually self-limiting, within the first 5 years (5). The disease-related mortality in the pre-corticosteroid era was 24%. Now mortality varies between 0–40% (3). The treatment with systemic corticosteroids may also lead to increased mortality. This has increased the interest in alternative treatments. With current treatment strategy the authors experience the mortality figure of 40% too high. Patients with BP have generally poor health and high age (7–9). It has been concluded that there is not an increased risk for malignancy among patients with BP compared to age- and sex-controlled groups (5). Therefore, there is no need to investigate for malignancies in patients with BP.

The clinical picture

The prodromal phase of classical BP may be up to one year, and manifests itself mostly as erythematous or urticaria-like lesions (6, 10), in particular on the flexor sides of the arms, lower legs, armpits, groin and stomach. Classical BP is characterized by large, tense, water clear, yellowish or bloody blisters on red or normal skin. They heal very rarely with milia or scarring. Patients almost always experience severe itch (11). Large areas of the body can be affected. Sometimes one can see a localized form for example on a limb (1) (Fig. 1). Classic BP exhibits mucosal involvement in fewer than half of patients, most common in the oral cavity. There is a controversy as to how common mucosal involvement is (2, 3, 5, 6, 9, 12, and 13). In the authors' own experiences 50% seem like a too high figure regarding mucosal involvement in classical BP.

Method

Method to investigate the practice at the dermatological clinics in Karlstad (CSK) and Örebro (USÖ)

The substrate of this article is partly based on literature search and partly on a questionnaire answered by the dermatologists at CSK and USÖ. The aim was to compare clinical practice with published scientific evidence regarding investigation, management and treatment of BP. The questionnaire is based on two articles (1, 5), with partially open questions which all specialists at some point guiding the registrars were asked to answer. At CSK 6 and at USÖ 4 of the consultants answered. The answers were compiled at group level, and sent out together with a few more questions, going more on the depth according to the so called Delphi method (http://en.wikipedia.org/wiki/Delphi method). The second time totally 5 doctors answered.

Method for gathering scientific evidence

Searches were made in the database PubMed, the National Board of Health (Socialstyrelsen) (0 hits), the Swedish Council on Technology Assessment in Health Care (SBU)'s website (0 hits) and the database Best practice. In the Cochrane library a search with the key-word "bullous pemphigoid" found a survey from 2010 (2). The database Best practice results found the condition with the key-word "bullous pemphigoid" (6),

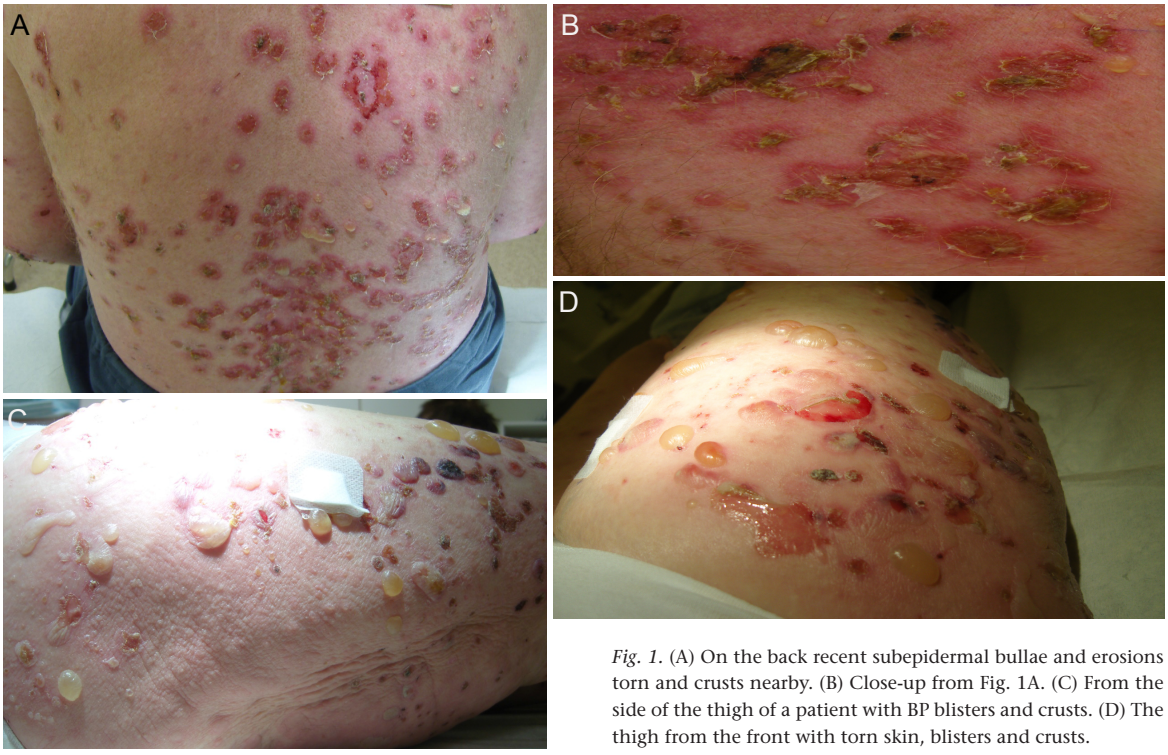

Fig. 1. (A) On the back recent subepidermal bullae and erosions torn and crusts nearby. (B) Close-up from Fig. 1A. (C) From the side of the thigh of a patient with BP blisters and crusts. (D) The thigh from the front with torn skin, blisters and crusts.

and a link to a guide from 2002 (5). Search routine is shown in Table I and Fig. 2. One hundred and sixty-four articles came up and after thinning 16 of those were left.

Results

Diagnosis

Diagnostics at CSK and USÖ. The practice of diagnosing BP is based on clinical findings, skin biopsy for pathological anatomical diagnosis (PAD) and immunopathological findings with direct (DIF) or indirect immunoflouresence (IIF). Seven out of 10 specialists believe that there are a minimum of requirements for diagnosing BP, and different suggestions for this skin condition were given (Table II).

During the patient's first visit, 8 out of 10 doctors do a skin biopsy (Fig. 3). If possible a skin biopsy should take an entire blister. If the blister is larger than the punch instrument, the biopsy is taken 2 mm from the blister. This is done to avoid fragmentation between the epidermis and dermis (Fig. 3). All the responding doctors did take DIF and more than 50% took IIF.

Diagnosis according to scientific evidence. The patient's age may be of significance since BP is most common in people over the age of 60 years (9). After taking a history, the skin, including mouth and genital area, is inspected (6). A skin biopsy is taken for PAD. Histology of BP shows subepidermal blistering dermal inflammation with eosinophilic cells are seen (5) (Fig. 4). The DIF should always be interpreted in relation to clinical find-

Table I. *Describing search history*

Database	Search word	Limit	Number of findings
PubMed 2011-02-25	” Bullous Pemphigoid” as main topic, and ”diagnosis”, ”drug therapy”, ”pathology” as subtopics.	The limits were ”humans”, the languages ”English, Danish, Norwegian, Swedish”, age categories ”all adult; 19+ years”, and finally ”published in the last 10 years” 2001-02-28 to 2011-02-25.	Totally 164 articles were found and of these 16 were review articles.
PubMed 2011-03-24	During a new search in March 2011 at Pubmed, the Mesh-words ”Bullous pemphigoid”, and ”diagnosis”, ”prevention and control” and ”therapy” were used.	The limits were ”humans, clinical trial, meta-analysis, practical guideline, randomized controlled trial, English, all adult: 19+ years”, and “published in the last 10 years”.	15 review articles where several were coincident with those already received at the first search in PubMed.

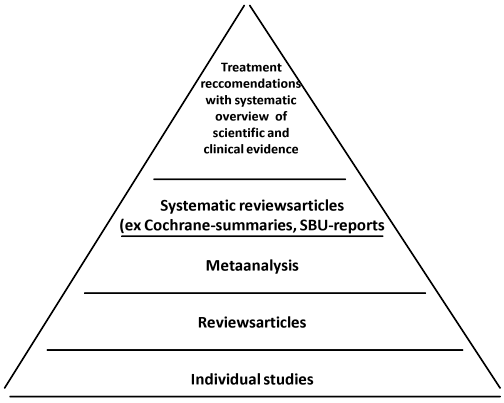

Fig. 2. A pyramid that shows the type of document to start looking for to find the scientific evidence.

Table II. *Practice at USÖ and CSK*

Criteria	Specialists %
Clinical picture and histology	30
Blistering of the skin or redness and skin biopsy that describes a subepidermal blister. One of these has in addition written positive indirect immunfluoressence study (IIF), a pemfigoid serologi from serum or blister fluid (if not available serum).	20
Intact blistering in a reddish skin	10
Positive direct immunofluoressence investigation (DIF)	90
Aged patients	70
Pruritus	50
Tensed blisters	100

ings. DIF is more crucial than the IIF (1). DIF microscopy to diagnose BP has a sensitivity of 90%, specificity of 83% and a high positive predictive value (1). IIF is done in a laboratory where the patient's serum is added to monkey esophagus (6). The test is positive (titer for antibodies against the antigen BP) in up to 96% of patients if the patient has not been on immunosuppressive therapy for a longer time. If DIF and IIF does not provide enough diagnostic information, prescribe an ELISA (enzyme-linked immunosorbent assay) test after special consideration, which is quite specific and sensitive for a domain of BP180 (6).

Differential diagnoses. To rule out other diagnoses PAD, DIF, IIF, bacterial culture, and possibly viral PCR.

Management/treatment of CSK and USÖ. Most specialists (70%) at CSK and at USÖ prescribe a combination of topical and systemic treatment. Except for patients with much localized symptoms, who can not use oral medication, or where there are drug interactions, almost all of the patients are prescribed systemic treatments. One doctor does not specify why he/she does not start with systemic treatment at the first visit. First choice of oral treatment is corticosteroids. 60% of the doctors do not give bisphosphonates and/or calcium together with the corticosteroids. According to two of the doctors this depends

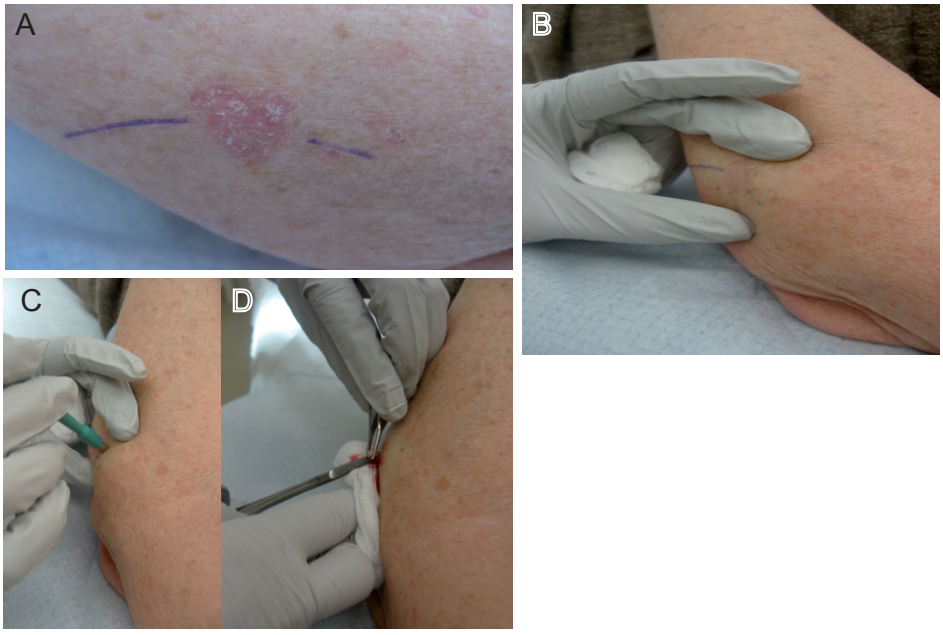

Fig. 3. (A) The place to take a biopsy. A skin biopsy should not be smaller than 4 mm in diameter, if possible. (B) After local anaesthesia the skin is stretched perpendicular to the skin lines with the thumb and forefinger. (C) A skin biopsy is performed with rotating movements of the other hand holding biopsy rod vertically through the epidermis, down to the dermis and the subcutis. (D) After the biopsy is taken the released skin is provided by an elliptical wound that may be sutured in order to make the scar to fall in the direction of the skin lines.

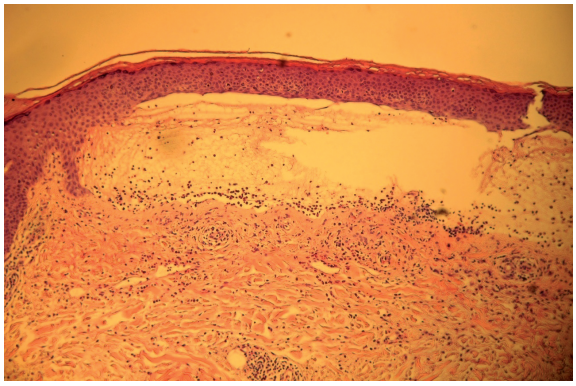

Fig. 4. Histopathologic image from a BP blister on the thigh of a 70 year old woman. Microscopically viewed skin subepidermalt detached from the epidermis which is otherwise intact. Subepidermal blistering. The lumen of the blister is filled with serum and inflammatory eosinophilic and neutrophilic cells. In the underlying dermis there is seen an abundant presence of eosinophilic granulocytes interstitially and in the perivascular part. In the last mentioned part there is also a lymphocytic infiltrate.

on the expected duration of treatment, and another gives the patient bisphosphonates after bone density measurements. Due to oral corticosteroids and impetiginised large skin areas, one of the specialists also gives heracillin. At CSK and USÖ prednisolone is used as first-line systemic therapy. Methotrexate (MTX) is used as a steroid-saver. Patients with BP in the oral cavity can be treated with clobetasol propionate oral gel and nystatin oral suspension. Half of the dermatologists take blood tests before starting with MTX. Only one doctor used azathioprine as a third choice. Monitoring of the BP patients differs between the doctors in CSK, while it is more uniform in USÖ (Table III).

Inpatient care according to standard practice in Karlstad and Örebro. Five of the doctors put elderly patients with widespread symptoms on treatment with systemic therapy. Three other doctors consider it to depend on the patient's general condition and whether he/she could get help with daily care. One of the specialists often uses outpatient care, unless the patient has large erosions on the skin or pain problems during dressing. Another doctor uses outpatient care if the patient can get help at home. For a dementia patient, it is often an advantage to stay where he/she knows the staff. In assessing outpatient contact versus hospitalized care different aspects are weighed against each other.

Management/treatment according to scientific evidence. Treatment aims to increase patient comfort (reduce blistering, reduce urticarial lesions, relieve itching, prevent secondary infection and improve quality of life, and avoid death) (3, 12). Systemic corticosteroid has over time been the golden standard. With 0.5 mg/kg body weight/day, the disease is often controlled within some weeks. Over time, the dose may be reduced (2, 3).

Table III. *Differences in monitoring the BP patients between hospitals*

	Follow-up at CSK	Follow-up at USÖ
Reconsultations	Two of doctors think it is necessary with visits if the patient absolutely must be examined clinically and can cope with long travelling routes which often are to hospital. Another doctor has a reappointment after 4-6 weeks. One of the specialists gives appointments only when there is deterioration. The 5th doctor recommends a reconsultation after 2–3 weeks. The 6th doctor chooses frequency of consultations depending on the patient's age, symptoms and the distribution of the blisters.	All patients with BP will get a reconsultation within 6 months. Two docors write that it is after 4 weeks and then more seldom.
Telephone call	2 of the doctors, first, follow up phone calls. The frequency varies from 7–10 days to 2–3 weeks after the first consultation, then thinned until every 4 until 12 weeks in the first half year. One doctor has a telephone controll 4–6 weeks after a reconsultation. The fifth doctor calls once a month after the reconsultation, then more rare.	None at the Dermatology clinic monitors BP patients through telephone calls with patients or staff.

In one article it is recommended that if more than 40% of the body surface gets involved steroids should be given as systemic treatment, but in other cases, the disease may respond well to only topical steroid treatment)11). In Sweden prednisolone is used. Abroad prednisone can be used instead (2). According to Cochrane studies the BP patient might be better off with prednisone than prednisolone (2).

Often elderly patients

Patients with BP are elderly who also have other diseases and medications. The risk of interactions and side effects of drugs given against BP has to be considered. Treatment must never make the patient more ill than the skin disease itself (5). It is known that immunosuppressive therapy with oral corticosteroids increases the risk for infection, weight gain, hypertension, psychosis, osteoporosis, congestive heart failure, stomach ulcers, and diabetes mellitus (3, 11). Systemic corticosteroid therapy is sometimes poorly tolerated by elderly patients with BP. It has been suspected that this treatment has contributed to increased mortality rates in cohort studies with older patients (13, 14). That is why efforts have been made trying to find alternatives to oral steroids (13, 15). Topical steroids may cause skin atrophy and eccymosis.

The risk increases with steroid strength, duration of use and also depends on skin area treated. If a highly potent topical steroid (dermovat) is used, the skin can absorb so much that it can give systemic consequences (2). This has according to the authors not been a problem in everyday clinical practice. Survival among patients with topical corticosteroid treatment is significantly greater ($p \leq 0.02$) than for patients who are treated with systemic corticosteroid therapy, according to a randomized, non-blinded study (13).

According to Best Practice (6), patients with large areas of the skin affected by BP and contraindication to systemic steroids should get dapsone unless the patient has glucose-6-phosphate dehydrogenase (G6PD) deficiency (6). As steroid-sparing treatments you can try other immunosuppressive drugs like azathioprine, cyclophosphamide, MTX, chlorambucil, cyclosporine or mycophenolate mofetil (14). Many of the immunosuppressive drugs above requires several weeks to induce a therapeutic effect. It is therefore recommended to combine local therapy with oral corticosteroids in the first weeks (9, 12). An open, prospective, non-comparative study (16) of 16 patients in which all received treatment with MTX (maximum 15 mg/week) combined with topical corticosteroid as needed, showed clinical remission for 14 of 16 patients. Mean follow-up was 11.4 months. It is important to avoid overtreatment. The systemic treatment of BP is decreased when the skin disease has been under control for a month or more (3, 5).

All BP patients do not respond to conventional therapy

Up to 24% of patients with BP do not respond to oral prednisone or prednisolone in combination with other immunosuppressants (14). This group of patients, where 65–80% of the skin is affected, has in one case report been demonstrated to benefit from intravenous immunoglobulin therapy. Patients responded within 2–4 months (14). A case report shows successful treatment of BP with anti-CD20 monoclonal antibody (rituximab) (2).

Follow-up

Little is written in the literature about recommendations for follow-up of BP. Follow-up is done on the basis of a study protocol, but how often and in what way is not always clear. Since these patients are not common in primary care, dermatology clinics should follow them as long as they are on oral drugs against BP. The clinical picture (5), distance to the hospital, help from the district nurse or staff accommodation, the patient's general condition, possible dementia, and how the patient responds to treatment are factors to be considered tailoring individualized follow-up.

Prognosis

Remission within the first 5 years is common, but relapses and exacerbations occur. Mortality after introduction of the corticosteroids varies from 0–40% within a year (2). Mortality rate does not need to be due to skin disease. Patients with BP are often elderly and may have other causes of death [2, 6]. In a German study (9) the factors that increase the risk for people with BP to die within the first year after diagnosis have been investigated.

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IN SUMMARY

Box 1. Bullous pemphigoid (BP) (1, 2, 5, 6, 11, 15)

The most frequent autoimmune blistering disease.

Most common in elderly people, but can rarely occur in children.

Equally common in both sexes.

Incompletely known aetiology. Autoantibodies are important.

Can occur in the mucous membranes, such as in the oral cavity.

Different variations of BP are:

- Classic pemphigoid
- Lokalized pemphigoid
- Mucous membrane pemphigoid
- Cicatricial pemphigoid
- Pemphigoid associated to medication
- Pemphigoid nodularis (reminds of prurigo nodularis)
- Vesicular BP
- Erythrodermic BP
- Non-bullous BP

Box 2. Questions to help during history taking

Do you have any blisters?

Do you have any itch?

Are the lesions stationary or moving around?

Do you have any rash in your mouth or on your genitals?

Medication? (immunosuppressive drugs may cause false negative indirect immunofluoressence (IIF)), see Diagnostics according to scientific evidence).

Box 3. Diagnosing according to scientific evidence (1, 2, 4, 5, 6, 10)

After history taking the entire skin is examined as well as mouth and genitals.

Typically large, tense blisters are seen that do not break easily, placed on reddish or normal skin. Almost always concomitant itch.

A skin biopsy should be taken for PAD:

- In a newly formed blister; if it is possible to take the entire blister for histopathologic examination
- If the blister is too big, the biopsy should be taken 2 mm from the edge of the blister. This has to be done carefully so the epidermis does not separate from dermis.
- If there is not any blister at all, the biopsy is taken from reddish skin.

There is also a skin biopsy made for immunopathology study: Direct immunoflouresence study (DIF). NOTE! DIF can be false negative if the patient has been using immunosuppressive therapy during a longer period before the test.

If both DIF and IIF are negative but the skin biospy and the clinical picture suggests the diagnose of BP, futher investigation can be done with ELISA in selected cases.

Box 4. Agreement and disagreement

Mostly doctors agree that

Bullous pemphigoid is the most common blister disease in the Western world

The treatment of bullous pemphigoid is based primarily on clinical experience. Controlled studies are not available

The etiology is not completely known

The majority of patients with bullous pemphigoid are elderly people who do also have other diseases and medications

Skin biopsies for PAD and DIF are taken during the first visit

At the first visit the treatment of the patient is often started with oral corticosteroids and calciumtablets in combination with applications of topical corticosteroid

Opinions differ related to

Minimum requirements for the diagnosis of BP

When to investigate with an IIF test

How often BP may involve mucous membranes

Differential diagnoses to BP

Box 5. Differential diagnoses to classic BP according to the authors

Pemphigus vulgaris
Epidermolysis bullosa aquisita
Torn patient because of pruritus
Lineary IgA dermatosis
Dermatitis herpetiformis
Porfyria cutanea tarda
Cicatricial pemphigoid
Erythema multiforme
Impetigo
Epidermolysis bullosa
Pemphigoid gestationis

Box 6. Clinical differences according to the authors

Clinical picture	Bullous pemphigoid	Pemphigus vulgaris
Blisters	Tense and filled, they are not easily broken	Loose, or broken remains of blisters, are not always seen
Mucous membrane rashes	Seldom	Often
Level-engagement often	Below the mamills	Above the mamills
Age	Aged	Middle-aged

Box 7. Risk factors to die within a year after the diagnosis of bullous pemphigoid (9)

Elderly patients (over 80 years)

In need of a high dose of oral glukocorticoids (37 mg/24 h or more) after stay in hospital

Low serum albumin (36 mg/l or less)

High erythrocyte sedimentation speed (SR) (30 mm/h or more)