Complete Summary

GUIDELINE TITLE

Guidelines for the management of bullous pemphigoid.

BIBLIOGRAPHIC SOURCE(S)

Wojnarowska F, Kirtschig G, Highet AS, Venning VA, Khumalo NP. Guidelines for the management of bullous pemphigoid. Br J Dermatol 2002 Aug;147(2):214-21. [48 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
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SCOPE

DISEASE/CONDITION(S)

Bullous pemphigoid

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Dermatology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide evidence-based guidance on the treatment of patients with bullous pemphigoid

TARGET POPULATION

Patients with bullous pemphigoid

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Biopsy
2. Histological examination of tissue
3. Immunopathological examination of tissue (direct) or serum (indirect) immunofluorescence
4. Differential diagnosis

Treatment

1. Systemic corticosteroids
2. Topical corticosteroids
3. Antibiotics
4. Nicotinamide (niacinamide)
5. Azathioprine
6. Dapsone
7. Sulphonamides
8. Other treatments (not recommended routinely)
    - Cyclophosphamide
    - Methotrexate
    - Cyclosporin
    - Mycophenolate mofetil
    - Intravenous immunoglobulin
    - Chlorambucil
    - Plasmapheresis

Management

1. Follow-up
2. Monitoring of drug therapy

MAJOR OUTCOMES CONSIDERED

- Reduction of disease signs and symptoms
- Complete remission
- Adverse effects of treatment

- Disease recurrence

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A systematic review of treatment for bullous pemphigoid was carried out by searching Medline, Embase and the Cochrane library. The review identified only six randomized controlled trials with a total of 293 patients. The characteristics of the five relevant studies are summarized in Table 1 of the original guideline document.

NUMBER OF SOURCE DOCUMENTS

Five randomized controlled trials

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

I: Evidence obtained from at least one properly designed, randomized controlled trial

II-I: Evidence obtained from well designed controlled trials without randomization

II-ii: Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than one centre or research group

II-iii: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

IV: Evidence inadequate owing to problems of methodology (e.g., sample size, or length or comprehensiveness of follow-up or conflicts of evidence)

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendation Grades

A. There is good evidence to support the use of the procedure.
B. There is fair evidence to support the use of the procedure.
C. There is poor evidence to support the use of the procedure.
D. There is fair evidence to support the rejection of the use of the procedure.
E. There is good evidence to support the rejection of the use of the procedure.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Draft guidelines are edited by the Therapy Guidelines and Audit Sub-committee (TGA) and subsequently returned to the task force for revision. The approved draft version is published in the quarterly British Association of Dermatologists (BAD) newsletter, and all BAD members are given the opportunity to respond, positively or negatively, but hopefully helpfully, within three months of publication. Finalised guidelines are approved by the TGA and the Executive Committee of the BAD and finally published in the British Journal of Dermatology.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (I-IV) and strength of recommendation ratings (A-D) are defined at the end of the "Major Recommendations" field.

Diagnosis

Laboratory Diagnosis of Bullous Pemphigoid (BP)

The diagnosis is established clinically, histologically, and immunopathologically (direct and/or indirect immunofluorescence [IF]). All these investigations can be done after treatment has been started, although prolonged treatment will reduce the number of positive IF results.

Biopsy of a fresh blister shows a subepidermal cleft with a mixed dermal inflammatory infiltrate often containing numerous eosinophils. Direct IF of perilesional skin shows linear deposits of immunoglobulin G (IgG) and/or C3 at the basement membrane zone (other immunoglobulins may also be present). Indirect IF using serum (blister fluid or urine if no serum can be obtained) demonstrates circulating IgG (sometimes with other immunoglobulins) or C3 binding in a linear pattern at the basement membrane of squamous epithelia (normal skin or monkey oesophagus substrates).

The class of immunoglobulin bound to the basement membrane zone on direct IF distinguishes linear IgA disease (LAD) (only IgA on direct IF) from BP. Indirect IF performed on salt-split skin will differentiate BP from epidermolysis bullosa acquisita (EBA) and from a subgroup of cicatricial pemphigoid (CP). The antibodies are detected at the roof of the artificial blister in BP and at the base in laminin 5-CP and in EBA. However, this is not relevant to most clinical practice, as both CP and EBA are far rarer diseases and none of the published controlled clinical trials in BP has used this method to classify patients.

Differential Diagnosis

Other subepidermal autoimmune bullous diseases such as CP, EBA, and LAD are the most difficult to differentiate, and this is usually done on the combination of the clinical picture (which may evolve with time), direct IF, and indirect IF on salt-split skin.

Erythema multiforme, generalized fixed drug eruption, impetigo and, acute viral infections (particularly chickenpox in adults) can all be confused with BP on first presentation. The clinical course, bacterial and viral studies, histopathology, and IF studies will all help to achieve a diagnosis.

Treatment

Systemic Corticosteroids

Systemic corticosteroid therapy seems the best established initial treatment for BP (Strength of recommendation A, Quality of Evidence II).

Topical Corticosteroids

Topical corticosteroids alone are likely to be most useful for localized and mild to moderate disease (A, III). They may be a useful adjunct to systemic treatment.

Antibiotics and Nicotinamide

There is some evidence, one small randomized controlled trial (see Table 1 in original guideline document), small uncontrolled trials, and case reports that antibiotics and nicotinamide (niacinamide) should be considered as the first line of treatment for both localized and mild to moderate disease (B, II-ii/iii).

Erythromycin should be considered for treatment, particularly in children (adult dose 1,000-3,000 mg daily) and perhaps in combination with topical corticosteroids. A beneficial effect may be seen within 1 to 3 weeks after commencing treatment (B, II-iii).

Tetracyclines and nicotinamide should be considered for treatment in adults, perhaps in combination with topical corticosteroids (B, II-ii). The optimum doses are not established. Tetracycline should be avoided in renal impairment and doxycycline and minocycline in patients with hepatic impairment. Minocycline should be stopped if hyperpigmentation occurs. When blister formation is suppressed sufficiently the antibiotics and nicotinamide must be reduced slowly, one at a time, over several months to avoid relapse.

Azathioprine

Azathioprine dose should be optimized both with regard to efficacy and myelosuppression risk by prior measurement of thiopurine methyltransferase (TMPT) activity, although this test is not universally available. In view of its side-effect profile, it is recommended that azathioprine is only considered as a second-line treatment to prednisolone where response has been inadequate and either the disease is not suppressed or the side-effects are troublesome and unacceptable (B, IV).

Dapsone and Sulphonamides

Glucose-6-phosphate dehydrogenase deficiency predisposes to haematological side effects and should be excluded in predisposed races. The side-effect profile of dapsone and sulphonamides is potentially hazardous in the elderly. These treatments should be considered only if other treatments are ineffective or contraindicated (B, III).

Other Immunomodulatory Treatments

The following treatments may be useful in individual resistant cases.

Cyclophosphamide

Cyclophosphamide should be considered only if other treatments have failed or are contraindicated (D, IV).

Methotrexate

Methotrexate should be considered in patients with concomitant psoriasis and BP (B, IV).

Cyclosporin

Experience with cyclosporin is limited to five individual case reports and a small series of seven patients. The evidence for benefit is conflicting, even with relatively high dosage, >6 mg/kg daily, and responses mainly occurred in patients treated with concomitant oral corticosteroids (D, IV).

Mycophenolate Mofetil

Mycophenolate mofetil is an inhibitor of purine synthesis in activated T and B cells and is a generally well-tolerated immunosuppressive agent used since 1997 in the prevention of renal graft rejection. It has been used successfully at doses of 0.5 to 1 g twice daily to control BP in six individual cases, in three cases as an adjunct to oral prednisolone. Further evidence is needed for its role in BP.

Intravenous Immunoglobulin

The total published experience of intravenous immunoglobulin in BP amounts to five small series that suggest that it is of limited value. Used mainly at a dose of 0.4 mg/kg polyvalent immunoglobulin daily for 5 days, either as a sole treatment or with oral prednisolone, it produced some occasional dramatic but unfortunately very transient responses that were too short-lived to be useful. (D, III).

Chlorambucil

Chlorambucil should be considered as an alternative to other more established immunosuppressants if these have failed or are poorly tolerated or contraindicated. Careful monitoring is required for possible haematological toxicity (B, III).

Plasmapheresis

There is no evidence to support the use of plasmapheresis in routine treatment of BP, although at low corticosteroid doses a steroid-sparing effect was seen (D, II-i). There may be a limited role for plasmapheresis in resistant cases of BP where side-effects are a major issue or the disease is uncontrolled (B, III).

Follow-up

BP is a long-term disease, and ideally all patients should be followed until they are in complete remission and off all treatment. They should be regularly reviewed to ensure that they are not being continued on higher doses of topical or systemic treatment than are necessary to provide sufficient control of their disease. The occasional urticated lesion or blister is acceptable, and indicates that the patient is not being over-treated. The guideline developers suggest attempted reduction of medication every 1 to 2 months in stable patients; this should be done on clinical rather than IF criteria.

Summary of Recommendations

Bullous pemphigoid (BP) is a common disease of the elderly. With our aging population it will become increasingly frequent, and the age of the patients will add to the complexity of treatment. There is a clear need to determine how to stratify patients clinically, and to ascertain the optimum regimens for treating mild, moderate, and severe BP.

- Systemic corticosteroids are the best established treatment. Recommended initial doses of prednisolone are 20 mg or 0.3 mg/kg daily in localized or mild disease, 40 mg or 0.6 mg/kg daily in moderate disease, and 50-70 mg or 0.75-1 mg/kg daily in severe disease. Measures to prevent osteoporosis must be implemented from the start of systemic corticosteroid therapy, whenever practicable.
- For localized BP, very potent topical corticosteroids are worth trying first.
- For mild to moderate disease tetracycline and nicotinamide should be considered.
- Immunosuppressants cannot be recommended routinely from the outset but should only be considered if the corticosteroid dose cannot be reduced to an acceptable level. Azathioprine is the best established; methotrexate may be considered in patients with additional psoriasis.
- Topical corticosteroids should be considered in any patient with BP; they may help to achieve control if this is only borderline using systemic agents. The aim of treatment is to suppress the clinical signs of BP sufficiently to make the disease tolerable to an individual patient. The guideline developers recommend to aim for reduction, but not complete suppression, of blister formation, urticarial lesions, and pruritus.

Definitions:

Levels of Evidence

I: Evidence obtained from at least one properly designed, randomized controlled trial

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III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

IV: Evidence inadequate owing to problems of methodology (e.g., sample size, or length or comprehensiveness of follow-up or conflicts of evidence)

Recommendation Grades

A. There is good evidence to support the use of the procedure.
B. There is fair evidence to support the use of the procedure.
C. There is poor evidence to support the use of the procedure.
D. There is fair evidence to support the rejection of the use of the procedure.
E. There is good evidence to support the rejection of the use of the procedure.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected treatment recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate and high level quality of care for patients with bullous pemphigoid

POTENTIAL HARMS

- The introduction of measures for prevention of corticosteroid-induced osteoporosis must be considered at the outset of systemic corticosteroid treatment in all patients, and implemented whenever practicable.
- High dose oral corticosteroids are associated with mortality and morbidity, weight gain, diabetes, hypertension, and infection.
- Topical corticosteroids may be associated with cutaneous infection and skin atrophy.
- Minocycline has been associated with pneumonia and eosinophilia and a lupus-like syndrome and should be stopped if hyperpigmentation occurs.
- Azathioprine is associated with a risk of myelosuppression.
- The side-effect profile of dapsone and sulphonamides is potentially hazardous in the elderly.
- Careful monitoring is required for possible haematological toxicity with chlorambucil treatment.

CONTRAINDICATIONS

CONTRAINDICATIONS

Tetracycline should be avoided in renal impairment and doxycycline and minocycline in patients with hepatic impairment.

QUALIFYING STATEMENTS

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- These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data: the results of future studies may require alteration of the conclusions or recommendations of this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients or special circumstances. Just as adherence to these guidelines may not constitute a defence against a claim of negligence, so deviation from them should not be deemed negligent.
- Caution should be exercised in interpreting the data obtained from the literature because only six randomized controlled trials are available involving small groups of patients.
- It is important that these guidelines are used appropriately in that they can only assist the practitioner and cannot be used to mandate, authorise, or outlaw treatment options. Of course it is the responsibility of the practising clinician to interpret the application of guidelines, taking into account local circumstances.
- Guidelines are inherently a fluid, dynamic process and will be updated on the British Association of Dermatologists (BAD) Web site on a regular basis.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Audit

There is no established optimum treatment for bullous pemphigoid (BP), and thus no gold standard against which to audit clinical practice.

Suggested audit points:

- Evidence of a clear management strategy
- Scrutiny of prednisolone dosage used
- Implementation of measures to minimize and reduce corticosteroid dosage
    - Implementation of osteoporosis prophylaxis if steroids are given
- Indications for use of azathioprine and other immunosuppressants
- Monitoring of drug therapy
    - Corticosteroid side-effects in relation to dose
    - Thiopurine methyltransferase (TMPT) screening prior to the use of azathioprine
    - Drug monitoring of dapsone, sulphonamides, or immunosuppressant treatment

IMPLEMENTATION TOOLS

Audit Criteria/Indicators

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Wojnarowska F, Kirtschig G, Highet AS, Venning VA, Khumalo NP. Guidelines for the management of bullous pemphigoid. Br J Dermatol 2002 Aug;147(2):214-21. [48 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Aug

GUIDELINE DEVELOPER(S)

British Association of Dermatologists

SOURCE(S) OF FUNDING

British Association of Dermatologists

GUIDELINE COMMITTEE

British Association of Dermatologists Therapy Guidelines and Audit Subcommittee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the British Association of Dermatologists Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Griffiths CE. The British Association of Dermatologists guidelines for the management of skin disease Br J Dermatol. 1999 Sep;141(3):396-7.

Electronic copies: Available in Portable Document Format (PDF) from the British Association of Dermatologists Web site.

PATIENT RESOURCES

None available

NGC STATUS

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