Complete Summary

GUIDELINE TITLE

Guidelines for the management of pemphigus vulgaris.

BIBLIOGRAPHIC SOURCE(S)

Harman KE, Albert S, Black MM. Guidelines for the management of pemphigus vulgaris. Br J Dermatol 2003 Nov;149(5):926-37. [112 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references drugs for which important revised regulatory information has been released.

- June 30, 2008, CellCept (mycophenolate mofetil) and Myfortic (mycophenolate acid): Novartis and Roche have agreed to include additional labeling revisions to the WARNINGS and ADVERSE REACTIONS sections of the Myfortic and CellCept prescribing information, based on post-marketing data regarding cases of Progressive Multifocal Leukoencephalopathy (PML) in patients treated with these drugs.
- October 29, 2007, CellCept (mycophenolate mofetil): Roche has agreed to include additional labeling revisions to the BOXED WARNING, WARNINGS/Pregnancy and Pregnancy Exposure Prevention, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Postmarketing Experience sections.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **
SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

SCOPE

DISEASE/CONDITION(S)

Pemphigus vulgaris

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Dermatology
Family Practice
Internal Medicine
Pathology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide evidence based guidance for the management of patients with pemphigus vulgaris

TARGET POPULATION

Patients with pemphigus vulgaris

INTERVENTIONS AND PRACTICES CONSIDERED

Baseline Investigations

1. Biopsy for histology and direct immunofluorescence
2. Indirect immunofluorescence (IIF)
3. Full blood count and differential
4. Urea and electrolytes
5. Liver function tests
6. Blood glucose
7. Antinuclear antibody (differential of pemphigus erythematosus)
8. Thiopurine methyltransferase (TPMT) levels (if azathioprine is to be used)
9. Chest x-ray
10. Urinalysis
11. Blood pressure

12. Bone density scan

Treatment

1. Corticosteroids
    - Oral corticosteroids
    - Pulsed intravenous (IV) steroids
2. Adjuvant Drugs
    - Azathioprine
    - Oral cyclophosphamide
    - Pulsed intravenous cyclophosphamide
    - Methylprednisolone
    - Mycophenolate mofetil
    - Gold
    - Methotrexate
    - Tetracyclines/nicotinamide
    - Dapsone/sulphonamides
    - Chlorambucil
3. Intravenous immunoglobulin (IVIG)
4. Plasma exchange
5. Extracorporeal photopheresis
6. Topical therapy
7. Follow-up

Therapies Considered But Not Recommended

Oral ciclosporin

MAJOR OUTCOMES CONSIDERED

- Disease remission
- Mortality
- Relapse rate
- Advantages and disadvantages of different therapies
- Side effects of therapies

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

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

Review

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

Levels of evidence **(I-IV)** and grading of recommendations **(A-E)** are defined at the end of the "Major Recommendations" field.

Laboratory Diagnosis

A skin or mucosal biopsy should be taken for histology and direct immunofluorescence (DIF), the latter requiring perilesional, intact skin or clinically uninvolved skin. Suprabasal acantholysis and blister formation is highly suggestive of pemphigus vulgaris (PV) but the diagnosis should be confirmed by the characteristic deposition of immunoglobulin G (IgG) in the intercellular spaces of the epidermis. Indirect immunofluorescence (IIF) is less sensitive than DIF but may be helpful if a biopsy is difficult (e.g., children and uncooperative adults). Enzyme-linked immunosorbent assays (ELISA) are now available for direct measurement of desmoglein (Dsg)1 and Dsg 3 antibodies in serum. They offer advantages over IIF and may supersede this technique. Five millilitres of blood is sufficient for IIF and ELISA.

In patients with oral pemphigus, an intraoral biopsy is the optimum but IIF or DIF on a skin biopsy may suffice. One study showed that the sensitivity of DIF was 71% in oral biopsies compared with 61% in normal skin taken from 28 patients with oral PV. Another study reported that the sensitivity of DIF was 89% in oral biopsies compared with 85% for IIF.

Baseline Investigations

The following investigations are suggested prior to commencing treatment: biopsy (or IIF) as above, full blood count and differential, urea and electrolytes, liver function tests, glucose, antinuclear antibody (differential of pemphigus erythematosus), thiopurine methyltransferase (TPMT) levels (if azathioprine is to be used), chest x-ray, urinalysis, and blood pressure. Current guidelines on osteoporosis should be followed, so a bone density scan early in the course of treatment may be recommended.

General Principles of Management

The initial aim of treatment is to induce disease remission. This should be followed by a period of maintenance treatment using the minimum drug doses required for disease control in order to minimize their side-effects. Occasional blisters are acceptable and indicate that the patient is not being overtreated. The ultimate aim of management should be treatment withdrawal and a recent study reported complete remission rates of 38%, 50%, and 75% achieved 3, 5, and 10 years from diagnosis.

Most patients are treated with systemic corticosteroids (CS), which are effective. Adjuvant drugs are commonly used in combination with the aims of increasing efficacy and of having a steroid-sparing action, thereby allowing reduced maintenance CS doses and reduced CS side effects. Although mortality and complete remission rates have improved since the introduction of adjuvant drugs, this is in comparison with historical controls; a more recent study of PV patients treated with CS alone demonstrated outcomes comparable with studies using adjuvants. There are no prospective, controlled studies that conclusively demonstrate the benefits of adjuvant drugs in PV. Therefore, some respected authorities do not use adjuvant drugs unless there are contraindications or side-effects of CS, or if tapering the CS dose is associated with repeated relapses. However, most centres do use adjuvant drugs as standard practice. In general, adjuvant drugs are slower in onset than CS and are therefore rarely used alone to induce remission in PV.

Oral Corticosteroids (CS)

Systemic CS are the best established therapy for the management of PV **(Strength of recommendation A, Quality of evidence II-iii)**.

Pulsed Intravenous Corticosteroids

Pulsed CS could be considered in severe or recalcitrant PV to induce remission, particularly if there has been no response to high oral doses **(C, IV)**.

Adjuvant Drugs

Azathioprine

Azathioprine is a well-established choice as an adjuvant drug for the management of pemphigus **(B, II-iii)**.

Oral Cyclophosphamide

Oral cyclophosphamide could be considered as an alternative to azathioprine **(B, III)**.

Pulsed Intravenous Cyclophosphamide with Dexamethasone or Methylprednisolone

Pulsed CS cyclophosphamide therapy could be considered in severe or recalcitrant cases of PV. However, it may not be practical to administer repeated courses **(B, II-iii)**.

Mycophenolate Mofetil

On the basis of current evidence, MMF could be considered in recalcitrant cases or when azathioprine and cyclophosphamide cannot be used **(B, III)**.

Gold

Gold could be considered as an alternative to more established adjuvant drugs if they cannot be used **(B/C, III)**.

Methotrexate

Methotrexate could be considered as an adjuvant drug if more established drugs cannot be used **(C, III)**.

Ciclosporin

On the basis of current evidence, ciclosporin cannot be recommended as an adjuvant drug in PV **(C, I)**.

Tetracyclines/Nicotinamide

Tetracyclines with or without nicotinamide could be considered as adjuvant treatment, perhaps in milder cases of PV **(C, IV)**.

Dapsone/Sulphonamides

Dapsone was reported to be beneficial as an adjuvant drug in four cases of PV. However, in two of these cases, it was started either with or shortly after prednisolone, and in two cases it was started after the long-standing prednisolone was increased to high doses. Therefore, it is difficult to be certain if dapsone had a significant role and there is little evidence to recommend the use of dapsone in PV **(C, IV)**.

Chlorambucil

Chlorambucil could be considered as an adjuvant drug if more established options cannot be used but there are limited data to support its use (**C, IV)**.

Intravenous Immunoglobulin (IVIG)

Repeated courses of intravenous immunoglobulin could be considered as an adjuvant, maintenance agent in patients with recalcitrant disease who have failed more conventional therapies. In view of reports of a rapid action in some cases, it could be used to help induce remission in patients with severe PV while slower-acting drugs take effect **(B, III)**.

Plasma Exchange (PE)

Plasma exchange cannot be recommended as a routine treatment option in newly presenting patients with PV. However, it could be considered in difficult cases if combined with CS and immunosuppressant drugs (**C, I)**.

Extracorporeal Photopheresis (ECP)

ECP could be considered in recalcitrant cases of PV where there has been failure to improve with more conventional therapy **(B, III)**.

Topical Therapy

PV is largely managed with systemic therapy but adjuvant topical therapy may be of additional benefit, although there are no controlled studies to confirm this. Rarely, patients with mild disease, particularly if confined to the mucosal surfaces, can be managed on topical therapy alone.

For oral pemphigus, measures such as soft diets and soft toothbrushes help minimize local trauma. Topical analgesics or anaesthetics, for example benzydamine hydrochloride 0.15% (Difflam Oral Rinse®), are useful in alleviating oral pain, particularly prior to eating or tooth brushing. Oral hygiene is crucial. Otherwise PV may be complicated by dental decay; tooth brushing should be encouraged and antiseptic mouthwashes may be used, such as chlorhexidine gluconate 0.2% Corsodyl®), hexetidine 0.1% (Oraldene®), or 1:4 hydrogen peroxide solutions. Patients are susceptible to oral candidiasis, which should be treated. Topical CS therapy may help reduce the requirement for systemic agents. For multiple oral erosions, mouthwashes are most practical, for example, soluble betamethasone sodium phosphate 0.5 mg tablet dissolved in 10 mL water may be used up to four times daily, holding the solution in the mouth for about 5 minutes. Isolated oral erosions could be treated with application of triamcinolone acetonide 0.1% in adhesive paste (Adcortyl in Orabase®), 2.5 mg hydrocortisone lozenges or sprayed directly with an asthma aerosol inhaler, for example beclomethasone dipropionate 50-200 micrograms or budesonide 50-200 micrograms. Topical ciclosporin (100 mg/mL) in oral pemphigus has been described and may be of some benefit but is expensive.

Follow-up

Once remission is induced, there should follow a period of maintenance treatment using the minimum drug doses required for disease control and during which occasional blisters are acceptable. Drug doses should be slowly reduced and patients should remain under follow-up while they remain on therapy. Ultimately,

treatment may be withdrawn if there has been prolonged clinical remission. This decision should largely be clinical but the chances of relapse are reduced if immunofluorescence studies are negative (e.g., the risk of relapse is 13-27% if DIF is negative, 44-100% if DIF is positive, 24% if IIF is negative, and 57% if IIF is positive). However, DIF can occasionally remain positive in patients who are in remission and off treatment.

Definitions:

Levels of Evidence

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

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

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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 available

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

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

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Consistent quality of care for patients with pemphigus vulgaris
- Reduced mortality from pemphigus vulgaris

POTENTIAL HARMS

- Oral steroids -- Diabetes; osteoporosis; adrenal suppression; peptic ulceration; weight gain; increased susceptibility to infection; mood changes; proximal myopathy; Cushing's syndrome; cataracts
- Pulsed intravenous steroids -- Mood changes; flushing
- Azathioprine -- Myelosuppression and nausea (related to thiopurine methyltransferase activity [TPMT]); hepatotoxicity and hypersensitivity reactions (unrelated to TPMT activity); increased susceptibility to infection
- Oral cyclophosphamide -- Neutropenia; alopecia; gastrointestinal disturbances; raised transaminases; thrombocytopenia; secondary infertility; potential risk of haemorrhagic cystitis and carcinoma of bladder
- Pulsed cyclophosphamide and dexamethasone or methylprednisolone -- Alopecia, infections; amenorrhoea; ovarian/testicular failure; haemorrhagic cystitis; acne; hiccup
- Mycophenolate mofetil - Gastrointestinal disturbances; lymphopenia; anaemia; thrombocytopenia; increased risk of opportunistic infections
- Gold -- Rashes; nephrotic syndrome; myelosuppression; hypersensitivity syndromes
- Methotrexate -- Myelosuppression; hepatotoxicity; pneumonitis
- Tetracyclines and nicotinamide -- Flushing and headaches due to vasodilation with nicotinamide; gastrointestinal upset (tetracyclines); hyperpigmentation, particularly at sites of blistering (minocycline); discoloration of teeth (avoid tetracyclines in children and pregnant/lactating females)
- Dapsone/sulphonamides -- Haemolysis; methaemoglobinaemia; hypersensitivity reactions
- Chlorambucil -- Myelosuppression
- Intravenous immunoglobulin (IVIG) -- During infusion, chills, tachycardia, hypertension, muscle pains, pyrexia, nausea and headache are common, self-limited and respond to slowing the infusion; anaphylaxis is rare
- Plasma exchange -- Septicaemia; fluid and electrolyte imbalance
- Extracorporeal photopheresis -- Symptoms of hypovolaemia during procedure

CONTRAINDICATIONS

CONTRAINDICATIONS

Avoid tetracyclines in children and pregnant/lactating females.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- 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 in this report. It may be necessary or even desirable to depart from the guidelines in the interests of patients and special circumstances. Just as adherence to guidelines may not constitute a defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.
- 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

Suggested Audit Topics

- Measurement of baseline parameters prior to starting treatment
- Appropriate investigations to establish diagnosis
- Evidence of appropriate drug monitoring
- Adherence to guidelines for prophylaxis and management of steroid-induced osteoporosis

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources

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)

Harman KE, Albert S, Black MM. Guidelines for the management of pemphigus vulgaris. Br J Dermatol 2003 Nov;149(5):926-37. [112 references] PubMed

ADAPTATION

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

DATE RELEASED

2003 Nov

GUIDELINE DEVELOPER(S)

British Association of Dermatologists - Medical Specialty Society

SOURCE(S) OF FUNDING

British Association of Dermatologists

GUIDELINE COMMITTEE

British Association of Dermatologists Therapy Guidelines and Audit Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

None 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

The following is available:

- Pemphigus vulgaris. Patient information leaflet. London (England): British Association of Dermatologists; 2004 Oct. 4 p.

Available from the British Association of Dermatologists Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on April 20, 2005. The information was verified by the guideline developer on August 16, 2005. This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on CellCept (mycophenolate mofetil). This summary was updated by ECRI Institute on July 8, 2008, following the updated U.S. Food and Drug Administration (FDA) advisory on CellCept (mycophenolate mofetil) and Myfortic (mycophenolate acid).

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