RECENT TRENDS IN THE MANAGEMENT OF PEMPHIGUS VULGARIS

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ABSTRACT

Pemphigus vulgaris is perhaps the most formidable disease encountered by dermatologists. In the days before steroid therapy the mortality rate was 95 per cent, death occuring usually within 14 months. The cause of death was septicaemia, starvation and toxic state. Corticosteroid, immunosuppressants and adjuvant therapy have reduced the mortality to 10-40 per cent with the cause of death being uncontrolled pemphigus, complications of corticosteroid and immunosuppressant therapy, septicaemia and thrombo-embolism. Elderly patients and patients with extensive lesions have higher mortality rate. Prognosis has further improved by intensive care, adequate fluid replacement, nutritional support, a co-herent antibacterial policy alongwith aggressive corticosteroid therapy and immunosuppressants. Plasmapheresis has been used in patients who fail to respond to conventional management. Extracorporeal photophoresis has been reported to be effective in patients with 'treatment resistance' pemphigus vulgaris.

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Pemphigus Vulgaris (PV) is an autoimmune blistering disease of the skin and mucous membranes characterized histologically by in vivo bound and circulating IgG auto antibody directed against the cell surface of keratinocytes. The PV antigen [1] is a 130-KD glycoprotein that has been named, desmoglein 3.

In the days before corticosteroid therapy, the mortality rate of PV was 95 per cent, death occurring usually within 14 months [2]. Corticosteroid therapy and other symptomatic measures have now reduced the mortality rate to 10-40 per cent [3].

Symptomatic management of PV must focus on bacteriological investigations, antibacterial therapy, nutritional support and electrolyte equilibrium. Major fluid losses are rarely a problem in this disease. Profound hypoproteinaemia and hypoalbuminaemia due to loss of proteins from blisters promote thrombo-embolism and impaired defence against infection. Poor nutrition, old age, oral lesions, escape of protein from the blisters and hypercatabolism resulting from corticosteroids are frequently underestimated [4].

All the needs for water and electrolytes of patients with PV should be maintained by a nasogastric silicone tube and venous access are used only a few hours a day for a discontinous supply of macromolecules. Intravenous fluids are supplemented with potassium phosphate in order to correct hypophosphataemia. In addition, all patients are given 1500 ml of nasogastric feeding during the first 24 hours. On the following days oral supplies are progressively increased and intravenous fluids decreased [5].

Aggressive nutritional support [6], is needed to minimize the protein losses and to promote tissue synthesis during the healing of cutaneous lesions. The diet should be of high protein with 2-3 g/kg body weight of protein daily in adults. A nasogastric feeding tube is required in most patients, as mucosal erosions impair oral feeding. In patients who are able to eat, discontinuous tube feeding supplements are administered during the night. In all cases enteral alimentation is preferable to parenteral therapy considering the risk of venous line contamination.

Patients with extensive skin lesions usually have fever and shivering, even in the absence of infection. Interleukin I, which is produced by epidermal cells, plays a key role in inducing fever [7]. If patients have high fever any attempt to decrease their central temperature by a cooler environment will result in added energy expenditure and be an additional threat to survival. On the other hand lowering of the central body temperature by antipyretics will contribute to the reduction of cutaneous heat loses and improve the cardiac index [6]. Environment temperature should be raised to 30-32° C. The temperature of antiseptic baths should be carefully monitored and set to 35-38° C.

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Infrared lamps and an air fluidized bed are of great help for the patients warming [6].

Damaged skin and exudates support the growth of a wide spectrum of micro-organisms. At the beginning of the hospital stay *Staph. aureus* is the main suspect while later *Pseudomonas sp.* and enterobacteriaceae are most likely responsible for severe infection. Routine prophylactic systemic antibiotics do not prevent infection but rather lead to the emergence of resistant bacterial strains and of fungi [3]. There is no ideal antibiotic and the choice will be based on the antibiotic sensitivity test against the bacterial strains isolated from the lesions of the skin.

Patients are bathed once or twice a day in 0.05 per cent aqueous chlorhexidine or 1:10000 potassium permanganate solution. In between the skin lesions are painted every 4 hourly with 0.05 per cent aqueous silver nitrate or 0.05 per cent aqueous cholrhexidine. When oozing from the skin lesions subside the lesions are treated with 1 per cent silver suphadiazine cream or sofratulle dressing. Efficiency of antiseptic therapy is monitored by bacterial sampling on several sites of altered skin every two days [6].

Intralesional steroids have been used for the treatment of localized, or recalcitrant localised blistering lesions. The lesions are injected with 0.05 to 1 ml of Triamcinolone acetonide 5 to 10 mg/ml in skin lesion and 10 to 20 mg/ml for oral lesions per site every 1-2 weeks until healing occurs. This modality may be useful to treat new lesions in patients whose systemic therapy is being tapered off. It hastens the resolution of individual lesions without increasing the dosage of steroids.

Patients with mild disease may respond to as little as 20 mg per day of prednisolone while those with severe and extensive involvement tend to require higher dosages, [8] such as 60 to 80 mg per day, (1 to 1.5 mg/kg/day). In patients whose disease fails to respond to the initial dose of prednisolone, the dosage is increased by 50 per cent every four to five days until initial control is reached. Patients whose skin continues to blister while they are receiving relatively higher dosages of prednisolone, 120 mg/day, split doses, e.g. 80 mg in the morning and 40 mg in the evening may be tried for better control. Once new blistering has ceased, the dosage of prednisolone is maintained until the majority of the erosions have healed. Once the majority of lesions have healed, slow judicious tapering of prednisolone dosage can begin [6].

Long term side effects associated with corticosteroid use include osteoporosis, peptic ulcer disease, aseptic vascular necrosis, cataract formation and unmasking of diabetes mellitus [6]. Current agents which used to mitigate against osteoporosis include vitamin D2, 400 IU per day and calcium carbonate 1 gm per day. Patients with a history of renal insufficiency or renal stones are not the candidates for calcium and vitamin D2 supplementation. The drugs currently under investigation, to prevent osteoporosis are the use of biphosphonates and calcitonin. Intranasal calcitonin is highly promising as an effective, well tolerated agent to prevent bone loss in susceptible persons.

The strategies to minimise these side effects include alternate day conticosteroid therapy, and the use of adjuvants. Concomitant use of immunosuppressives or other adjuvants are advocated only if there are relative contraindications to the use of steroids, development of serious side effects due to steroids or if a reduction in their dose is not possible because of repeated exacerbations in the disease activity.

Nicotinamide 1.5 gm per day and tetracycline, 2 gm per day have been reported to control PV in an uncontrolled trial [10]. A few patients with mild disease have improved with gold, but concomitant steroid therapy is required [11]. Auranofin, an oral formulation of gold is less toxic than parenteral formulations [12]. Dapsone, 100-300 mgs per day, alone is effective in pemphigus erythematosus and foliaceous [13] and may also be used in PV as a steroid sparing agent [9].

Immunosuppressants [14], azathioprine [15], cyclophosphamide [16] and cyclosporine [17], are now used in the management of PV. Patients do not respond to immunosppressant until six to eight weeks after initiating therapy, so adequate dosages of steroids should be maintained [15-17].

Azathioprine 1 to 3 mg/kg/day is effective as an adjuvant in managing patients with PV [15]. Among the major toxic effects associated with their use are bone marrow suppression, including leukopenia, anemia, thromobocytopenia, and those secondary to immunosuppression, including atypical infections and the enhanced development of malignancies particularly lymphoma.

Cyclophosphamide 2 to 3 mg/kg/day has been reported to be effective both as a first line adjuvant and in the treatment of those whose disease has previously failed to respond to azathioprine [16]. Patients can be well hydrated before therapy and the risk of hemorrhagic cystitis significantly lessened [16].

Cyclosporine [17,18] has been used in small series of PV patients with an usual dosage range between 5

and 10 mg/kg/day. Toxic effects associated with cyclosporine include hypertension, and nephrotoxicity [17].

Pulse steroid therapy has been used in PV patients refractory to oral corticosteroids and immunosuppressants [19]. It consists of giving a mega dosage of intravenous corticosteroids, 1 gm methylprednisolone 3-12 hourly repeated on 3 or 5 more consecutive days. Complications associated with pulse steroids include sepsis and electrolyte imbalances that have been associated with fatal arrhythmias [19].

Dexamethasone - cyclophosphamide pulse therapy [20] has been used in PV cases. It involves the intravenous administration of 100 mg dexamethasone with 500 mg of cyclophosphamide in 500 ml of 5 per cent glucose solution, over 1-2 hours on day 1 followed by dexamethasone alone on the next 2 days [20]. Such pulses are repeated every month. On the remaining days cyclophosphamide 50 mg per day is administered orally. The major advantages are the quick healing of lesions and absence of long term side effects of dexamethasone [20].

In patients whose disease fail to respond to high dosage corticosteroids and immunsuppressants, plasmapheresis has been used in PV [22]. Plasmapheresis rapidly depletes the level of circulating autoantibodies in patients with high titre circulating autoantibodies. However, patients may experience a rebound phenomenon with increased autoantibody production and clinical exacerbation [2,3]. Hence, immunosuppressive drug, cyçlophosphamide is concomitantly administered to suppress antibody formation. Side effects from this therapy include sepsis, hypotension, depletion of clotting factors.

Extracorporeal photophoresis [24] has been reported to be effective in a limited series of patients with treatment resistant PV. Patients were treated with two treatments per week every two to four weeks with ingestion of 8-methoxypsoralen followed by passage of patients blood through an apparatus that exposes it to UVA irradiation. Side effects of extracorporeal photophoresis include post-infusion fever, hypotension, sepsis, thrombocytopenia, and elevated results of liver function test. Limited availability of this expensive procedure may not make this therapeutic option practical for many patients [25].

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