Skin Therapy Letter ©

Volume 19 • Number 5 • September-October 2014

Indexed by the US National Library of Medicine and PubMed

EDITOR: DR. STUART MADDIN

Updates on the Management of Autoimmune Blistering Diseases

Joanna N. Hooten, MD[1]; Russell P. Hall 3rd, MD[1,2]; Adela R. Cardones, MD[1,2]

[1]Department of Dermatology, Duke University School of Medicine, Durham, NC, USA

[2]Division of Dermatology, Department of Medicine, Duke University Medical Center, Durham VA Medical Center, Durham, NC, USA

ABSTRACT

Autoimmune blistering diseases are rare, but potentially debilitating cutaneous disorders characterized by varying degrees of mucosal and cutaneous bullae formation. Topical therapy is appropriate for mild and even some moderate disease activity, but systemic treatment can be considered for more extensive involvement. Corticosteroids remain the first-line systemic therapy for patients with moderate to severe bullous pemphigoid and pemphigus vulgaris. While the use of systemic steroids has dramatically reduced mortality from these two autoimmune blistering disorders, treatment is also associated with multiple side effects, especially when used long-term. Steroid sparing agents, therefore, are invaluable in inducing long-term remission while minimizing steroid associated side effects. Treatment must be tailored to the individual patient's condition, and several other factors must be carefully considered in choosing appropriate therapy: 1) diagnosis, 2) severity of the condition and body site affected, 3) presence of comorbidities, and 4) ability to tolerate systemic therapy.

Key words: autoimmune blistering skin diseases, bullous pemphigoid, cicatricial pemphigoid, basement membrane zone, epidermolysis bullosa acquisita, pemphigus vulgaris

Introduction

Autoimmune blistering diseases (AIBD) are a heterogeneous group of chronic, acquired disorders characterized by blister formation within the epidermis, at the dermal-epidermal junction or at the basement membrane zone, and by the presence of autoantibodies directed against structural components of cellular adhesions molecules. AIBD are classified into different groups based on clinical and immunopathological criteria. Large-scale, randomized studies on effective therapeutic strategies for AIBD are limited and treatment varies widely among providers. The patient population tends to be a heterogeneous mix of age, gender and comorbidities, and the mechanisms of injury to the skin are variable between blistering diseases. Management of these disorders, therefore, requires an understanding of the spectrum of available therapies. A complete discussion of the treatment of AIBD is beyond the scope of this review, however, we present some recommendations in approaching patients with pemphigus, pemphigoid, and epidermolysis bullosa acquisita (EBA). A brief description of the available medications and their roles in treating AIBD will be provided, but a thorough review of therapeutic and monitoring guidelines must be done before treatment is initiated.[1]

Approach to Patients with AIBD

Several factors need to be considered in treating a patient with an AIBD (Table 1). A complete history and thorough physical examination of the skin and mucous membranes must be performed. A skin biopsy, with direct and indirect immunofluorescence analysis, is important in arriving at the correct diagnosis and planning therapy. Determining titers of autoantibodies are not always necessary to confirm the diagnosis, but may be helpful in following the patient's progress.[2-4]

First, an accurate diagnosis will help determine the likelihood of disease remission, potential for mucous membrane involvement, risk of scarring, and other long-term sequelae that may affect treatment plans. For example, bullous pemphigoid (BP) and EBA may demonstrate a similar clinical presentation, but have a different natural history. A clinician may plan to wean a BP patient off all medications in 9-12 months, whereas longer-term therapy is often needed in patients with EBA.

Second, severity and extent of disease has to be carefully evaluated. The extent of the disease can be variable in all types of AIBD. Additionally, the definition of mild, moderate and severe disease differs among experts. Some authors define limited disease as <10% body surface area, while others use the cut-off point of <10 new blisters per day to delineate between limited and severe disease.[5,6] Nevertheless, even in the absence of new blisters and regardless of affected areas, the involvement of functional critical sites (e.g., hands and feet or mucosal surfaces) may require more aggressive therapy. Ocular disease, which can result in permanent scarring or blindness, warrants systemic treatment, in addition to subspecialty referral to ophthalmology.

ALSO IN THIS ISSUE: **Pregnancy-Specific Skin Disorders** *(page 7)* & **Update on Drugs** *(page 10)*

Third, the presence of comorbidities may dictate the type and dosage of medication that can be used and must be accompanied by careful assessment. Diseases such as diabetes mellitus, hypertension, chronic infections (e.g., hepatitis or HIV), and previous or existent malignancies need to be considered. Patients who would otherwise be treated aggressively, but whose comorbidities preclude therapy with systemic corticosteroids (i.e., elderly patients or those with uncontrolled diabetes or hypertension) or more traditional steroid sparing agents, may instead have to be treated with topical, antibiotic or anti-inflammatory medications.

Finally, the choice of medications may be restricted by side effects experienced by the patient. Potential side effects, which can be significant, include alterations in mental status, sleep disturbances, and gastrointestinal (GI) discomfort. The assessment of all adverse effects throughout therapy is critical to treatment success in AIBD. The clinician must exercise judgment in weighing the risks and benefits of initial therapy in an effort to maximize efficacy while minimizing systemic toxicity.

Approach to Patients with AIBD

1. Diagnosis
2. Severity of the condition: extent of disease or site affected
3. Comorbidities
4. Ability to tolerate systemic therapy

Table 1. Factors in determining appropriate therapy

Mild to Moderate Disease

Topical Therapy

For pemphigus vulgaris (PV) patients with mild and even moderate cutaneous and oral mucosal[7] involvement, BP or EBA, a high potency topical steroid such as clobetasol 0.05% ointment or gel applied 2-3 times daily is appropriate.[5] Even in the setting of extensive disease, potent topical steroids remain an option if the patient is elderly or has numerous risk factors. Clobetasol 0.05% cream 40 g/day is at least as effective as oral prednisone in treating moderate to severe BP.[8] Some degree of systemic absorption may contribute to the efficacy of topical steroids, however, the side effect profile is still acceptable.

Antimicrobials

Antimicrobials decrease local inflammation, but have no effect on circulating autoantibodies.[9] The combination of tetracycline 2 g PO daily plus nicotinamide 1.5 g PO is a reasonable alternative for the treatment of BP in patients who are not candidates for systemic steroid therapy. In a randomized trial of 18 patients comparing prednisone with tetracycline and nicotinamide, there was no statistically significant difference in response between the two groups. In addition, 83% of patients treated with tetracycline plus nicotinamide had some improvement and 42% experienced a complete response. At long-term follow-up, a small subset of patients in the tetracycline plus nicotinamide treatment group remained in remission with tapering of the medication.[10] Several other small studies have also demonstrated variable improvement with this treatment combination.[9,11]

Colchicine

Colchicine is an anti-inflammatory drug with a mild side effect profile. High doses of colchicine have been effective in patients with classical and inflammatory EBA.[12-14] The typical dosing ranges from 0.6 mg PO BID to TID. The most frequent side effects are GI complaints, particularly diarrhea, which can limit the utility of this therapy.

Moderate to Severe Disease

Systemic Corticosteroids

Much of the disease morbidity and mortality, particularly with PV and BP, has decreased with the introduction of corticosteroid therapy. Corticosteroids are the first-line systemic treatment for moderate to severe BP and PV and may have a role in treating the inflammatory subset of EBA, evidence is admittedly scant for the latter.[2,15] There is no universal consensus on dosing and tapering systemic corticosteroids for AIBD. Some guidelines use weight-based dosing, whereas others recommend a starting dose of 40-60 mg PO daily.[5,6] Patients with milder BP, PV and EBA can often be adequately managed with 0.5-0.75 mg/kg/day. However, in patients with severe disease (>10 new lesions per day), a starting dose between 0.75-1.0 mg/kg/day can be used.

Long-term use of corticosteroids is associated with multiple adverse effects including increased risk for infection, weight gain, high blood pressure, osteoporosis, fluid retention, elevated blood sugar, cognitive disturbances, cataracts, and glaucoma. Therefore, once the disease stabilizes, careful tapering of the medication is strongly recommended. We suggest re-evaluating the patient 1-2 weeks after initiating therapy. If the disease is stable, a slow tapering of prednisone may be initiated, decreasing the dose by 5-10 mg every month as tolerated. However, in patients who cannot tolerate long-term prednisone use (i.e., patients with labile blood sugar or blood pressure, significant agitation or neurologic side-effects) a more rapid tapering may be required, decreasing the dose by 5-10 mg each week. If the disease remains active, then a decision can be made to either increase the dose or initiate adjunctive therapy with steroid sparing agents. The American College of Rheumatology has established recommendations for monitoring steroid-induced osteoporosis in patients on long-term corticosteroids.[16,17]

Steroid Sparing Agents

In patients who cannot be tapered off steroids without inducing disease flares, steroid sparing agents are invaluable in achieving prolonged remission. Careful review of monitoring guidelines is essential before initiating therapy.[1] Traditional immunosuppressive agents such as mycophenolate mofetil and azathioprine are more commonly used. However, with the advent of biologic therapy, treatment options such as intravenous immunoglobulin and rituximab are increasingly being employed earlier in the course of therapy.[18-20]

Azathioprine

When used as adjunctive therapy, azathioprine enables a significant dosage reduction of prednisone in patients with moderate to severe BP.[5,21] Azathioprine appears to be a superior steroid-sparing agent for PV when compared to cyclophosphamide and mycophenolate mofetil,[22] although there is some evidence that cyclophosphamide may induce a quicker and more sustained remission.[23] Genetics play a role in the efficacy and safety of azathioprine. The metabolism of azathioprine is dependent on xanthine oxidase and thiopurine methyltransferase

(TMPT). Ten percent of the population is heterozygous with intermediate TPMT enzyme activity and 1/300 patients is homozygous or compound heterozygous with low enzyme activity.[21,24] Although the effect on heterozygotes is still unclear, homozygotes are at risk of severe neutropenia.[25] Other adverse effects include cytopenia, hepatitis, pancreatitis and infection. Allopurinol inhibits xanthine oxidase, potentiating the risk of myelosuppression. Azathioprine may also decrease the efficacy of warfarin, therefore, dose adjustments may be required. The recommended dose of azathioprine is 1-3 mg/kg daily.[26] A lower dosage is recommended in the elderly or patients who have reduced TMPT levels.[1] When TMPT levels are extremely low, azathioprine should not be used.

Mycophenolate Mofetil

Mycophenolate mofetil (MM) is effective both as combination therapy and monotherapy in PV and BP.[27-32] In a randomized controlled trial comparing MM or placebo plus prednisone in the treatment of mild to moderate PV, the MM arm exhibited an improved time to and duration of response.[33] A study comparing MM vs. azathioprine as adjuvant therapy to oral methylprednisolone demonstrated similar efficacy in both groups, but increased hepatotoxicity was observed in those who received azathioprine.[34] Given its similar, if not superior, efficacy to azathioprine and better side effect profile, MM is becoming the first choice therapy for adjuvant treatment in BP and PV. The most common side effects are usually mild and include nausea, diarrhea, GI discomfort and malaise. However, hepatotoxicity, infections, leukopenia and anemia can occur.[20] The usual dosing range is between 1-3 g/day.

Cyclophosphamide

Cyclophosphamide has a faster onset of action than azathioprine or MM, but is also associated with significant adverse effects. Therefore, its use is usually reserved for patients with refractory or rapidly progressive disease, individuals unable to tolerate first-line therapies, or those with ocular cicatricial pemphigoid. Combination therapy with cyclophosphamide and systemic corticosteroids is recommended in patients with severe mucous membrane disease, in order to decrease the potentially severe morbidities.[7,35-37] Side effects are frequent and can be severe, and include nausea, vomiting, diarrhea, alopecia, and fatigue. More severe side effects are secondary to hematopoietic suppression leading to leukopenia, anemia and thrombocytopenia. An increased risk of transitional cell carcinoma and lymphomas is also concerning. One of the metabolites of cyclophosphamide, acrolein, can cause hemorrhagic cystitis in up to 40% of patients. Standard dosing of oral therapy is 2-2.5 mg/kg daily. Intravenous (IV) pulsed therapy is more frequently recommended in order to decrease the cumulative effect dose.

Cyclosporine

Several randomized controlled trials have failed to demonstrate a beneficial effect of oral cyclosporine either alone or as adjuvant therapy.[38-41] Topical cyclosporine has been used for oral and ocular cicatricial pemphigoid.[42,43] The most common adverse reactions to cyclosporine are renal dysfunction, hypertension, tremor, hirsutism, and gingival hyperplasia.

Methotrexate

Methotrexate (MTX) can be effective in treating BP and PV by decreasing disease activity and time to remission.[44-49] The most common side effects of MTX are fatigue, nausea and vomiting. More severe adverse effects include pancytopenia and hepatotoxicity, which can be exacerbated by renal disease, chronic nonsteroidal anti-inflammatory drug (NSAID) use, hepatic disease (e.g., hepatitis, alcohol use, diabetes mellitus, and obesity), and lack of folic acid supplementation. Photosensitivity and radiation recall are also potential adverse effects, and hepatic fibrosis and cirrhosis can occur with long-term use. The issue of if and when to perform a liver biopsy is controversial, however, depending on individual risk factors, a liver ultrasound and/or biopsy should be considered after prolonged use. Some guidelines recommend liver biopsy after a cumulative dose of 4 g in the absence of risk factors for hepatic disease.[50,51] Dosing is similar to that for rheumatoid arthritis, averaging 15 mg/week and 1 mg daily of folic acid.[49]

Dapsone

Dapsone inhibits the chemotaxis of polymorphonuclear leukocytes and is an extremely effective drug in treating neutrophilic dermatoses.[52-57] In many AIBD, dapsone is more successful as an adjunctive rather than single agent treatment. A 2009 meta-analysis of 170 BP patients demonstrated that 81% experienced clinical improvement with dapsone, but the best responses were observed in conjunction with steroids or other immunosuppressants.[58] A randomized, double-blind, placebo-controlled crossover trial of dapsone vs. placebo favored dapsone over placebo as a steroid sparing agent in maintaining remission among patients with PV, but the results were not statistically significant.[59]

Dose-dependent hemolytic anemia and methemoglobinemia will occur to some degree in all patients. Cimetidine, 400 mg PO 3 times daily, can reduce dapsone-induced methemoglobinemia without affecting the clinical response.[60] Dapsone may also cause agranulocytosis and hepatic function abnormalities. Distal motor neuropathy is a rare and reversible side effect, and monitoring by clinical examination and nerve-conduction studies must be done. The typical dose of dapsone ranges between 100-300 mg daily, although the effective dose varies significantly between individuals.[61] In low-risk patients, treatment can be initiated at a dosage of 100 mg daily.

Intravenous Immunoglobulin (IVIg)

IVIg has been shown in numerous small studies to be beneficial in refractory PV, BP and EBA.[62-81] A randomized, placebo-controlled, double-blind study demonstrated that pemphigus patients given a single cycle of high dose IVIg (400 mg/kg/day over 5 consecutive days) experienced a prolonged time to escape from the protocol compared to placebo.[82] An earlier retrospective study found no response to IVIg in 9 of 11 patients with AIBD.[83] Side effects are usually mild and self-limiting and include headache, back pain, chills, flushing, fever, hypertension, myalgia, nausea and vomiting. These may improve with decreased infusion rate or premedication with NSAIDs, antihistamines, or low-dose IV corticosteroids. Mild skin reactions including erythema, pain and phlebitis can occur at the infusion site. Potential severe side effects include anaphylaxis (particularly in IgA-deficient

individuals), renal failure, aseptic meningitis, and infection. The typical dosing cycle is 2 g/kg divided into 2 or 3 equal doses, given on 3 consecutive days, repeated every 4 weeks.[62]

Rituximab

Rituximab has shown the most promise as therapy in PV, although it may also be beneficial in the treatment of BP and refractory EBA.[84-89] A majority of patients treated with various protocols of rituximab achieved either complete or partial remission. Relapses are common, but can also be successfully treated with additional courses of rituximab.[90] A group of 25 patients with mucous membrane pemphigoid (5 with mucous membrane dominant EBA) also responded well to rituximab.[91] The data on rituximab use in BP is less robust due to the efficacy of steroids in this disease. In 11 patients with BP refractory to standard treatments, rituximab use resulted in either complete or partial remission.[89,92-94] The most common adverse effects are mild and self-limiting and include fever, headache, nausea, chills, hypotension, and thrombocytopenia. Many of these symptoms are infusion related. Infections can also occur and may be life threatening, particularly in immunosuppressed patients. A potentially severe consequence is progressive multifocal encephalopathy (PMLE). The estimated rate of PMLE after rituximab therapy is 4.06 per 100,000 patients. To date, no cases have been reported in patients treated for AIBD.[95,96] Nonetheless, clinicians and patients should be aware of the risk of this rare, but extremely serious, adverse event. Two dosing schedules exist for rituximab: the one traditionally used in lymphoma consists of weekly IV infusions of 375 mg/m^2 for 4 weeks and the other more commonly used in rheumatoid arthritis is two 1 g infusions, administered 2 weeks apart. The latter has become increasingly used as the standard protocol for AIBD.

Conclusion

The treatment of AIBD varies greatly, but usually consists of topical or systemic steroids or combination therapy with steroid sparing agents or immunomodulators.[97] For PV, BP and EBA, finding the optimal treatment can be very difficult and often requires several dose adjustments or trial of an alternative steroid-sparing agent before the disease is well-controlled. Supportive care is often necessary to reduce the risk of complications and improve quality of life. This often requires collaborative approaches to therapy with ophthalmology and/or otolaryngology, when severe mucous membrane disease is present. For PV, first-line therapy is systemic corticosteroids and first-line adjunctive therapy is usually azathioprine or MM. Rituximab has recently been gaining ground as a treatment for refractory cases. The treatment algorithm for BP is similar. However, because patients with BP tend to have more comorbidities, early transition to combination or steroid-sparing therapy may be necessary.

References

1. Wolverton SE, editor. *Comprehensive dermatologic drug therapy.* 3rd ed. Edinburgh: Sauders/Elsevier; 2013.
2. Schmidt E, Zillikens D. Modern diagnosis of autoimmune blistering skin diseases. *Autoimmun Rev.* 2010 Dec;10(2):84-9.
3. Mihalyi L, Kiss M, Dobozy A, et al. Clinical relevance of autoantibodies in patients with autoimmune bullous dermatosis. *Clin Dev Immunol.* 2012;2012:369546.
4. Tampoia M, Giavarina D, Di Giorgio C, et al. Diagnostic accuracy of enzyme-linked immunosorbent assays (ELISA) to detect anti-skin autoantibodies in autoimmune blistering skin diseases: a systematic review and meta-analysis. *Autoimmun Rev.* 2012 Dec;12(2):121-6.
5. Harman KE, Albert S, Black MM. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol.* 2003 Nov;149(5):926-37.
6. Wojnarowska F, Kirtschig G, Highet AS, et al. Guidelines for the management of bullous pemphigoid. *Br J Dermatol.* 2002 Aug;147(2):214-21.
7. Chan LS, Ahmed AR, Anhalt GJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol.* 2002 Mar;138(3):370-9.
8. Joly P, Roujeau JC, Benichou J, et al. A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: a multicenter randomized study. *J Invest Dermatol.* 2009 Jul;129(7):1681-7.
9. Hornschuh B, Hamm H, Wever S, et al. Treatment of 16 patients with bullous pemphigoid with oral tetracycline and niacinamide and topical clobetasol. *J Am Acad Dermatol.* 1997 Jan;36(1):101-3.
10. Fivenson DP, Breneman DL, Rosen GB, et al. Nicotinamide and tetracycline therapy of bullous pemphigoid. *Arch Dermatol.* 1994 Jun;130(6):753-8.
11. Berk MA, Lorincz AL. The treatment of bullous pemphigoid with tetracycline and niacinamide. A preliminary report. *Arch Dermatol.* 1986 Jun;122(6):670-4.
12. Cunningham BB, Kirchmann TT, Woodley D. Colchicine for epidermolysis bullosa acquisita. *J Am Acad Dermatol.* 1996 May;34(5 Pt 1):781-4.
13. Megahed M, Scharffetter-Kochanek K. Epidermolysis bullosa acquisita--successful treatment with colchicine. *Arch Dermatol Res.* 1994;286(1):35-46.
14. Tanaka N, Dainichi T, Ohyama B, et al. A case of epidermolysis bullosa acquisita with clinical features of Brunsting-Perry pemphigoid showing an excellent response to colchicine. *J Am Acad Dermatol.* 2009 Oct;61(4):715-9.
15. Kirtschig G, Murrell D, Wojnarowska F, et al. Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review. *Arch Dermatol.* 2002 Mar;138(3):380-4.
16. Khan YK, Kalaaji AN, Clarke BL. Glucocorticoid-induced osteoporosis in dermatologic practice: a review. *J Drugs Dermatol.* 2008 Nov;7(11):1053-9.
17. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken).* 2010 Nov;62(11):1515-26.
18. Leventhal JS, Sanchez MR. Is it time to re-evaluate the treatment of pemphigus? *J Drugs Dermatol.* 2012 Oct;11(10):1200-6.
19. Sandborn WJ. State-of-the-art: immunosuppression and biologic therapy. *Dig Dis.* 2010;28(3):536-42.
20. Schiavo AL, Puca RV, Ruocco V, et al. Adjuvant drugs in autoimmune bullous diseases, efficacy versus safety: facts and controversies. *Clin Dermatol.* 2010 May-Jun;28(3):337-43.
21. Aberer W, Wolff-Schreiner EC, Stingl G, et al. Azathioprine in the treatment of pemphigus vulgaris. A long-term follow-up. *J Am Acad Dermatol.* 1987 Mar;16(3 Pt 1):527-33.
22. Chams-Davatchi C, Esmaili N, Daneshpazhooh M, et al. Randomized controlled open-label trial of four treatment regimens for pemphigus vulgaris. *J Am Acad Dermatol.* 2007 Oct;57(4):622-8.
23. Olszewska M, Kolacinska-Strasz Z, Sulej J, et al. Efficacy and safety of cyclophosphamide, azathioprine, and cyclosporine (ciclosporin) as adjuvant drugs in pemphigus vulgaris. *Am J Clin Dermatol.* 2007;8(2):85-92.
24. Meggitt SJ, Anstey AV, Mohd Mustapa MF, et al. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. *Br J Dermatol.* 2011 Oct;165(4):711-34.
25. Newman WG, Payne K, Tricker K, et al. A pragmatic randomized controlled trial of thiopurine methyltransferase genotyping prior to azathioprine treatment: the TARGET study. *Pharmacogenomics.* 2011 Jun;12(6):815-26.
26. Patel AA, Swerlick RA, McCall CO. Azathioprine in dermatology: the past, the present, and the future. *J Am Acad Dermatol.* 2006 Sep;55(3):369-89.
27. Bohm M, Beissert S, Schwarz T, et al. Bullous pemphigoid treated with mycophenolate mofetil. *Lancet.* 1997 Feb 22;349(9051):541.
28. Nousari HC, Griffin WA, Anhalt GJ. Successful therapy for bullous pemphigoid with mycophenolate mofetil. *J Am Acad Dermatol.* 1998 Sep;39(3):497-8.
29. Powell AM, Albert S, Al Fares S, et al. An evaluation of the usefulness of mycophenolate mofetil in pemphigus. *Br J Dermatol.* 2003 Jul;149(1):138-45.
30. Strowd LC, Taylor SL, Jorizzo JL, et al. Therapeutic ladder for pemphigus vulgaris: emphasis on achieving complete remission. *J Am Acad Dermatol.* 2011 Mar;64(3):490-4.

31. Grundmann-Kollmann M, Kaskel P, Leiter U, et al. Treatment of pemphigus vulgaris and bullous pemphigoid with mycophenolate mofetil monotherapy. *Arch Dermatol.* 1999 Jun;135(6):724-5.
32. Grundmann-Kollmann M, Korting HC, Behrens S, et al. Mycophenolate mofetil: a new therapeutic option in the treatment of blistering autoimmune diseases. *J Am Acad Dermatol.* 1999 Jun;40(6 Pt 1):957-60.
33. Beissert S, Mimouni D, Kanwar AJ, et al. Treating pemphigus vulgaris with prednisone and mycophenolate mofetil: a multicenter, randomized, placebo-controlled trial. *J Invest Dermatol.* 2010 Aug;130(8):2041-8.
34. Beissert S, Werfel T, Frieling U, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. *Arch Dermatol.* 2006 Nov;142(11):1447-54.
35. Dawe RS, Naidoo DK, Ferguson J. Severe bullous pemphigoid responsive to pulsed intravenous dexamethasone and oral cyclophosphamide. *Br J Dermatol.* 1997 Nov;137(5):826-7.
36. Itoh T, Hosokawa H, Shirai Y, et al. Successful treatment of bullous pemphigoid with pulsed intravenous cyclophosphamide. *Br J Dermatol.* 1996 May;134(5):931-3.
37. Elder MJ, Lightman S, Dart JK. Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. *Br J Ophthalmol.* 1995 Mar;79(3):264-6.
38. Griffiths CE, Katsambas A, Dijkmans BA, et al. Update on the use of ciclosporin in immune-mediated dermatoses. *Br J Dermatol*. 2006 Jul;155 Suppl 2:1-16.
39. Lapidoth M, David M, Ben-Amitai D, et al. The efficacy of combined treatment with prednisone and cyclosporine in patients with pemphigus: preliminary study. *J Am Acad Dermatol.* 1994 May;30(5 Pt 1):752-7.
40. Martin LK, Werth V, Villanueva E, et al. Interventions for pemphigus vulgaris and pemphigus foliaceus. *Cochrane Database Syst Rev.* 2009(1):CD006263.
41. Stenveld HJ, Starink TM, van Joost T, et al. Efficacy of cyclosporine in two patients with dermatitis herpetiformis resistant to conventional therapy. *J Am Acad Dermatol.* 1993 Jun;28(6):1014-5.
42. Azana JM, de Misa RF, Boixeda JP, et al. Topical cyclosporine for cicatricial pemphigoid. *J Am Acad Dermatol.* 1993 Jan;28(1):134-5.
43. Holland EJ, Olsen TW, Ketcham JM, et al. Topical cyclosporin A in the treatment of anterior segment inflammatory disease. *Cornea.* 1993 Sep;12(5):413-9.
44. Bara C, Maillard H, Briand N, et al. Methotrexate for bullous pemphigoid: preliminary study. *Arch Dermatol.* 2003 Nov;139(11):1506-7.
45. Dereure O, Bessis D, Guillot B, et al. Treatment of bullous pemphigoid by low-dose methotrexate associated with short-term potent topical steroids: an open prospective study of 18 cases. *Arch Dermatol.* 2002 Sep;138(9):1255-6.
46. Heilborn JD, Stahle-Backdahl M, Albertioni F, et al. Low-dose oral pulse methotrexate as monotherapy in elderly patients with bullous pemphigoid. *J Am Acad Dermatol.* 1999 May;40(5 Pt 1):741-9.
47. Smith TJ, Bystryn JC. Methotrexate as an adjuvant treatment for pemphigus vulgaris. *Arch Dermatol.* 1999 Oct;135(10):1275-6.
48. Kjellman P, Eriksson H, Berg P. A retrospective analysis of patients with bullous pemphigoid treated with methotrexate. *Arch Dermatol.* 2008 May;144(5):612-6.
49. Gurcan HM, Ahmed AR. Analysis of current data on the use of methotrexate in the treatment of pemphigus and pemphigoid. *Br J Dermatol.* 2009 Oct;161(4):723-31.
50. Kremer JM, Alarcon GS, Lightfoot RW, Jr., et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. *Arthritis Rheum.* 1994 Mar;37(3):316-28.
51. Thomas JA, Aithal GP. Monitoring liver function during methotrexate therapy for psoriasis: are routine biopsies really necessary? *Am J Clin Dermatol.* 2005;6(6):357-63.
52. Booth SA, Moody CE, Dahl MV, et al. Dapsone suppresses integrin-mediated neutrophil adherence function. *J Invest Dermatol.* 1992 Feb;98(2):135-40.
53. Debol SM, Herron MJ, Nelson RD. Anti-inflammatory action of dapsone: inhibition of neutrophil adherence is associated with inhibition of chemoattractant-induced signal transduction. *J Leukoc Biol.* 1997 Dec;62(6):827-36.
54. Harvath L, Yancey KB, Katz SI. Selective inhibition of human neutrophil chemotaxis to N-formyl-methionyl-leucyl-phenylalanine by sulfones. *J Immunol.* 1986 Aug 15;137(4):1305-11.
55. Wozel G, Blasum C, Winter C, et al. Dapsone hydroxylamine inhibits the LTB4-induced chemotaxis of polymorphonuclear leukocytes into human skin: results of a pilot study. *Inflamm Res.* 1997 Oct;46(10):420-2.
56. Schmidt E, Reimer S, Kruse N, et al. The IL-8 release from cultured human keratinocytes, mediated by antibodies to bullous pemphigoid autoantigen 180, is inhibited by dapsone. *Clin Exp Immunol.* 2001 Apr;124(1):157-62.
57. Thuong-Nguyen V, Kadunce DP, Hendrix JD, et al. Inhibition of neutrophil adherence to antibody by dapsone: a possible therapeutic mechanism of dapsone in the treatment of IgA dermatoses. *J Invest Dermatol.* 1993 Apr;100(4):349-55.
58. Gurcan HM, Ahmed AR. Efficacy of dapsone in the treatment of pemphigus and pemphigoid: analysis of current data. *Am J Clin Dermatol.* 2009;10(6):383-96.
59. Werth VP, Fivenson D, Pandya AG, et al. Multicenter randomized, double-blind, placebo-controlled, clinical trial of dapsone as a glucocorticoid-sparing agent in maintenance-phase pemphigus vulgaris. *Arch Dermatol.* 2008 Jan;144(1):25-32.
60. Coleman MD, Rhodes LE, Scott AK, et al. The use of cimetidine to reduce dapsone-dependent methaemoglobinaemia in dermatitis herpetiformis patients. *Br J Clin Pharmacol.* 1992 Sep;34(3):244-9.
61. Piette EW, Werth VP. Dapsone in the management of autoimmune bullous diseases. *Immunol Allergy Clin North Am.* 2012 May;32(2):317-22, vii.
62. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol.* 2001 Dec;45(6):825-35.
63. Ahmed AR, Colon JE. Comparison between intravenous immunoglobulin and conventional immunosuppressive therapy regimens in patients with severe oral pemphigoid: effects on disease progression in patients nonresponsive to dapsone therapy. *Arch Dermatol.* 2001 Sep;137(9):1181-9.
64. Ahmed AR, Gurcan HM. Treatment of epidermolysis bullosa acquisita with intravenous immunoglobulin in patients non-responsive to conventional therapy: clinical outcome and post-treatment long-term follow-up. *J Eur Acad Dermatol Venereol.* 2012 Sep;26(9):1074-83.
65. Beckers RC, Brand A, Vermeer BJ, et al. Adjuvant high-dose intravenous gammaglobulin in the treatment of pemphigus and bullous pemphigoid: experience in six patients. *Br J Dermatol.* 1995 Aug;133(2):289-93.
66. Bewley AP, Keefe M. Successful treatment of pemphigus vulgaris by pulsed intravenous immunoglobulin therapy. *Br J Dermatol.* 1996 Jul;135(1):128-9.
67. Caldwell JB, Yancey KB, Engler RJ, et al. Epidermolysis bullosa acquisita: efficacy of high-dose intravenous immunoglobulins. *J Am Acad Dermatol.* 1994 Nov;31(5 Pt 1):827-8.
68. Engineer L, Ahmed AR. Role of intravenous immunoglobulin in the treatment of bullous pemphigoid: analysis of current data. *J Am Acad Dermatol.* 2001 Jan;44(1):83-8.
69. Godard W, Roujeau JC, Guillot B, et al. Bullous pemphigoid and intravenous gammaglobulin. *Ann Intern Med.* 1985 Dec;103(6 (Pt 1)):964-5.
70. Gourgiotou K, Exadaktylou D, Aroni K, et al. Epidermolysis bullosa acquisita: treatment with intravenous immunoglobulins. *J Eur Acad Dermatol Venereol.* 2002 Jan;16(1):77-80.
71. Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. *Br J Dermatol.* 1999 May;140(5):865-74.
72. Harman KE, Whittam LR, Wakelin SH, et al. Severe, refractory epidermolysis bullosa acquisita complicated by an oesophageal stricture responding to intravenous immune globulin. *Br J Dermatol.* 1998 Dec;139(6):1126-7.
73. Humbert P, Derancourt C, Aubin F, et al. Effects of intravenous gamma-globulin in pemphigus. *J Am Acad Dermatol.* 1990 Feb;22(2 Pt 1):326.
74. Kofler H, Wambacher-Gasser B, Topar G, et al. Intravenous immunoglobulin treatment in therapy-resistant epidermolysis bullosa acquisita. *J Am Acad Dermatol.* 1997 Feb;36(2 Pt 2):331-5.
75. Messer G, Sizmann N, Feucht H, et al. High-dose intravenous immunoglobulins for immediate control of severe pemphigus vulgaris. *Br J Dermatol.* 1995 Dec;133(6):1014-6.
76. Mohr C, Sunderkotter C, Hildebrand A, et al. Successful treatment of epidermolysis bullosa acquisita using intravenous immunoglobulins. *Br J Dermatol.* 1995 May;132(5):824-6.
77. Mosqueira CB, Furlani Lde A, Xavier AF, et al. Intravenous immunoglobulin for treatment of severe acquired bullous epidermolysis refractory to conventional immunosuppressive therapy. *An Bras Dermatol.* 2010 Jul-Aug;85(4):521-4.
78. Sami N, Bhol KC, Ahmed AR. Treatment of oral pemphigoid with intravenous immunoglobulin as monotherapy. Long-term follow-up: influence of treatment on antibody titres to human alpha6 integrin. *Clin Exp Immunol.* 2002 Sep;129(3):533-40.
79. Sami N, Letko E, Androudi S, et al. Intravenous immunoglobulin therapy in patients with ocular-cicatricial pemphigoid: a long-term follow-up. *Ophthalmology.* 2004 Jul;111(7):1380-2.

80. Sami N, Qureshi A, Ruocco E, et al. Corticosteroid-sparing effect of intravenous immunoglobulin therapy in patients with pemphigus vulgaris. *Arch Dermatol.* 2002 Sep;138(9):1158-62.
81. Wever S, Zillikens D, Brocker EB. Successful treatment of refractory mucosal lesions of pemphigus vulgaris using intravenous gammaglobulin as adjuvant therapy. *Br J Dermatol.* 1996 Nov;135(5):862-3.
82. Amagai M, Ikeda S, Shimizu H, et al. A randomized double-blind trial of intravenous immunoglobulin for pemphigus. *J Am Acad Dermatol.* 2009 Apr;60(4):595-603.
83. Wetter DA, Davis MD, Yiannias JA, et al. Effectiveness of intravenous immunoglobulin therapy for skin disease other than toxic epidermal necrolysis: a retrospective review of Mayo Clinic experience. *Mayo Clin Proc.* 2005 Jan;80(1):41-7.
84. Schmidt E, Benoit S, Brocker EB, et al. Successful adjuvant treatment of recalcitrant epidermolysis bullosa acquisita with anti-CD20 antibody rituximab. *Arch Dermatol.* 2006 Feb;142(2):147-50.
85. Salopek TG, Logsetty S, Tredget EE. Anti-CD20 chimeric monoclonal antibody (rituximab) for the treatment of recalcitrant, life-threatening pemphigus vulgaris with implications in the pathogenesis of the disorder. *J Am Acad Dermatol.* 2002 Nov;47(5):785-8.
86. Virgolini L, Marzocchi V. Anti-CD20 monoclonal antibody (rituximab) in the treatment of autoimmune diseases. Successful result in refractory pemphigus vulgaris: report of a case. *Haematologica.* 2003 Jul;88(7):ELT24.
87. Crichlow SM, Mortimer NJ, Harman KE. A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. *Br J Dermatol.* 2007 Jan;156(1):194-6.
88. Niedermeier A, Eming R, Pfutze M, et al. Clinical response of severe mechanobullous epidermolysis bullosa acquisita to combined treatment with immunoadsorption and rituximab (anti-CD20 monoclonal antibodies). *Arch Dermatol.* 2007 Feb;143(2):192-8.
89. Schulze J, Bader P, Henke U, et al. Severe bullous pemphigoid in an infant--successful treatment with rituximab. *Pediatr Dermatol.* 2008 Jul-Aug;25(4):462-5.
90. Zakka LR, Shetty SS, Ahmed AR. Rituximab in the treatment of pemphigus vulgaris. *Dermatol Ther (Heidelb).* 2012 Dec;2(1):17.
91. Le Roux-Villet C, Prost-Squarcioni C, Alexandre M, et al. Rituximab for patients with refractory mucous membrane pemphigoid. *Arch Dermatol.* 2011 Jul;147(7):843-9.
92. Fuertes I, Luelmo J, Leal L, et al. Refractory childhood pemphigoid successfully treated with rituximab. *Pediatr Dermatol.* 2013 Sep-Oct;30(5):e96-7.
93. Lourari S, Herve C, Doffoel-Hantz V, et al. Bullous and mucous membrane pemphigoid show a mixed response to rituximab: experience in seven patients. *J Eur Acad Dermatol Venereol.* 2011 Oct;25(10):1238-40.
94. Saouli Z, Papadopoulos A, Kaiafa G, et al. A new approach on bullous pemphigoid therapy. *Ann Oncol.* 2008 Apr;19(4):825-6.
95. Palazzo E, Yahia SA. Progressive multifocal leukoencephalopathy in autoimmune diseases. *Joint Bone Spine.* 2012 Jul;79(4):351-5.
96. Tavazzi E, Ferrante P, Khalili K. Progressive multifocal leukoencephalopathy: an unexpected complication of modern therapeutic monoclonal antibody therapies. *Clin Microbiol Infect.* 2011 Dec;17(12):1776-80.
97. Garcia-Romero MT, Werth VP. Randomized controlled trials needed for bullous pemphigoid interventions. *Arch Dermatol.* 2012 Feb;148(2):243-6.

Pregnancy-Specific Skin Disorders

Skyler White, BS; Rebecca Philips, MD; Megan Moody Neill, MD; Erica Kelly, MD

Department of Dermatology, University of Texas Medical Branch, Galveston, TX, USA

ABSTRACT

The pregnancy-specific skin disorders are pruritic, inflammatory eruptions. The current classification by Ambros-Rudolph et al. includes four entities: pemphigoid gestationis (PG), polymorphic eruption of pregnancy (PEP), atopic eruption of pregnancy (AEP), and intrahepatic cholestasis of pregnancy (ICP). Although these disorders are all characterized by intense pruritus during pregnancy, they can be distinguished by timing, morphology, histopathology, treatment and potential for fetal complications. Diagnosis is made by clinical presentation, histology, and immunofluorescence. PEP and AEP typically resolve without sequelae; however, PG may lead to prematurity and low birth weight, and ICP is associated with an increased risk of prematurity, fetal distress, and intrauterine fetal demise. The potential for serious fetal complications necessitates a thorough evaluation of pregnancy-related pruritus. This article will discuss the skin disorders specific to pregnancy, with a focus on clinical presentation, potential for fetal complications, pathogenesis, diagnosis, and treatment.

Key words: atopic eruption, intrahepatic cholestasis, pemphigoid gestationis, polymorphic eruption, pregnancy complications, pruritus, skin disease

Introduction

While pregnancy may result in a number of skin changes, there are pruritic eruptions that occur specific to pregnancy and the postpartum period.[1-3] In 1983, Holmes and Black proposed a classification of pregnancy-specific skin disorders, which included pemphigoid gestationis, polymorphic eruption of pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy.[4] In 1998, Shornick proposed the addition of intrahepatic cholestasis of pregnancy.[5] The current classification was proposed by Ambros-Rudolph et al. in 2006 on the basis of a large retrospective study of 505 patients, and includes four entities: pemphigoid gestastionis, polymorphic eruption of pregnancy, atopic eruption of pregnancy (encompassing prurigo of pregnancy and pruritic folliculitis of pregnancy), and intrahepatic cholestasis of pregnancy.[2]

A major etiology of skin changes in pregnancy involves alterations in the maternal immune system. To prevent fetal rejection, an imbalance is created between cellular and humoral immunity.[1-3] T helper type 2 (Th2) cytokine production is favored over Th1, enhancing humoral immunity and stunting cell-mediated immunity. The changes in maternal hormones are also believed to have an effect, as many skin disorders develop during the third trimester.[3]

This article will discuss the skin disorders specific to pregnancy, with a focus on clinical presentation, potential for fetal complications, pathogenesis, diagnosis, and treatment.

Discussion

Pemphigoid Gestationis

Pemphigoid gestationis (PG), previously known as herpes gestationis, is the most rare of the pregnancy-specific disorders, with incidence of 1:2,000 to 1:60,000, varying with the prevalence of human leukocyte antigens (HLA)-DR3 and HLA-DR4.[1,3] PG initially presents with pruritic, erythematous urticarial papules and plaques that progress to a vesiculobullous eruption. PG characteristically involves the umbilicus, and often spreads to the chest, back, and extremities.[3,4,6] Palms and soles can be affected, but not typically the face and mucosa.[3,4] The eruption develops most often in the third trimester.[3] The course fluctuates throughout pregnancy and, in 75% of patients, a flare occurs at delivery.[1] PG usually clears spontaneously within a few months after delivery. Recurrence during subsequent pregnancies is common, and is often characterized by earlier presentation and increased severity.[1,3] There have also been reports of flares during menstruation or with the use of oral contraceptives.[1,6,7] There is an increased incidence of prematurity and small-for-gestational age infants, especially with more severe maternal disease, marked by blister formation and onset before the third trimester.[1,3] Approximately 10% of infants develop a transient, bullous eruption due to the transfer of antibodies via the placenta.[1,3,4]

Autoimmune diseases commonly present during pregnancy due to the immunosuppression required to maintain fetal life. PG is an autoimmune condition in which antibodies develop against the NC16A domain of collagen XVII (BPAG2, BP180), which is present in the amniotic, placental, and umbilical cord tissues, in addition to the basement membrane of the skin.[3] The antibodies activate the complement cascade leading to inflammation and bullae formation.[1,3,8] Immunoglobulin G (IgG) is the main cross-reacting antibody seen in PG, specifically IgG4.[3,8] Women who present with this disorder are at a higher risk of autoimmune disease, particularly Grave's disease.[1] An association with HLA-DR3 and HLA-DR4 has been observed.[3]

Histologically, pre-bullous PG is characterized by dermal edema and perivascular inflammation with lymphocytes, histiocytes, and eosinophils. A sub-epidermal split is observed in the vesiculobullous lesions, with an eosinophil-predominant

infiltrate.[1,4,6] Direct immunofluorescence of peri-lesional skin shows linear deposition of complement 3 (C3) along the basement membrane zone in all patients.[1,3] Some patients also have IgG deposition along the basement membrane.[1] Enzyme-linked immunosorbent assay (ELISA) detects the specific antibodies against collagen XVII, which correlates with disease activity and can be monitored to assess treatment effectiveness.[1,3]

Treatment of PG is focused on managing pruritus and bullae formation.[1,3] In mild cases, topical corticosteroids and antihistamines are effective. In severe bullous PG, it is appropriate to use systemic corticosteroids. The dose can be decreased after adequate control is attained, however, it is often increased prior to delivery due to the high risk of flare.[3] Use of systemic corticosteroids does not increase fetal risk, and may actually decrease risk due to control of placental inflammation.[9]

Polymorphic Eruption of Pregnancy

Polymorphic eruption of pregnancy (PEP), previously called pruritic urticarial papules and plaques of pregnancy, is a benign, pruritic inflammatory disorder that affects approximately 1 in 160 pregnancies.[1,4,10] It is typically observed during the late third trimester or immediate postpartum period of first pregnancies, and the risk is increased with multiple gestations and rapid weight gain. Urticarial papules and plaques first appear within striae distensae on the abdomen, and unlike PG, spare the umbilicus. The eruption commonly spreads to the thighs and buttocks, and rarely may generalize.[1-3,10] One-to-two millimeter vesicles may develop, but in contrast to PG, bullae are not observed.[1] Target lesions and widespread erythema may also be present.[4] The eruption is self-limited and clears spontaneously in 4-6 weeks without relation to delivery. It does not typically recur; however, there have been recurrences with earlier presentation of the lesions in subsequent pregnancies that are multiple gestations. No adverse fetal outcomes have been described.[1,3]

It is theorized that connective tissue damage from excessive stretching plays a major role in the pathogenesis of the disorder. The stretching may elicit an immune response to the damaged connective tissue antigen.[1,3]

Histological findings are similar to PG. In early PEP, a superficial to mid-dermal perivascular infiltrate of lymphocytes, histiocytes, and sporadic eosinophils is observed with edema of the dermis. Later stages of PEP demonstrate epidermal spongiosis.[1,3,4,6] Immunofluorescence is negative, distinguishing PEP from PG.[1-3,10]

Treatment of PEP is based on symptomatic relief with the use of topical corticosteroids and antihistamines. If the rash becomes generalized, a short systemic corticosteroid taper can be used.[1,3]

Atopic Eruption of Pregnancy

Atopic eruption of pregnancy (AEP) is the most common pregnancy-specific skin disorder, accounting for almost 50% of cases. It has also been referred to by several other names including prurigo of pregnancy, prurigo gestationis, early-onset prurigo of pregnancy, Spangler's papular dermatitis of pregnancy, pruritic folliculitis of pregnancy, and eczema of pregnancy.[1-3] AEP is a benign disorder characterized by a pruritic eczematous or papular eruption.[1] It usually presents before the third trimester, in contrast to the other dermatoses of pregnancy.[1,4] Two-thirds of AEP cases are characterized by eczematous skin changes in the common atopic sites such as neck and flexor surfaces. The remaining cases are characterized by a papular eruption of the abdomen and extremities.[1] Lesions typically respond well to treatment and spontaneously clear postpartum; however, AEP is likely to recur in future pregnancies.[1,3] The fetus is unaffected, but is at increased risk for atopic dermatitis as an infant.[1]

It is thought that the pathogenesis of atopic eruption of pregnancy is initiated by pregnancy-related immune system changes.[1,3] There is a shift towards humoral immunity, with increased Th2 activation.[1] Patients who develop AEP may have an existing predisposition to atopic dermatitis, but 80% of the patients develop these skin changes for the first time during their pregnancy.[1] A family history of atopic dermatitis is frequently observed.[3]

AEP is commonly a diagnosis of exclusion, as diagnostic testing is nonspecific. Serum IgE levels are elevated in 20-70% of patients.[1] Other pregnancy-specific skin disorders, particularly ICP, must be excluded. Additionally, pruritic eruptions not specific to pregnancy, such as scabies and drug eruptions, must be considered in the differential diagnosis of AEP.

Topical corticosteroids are the mainstay of treatment. In severe cases, systemic corticosteroids and antihistamines may be indicated for short-term use. Phototherapy can also be considered.[1]

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP), known previously as obstetric cholestasis, cholestasis of pregnancy and jaundice of pregnancy, is a reversible cholestasis that appears to be hormonally triggered towards the end of pregnancy in predisposed women. It is characterized by pruritus of acute onset that often starts on the palms and soles and then generalizes. On exam, there are only secondary lesions, such as excoriations and prurigo nodules. Ten percent develop jaundice due to concomitant extrahepatic cholestasis. After delivery, pruritus resolves within a few weeks. There is a risk of recurrence in future pregnancies and with the use of oral contraceptives.[1,11]

Recognition of ICP is critical due to its association with serious sequelae. Potential fetal complications include prematurity, intrauterine fetal distress, and intrauterine fetal demise.[1,11] Fetal complication rates correlate with total bile acids in maternal serum, but do not increase significantly until bile acid levels exceed 40 µmol/L.[12] In cases of severe ICP complicated by jaundice, there is risk of maternal or fetal hemorrhage due to malabsorption of vitamin K.[1,11]

The severe pruritus present in ICP is due to elevated conjugated bile salts in the blood caused by impaired secretion, a multifactorial process influenced by genetics, environment and hormones.[1] There is a higher incidence of ICP in twin pregnancy.[11]

ICP is diagnosed by elevated bile acid level. Hyperbilirubinemia is noted in only the most severe cases, about 10-20%, and liver function tests can be normal in 30%. Histology is nonspecific and immunofluorescence is negative.[1,11]

Treatment targets serum bile acid levels to reduce fetal risk and control maternal symptoms.[1,11] Recommended treatment is ursodeoxycholic acid (UDCA).[1,3,11] Other drugs have been found

to decrease pruritus but not fetal risk, including antihistamines, S-adenosyl-L-methionine, dexamethasone, and cholestyramine.[1] Anion exchange resins, such as cholestyramine, can cause a vitamin K deficiency independent of ICP and, therefore, should be avoided.[11]

Conclusion

The four skin disorders specific to pregnancy, pemphigoid gestationis, polymorphic eruption of pregnancy, atopic eruption of pregnancy, and intrahepatic cholestasis of pregnancy, can be distinguished by clinical presentation, histopatholgy, pathogenesis, and potential for fetal complication. Only pemphigoid gestationis and intrahepatic cholestasis of pregnancy are associated with significant risk to the fetus. As these dermatoses are all characterized by pruritus, careful evaluation of any pregnancy related pruritus is essential to appropriately treat the mother and manage any potential risk to the fetus.

References

1. Ambros-Rudolph CM. Dermatoses of pregnancy - clues to diagnosis, fetal risk and therapy. *Ann Dermatol.* 2011 Aug;23(3):265-75.
2. Ambros-Rudolph CM, Mullegger RR, Vaughan-Jones SA, et al. The specific dermatoses of pregnancy revisited and reclassified: results of a retrospective two-center study on 505 pregnant patients. *J Am Acad Dermatol.* 2006 Mar;54(3):395-404.
3. Warshauer E, Mercurio M. Update on dermatoses of pregnancy. *Int J Dermatol.* 2013 Jan;52(1):6-13.
4. Holmes RC, Black MM. The specific dermatoses of pregnancy. *J Am Acad Dermatol.* 1983 Mar;8(3):405-12.
5. Shornick JK. Dermatoses of pregnancy. *Semin Cutan Med Surg.* 1998 Sep;17(3):172-81.
6. Shornick JK, Bangert JL, Freeman RG, et al. Herpes gestationis: clinical and histologic features of twenty-eight cases. *J Am Acad Dermatol.* 1983 Feb;8(2):214-24.
7. Lawley TJ, Stingl G, Katz SI. Fetal and maternal risk factors in herpes gestationis. *Arch Dermatol.* 1978 Apr;114(4):552-5.
8. Patton T, Plunkett RW, Beutner EH, et al. IgG4 as the predominant IgG subclass in pemphigoides gestationis. *J Cutan Pathol.* 2006 Apr;33(4):299-302.
9. Chi CC, Wang SH, Charles-Holmes R, et al. Pemphigoid gestationis: early onset and blister formation are associated with adverse pregnancy outcomes. *Br J Dermatol.* 2009 Jun;160(6):1222-8.
10. Ghazeeri G, Kibbi AG, Abbas O. Pruritic urticarial papules and plaques of pregnancy: epidemiological, clinical, and histopathological study of 18 cases from Lebanon. *Int J Dermatol.* 2012 Sep;51(9):1047-53.
11. Lammert F, Marschall HU, Glantz A, et al. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. *J Hepatol.* 2000 Dec;33(6):1012-21.
12. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. *Hepatology.* 2004 Aug;40(2):467-74.

Skin Therapy *Letter*© (ISSN 1201–5989) Skin Therapy *Letter*© is published 10 times annually by SkinCareGuide.com Ltd, 1003 - 1166 Alberni Street, Vancouver, British Columbia, Canada, V6E 3Z3. Printed on acid-free paper effective with Volume 1, Issue 1, 1995.

Subscription Information. Annual subscription: Canadian $94 individual; $171 institutional (plus GST); US $66 individual; $121 institutional. Outside North America: US$88 individual; $143 institutional. We sell reprints in bulk (100 copies or more of the same article). For individual reprints, we sell photocopies of the articles. The cost is $20 to fax and $15 to mail. Prepayment is required. Student rates available upon request. For inquiries: info@SkinTherapyLetter.com

Update on Drugs

Name/Company	Approval Dates/Comments
Tedizolid phosphate tablets and IV injection *Sivextro*™ Cubist Pharmaceuticals	In June 2014, the US FDA approved tedizolid, a novel oxazolidinone-class antibacterial agent, indicated for treatment of adult acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).
Hyaluronic acid-based dermal filler *Restylane® Silk* Valeant Pharmaceuticals	In June 2014, FDA marketing clearance was granted for Restylane® Silk injectable gel with 0.3% lidocaine, a device indicated for submucosal implantation for lip augmentation and dermal implantation for correction of perioral rhytids in patients over the age of 21.
Trifarotene Galderma R&D, LLC	In June 2014, the FDA granted Orphan Drug Designation to trifarotene for the treatment of congenital ichthyosis, a rare inherited skin scaling disorder.
Icatibant SC injection *Firazyr®* Shire Canada	In June 2014, Health Canada issued a Notice of Compliance for icatibant acetate ready-to-use injection for the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase inhibitor deficiency via blockade of bradykinin at the bradykinin B2 receptor.
C1 esterase inhibitor *Ruconest®* Pharming Group NV Salix Pharmaceuticals	In July 2014, the FDA approved the first recombinant human C1 esterase inhibitor for the treatment of acute angioedema attacks in adult and adolescent patients with HAE. This IV infused treatment can be administered by the patient after receiving training by a healthcare provider.
Methotrexate SC injection *Rasuvo*™ Medac Pharma	In July 2014, the FDA approved this SC injectable methotrexate therapy delivered in an auto-injector for rheumatoid arthritis (RA), polyarticular-course juvenile idiopathic arthritis (pJIA), and psoriasis. Ten dosage strengths will be available.
Tavaborole 5% topical solution *Kerydin*™ Anacor Pharmaceuticals	In July 2014, the FDA approved tavaborole, the first oxaborole antifungal agent approved for the topical treatment of onychomycosis of the toenails caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*. This clear, colorless, alcohol-based solution is applied with a dropper to the infected toenail once daily for 48 weeks.
Nivolumab IV infusion *Opdivo®* Ono Pharmaceutical Co.	In July 2014, the Ministry of Health, Welfare and Labor (Japan) granted manufacturing and marketing approval to this PD-1 monoclonal antibody for the treatment of unresectable melanoma. The drug is the first human PD-1 monoclonal antibody to gain regulatory approval.
Doxycycline hyclate tablets *Acticlate*™ Aqua Pharmaceuticals Almirall	In July 2014, the FDA approved this tetracycline-class antimicrobial agent indicated for a number of infections including adjunctive therapy in severe acne. Several dosing options are available with film-coated round 75 mg tablets and oval-shaped dual-scored 150 mg tablets.

Drug News

In July 2014, Galderma Canada announced regulatory approval for the expanded use of adapalene 0.1% + benzoyl peroxide 2.5% topical gel to include the treatment of acne vulgaris in patients ≥9 years of age. This new indication also coincides with a name change from Tactuo™ to TactuPump™and a new 70 g pump delivery system.

In July 2014, Health Canada's Natural Health Products Directorate approved DispersinB® skin cream and DispersinB® shampoo (Kane Biotech Inc.). Both products are antibiofilm-antimicrobial and antibiotic-free formulations that have anti-inflammatory and anti-pruritic effects.