NeP-positive patients. When the coexistence of NeP and depression was analyzed in our patients, only slightly more than half of the patients with indicators of depression had suspicion of comorbid NeP (Fig 1).

Our results further strengthen the findings that patients with HS suffer from pain and indicate that this HS-related pain may have elements of NeP. It is important that dermatologists assess the pain in patients with HS regularly and consult with other pain specialists to comprehensively treat their pain. Further studies are needed to analyze NeP in dermatologic conditions.

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## Diabetes mellitus and hyperglycemic complications in bullous pemphigoid

*To the Editor:* Corticosteroids remain the mainstay of treatment for bullous pemphigoid (BP).[1] Glucocorticoid-induced hyperglycemia and glucocorticoid-induced diabetes mellitus (DM) are

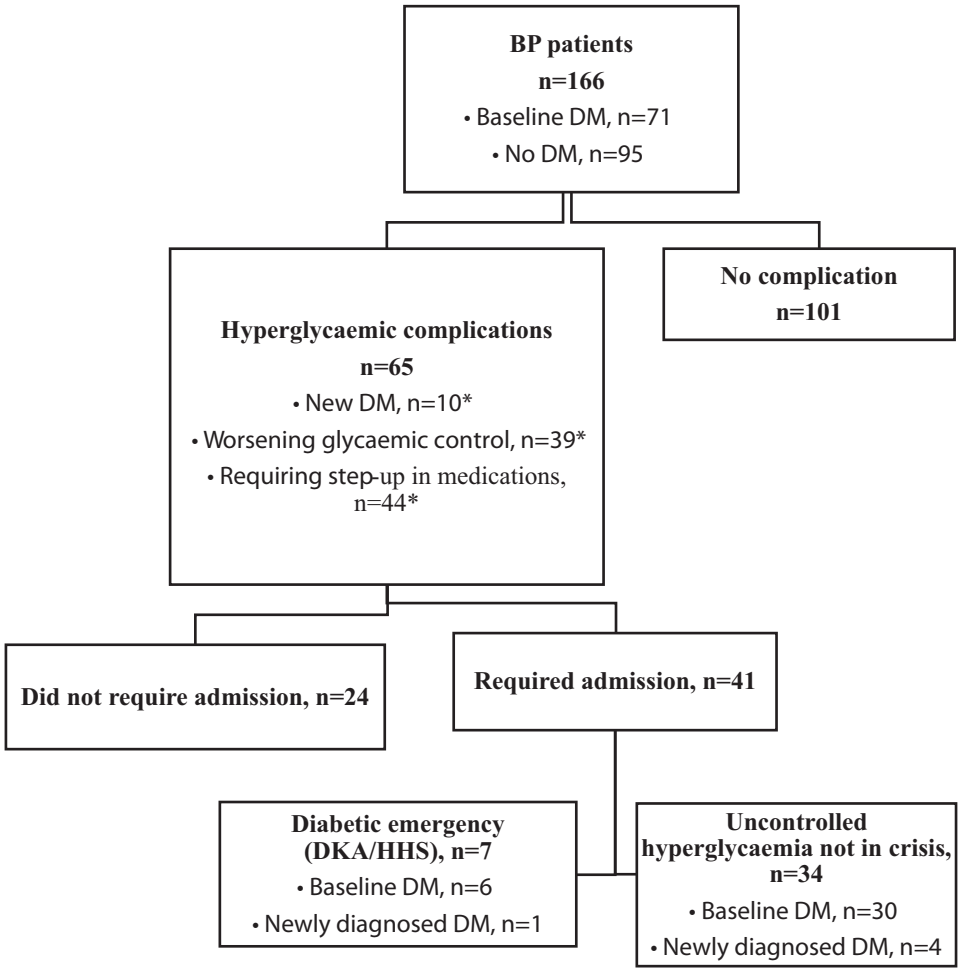


**Fig 1.** Hyperglycemic complications.

valid concerns given the age group of BP patients, multimorbidity, and chronicity of treatment.[2] The incidence of hyperglycemia and its impact and associated risk factors are largely unknown. We aim to determine the incidence and identify risk factors for hyperglycemic complications after a diagnosis of BP.

We performed a retrospective study of 166 patients diagnosed with BP in 2 tertiary hospitals in Singapore from 2005 to 2016 and collected data on demographics, comorbidities, BP treatment regimens, hyperglycemic complications, and mortality outcomes from the date of BP diagnosis to 1 year later. Hyperglycemic complications were defined as new-onset DM, pre-existing DM with worsening glycemic control, and pre-existing DM requiring step-up in medication for DM (Fig 1).

Hyperglycemic complications occurred in 39% patients, where 11% developed new-onset DM and 4% developed hyperglycemic crisis (Table I). Twenty-four percent required hospital admissions for hyperglycemia. First onset of hyperglycemic complications occurred at a mean duration of 1.2 months (range, 1-12) after BP diagnosis. Significant risk factors for developing hyperglycemic complications were pre-existing DM (odds ratio [OR], 24.25; 95% confidence interval [CI], 10.56-55.73), obesity (OR, 2.81; 95% CI, 1.06-7.48), hypertension (OR, 3.30; 95% CI, 1.46-7.45), chronic renal failure (OR, 3.49; 95% CI, 1.49-8.15), and hyperlipidemia (OR, 2.10; 95% CI, 1.05-4.19). Mortality within 1 year was significantly higher in patients who developed hyperglycemic complications (29% vs 14%). New-onset DM was

**Table I.** Association with the development of hyperglycemic complications

| | Hyperglycemic complications (n = 65) | No complications (n = 101) | Odds ratio (95% confidence interval) | *P* |
|---|---|---|---|---|
| Age, y, mean ± SD | 76.7 ± 9.5 | 76.7 ± 12.3 | | .97 |
| Gender | | | | |
| Male | 34 (52) | 45 (45) | 1.4 (0.7-2.6) | .34 |
| Female | 31 (48) | 56 (55) | 0.7 (0.4-1.4) | |
| Body mass index, kg/m$^2$, mean ± SD | 26.3 ± 6.5 | 23.7 ± 4.8 | | .05 |
| Obese (body mass index > 25 kg/m$^2$) | 16 (59) | 11 (41) | 2.8 (1.1-7.5) | .03 |
| Comorbidities | | | | |
| Diabetes mellitus | 54 (83) | 17 (17) | 24.3 (10.6-55.7) | <.01 |
| Hypertension | 56 (86) | 66 (65) | 3.3 (1.5-7.5) | <.01 |
| Hyperlipidemia | 24 (37) | 22 (21) | 2.1 (1.1-4.2) | .03 |
| Ischemic heart disease | 20 (31) | 27 (27) | 1.2 (0.6-2.4) | .60 |
| Cerebrovascular accidents | 27 (42) | 38 (38) | 1.2 (0.6-2.2) | .63 |
| Parkinson disease | 6 (9) | 17 (17) | 0.5 (0.2-1.4) | .25 |
| Dementia | 14 (22) | 19 (19) | 1.2 (0.6-2.6) | .69 |
| Chronic obstructive pulmonary disease | 0 (0) | 6 (6) | — | .08 |
| Gastrointestinal disease | 7 (11) | 10 (10) | 1.1 (0.4-3.1) | 1.00 |
| Chronic renal disease | 18 (28) | 10 (10) | 3.5 (1.5-8.2) | <.01 |
| Psychiatric illness | 6 (9) | 17 (17) | 0.5 (0.2-1.4) | .25 |
| Malignancies | 8 (12) | 14 (14) | 0.9 (0.3-2.2) | .82 |
| Autoimmune | 0 (0) | 2 (2) | — | .52 |
| Mortality (1 year) | 19 (29) | 14 (14) | 2.6 (1.2-5.6) | .02 |
| Treatment regimens | | | | |
| Oral steroid ± adjuvant ± topicals | 61 (94) | 90 (89) | 1.9 (0.6-6.1) | .41 |
| Starting dose of oral steroids, mg, mean ± SD | 25.7 ± 12.2 | 28.8 ± 14.3 | | .153 |

Values are n (%) unless otherwise defined.

diagnosed exclusively in patients who received glucocorticoids.

Hyperglycemic screening and management of diabetes in BP patients present many challenges. Glucocorticoids result mainly in postprandial hyperglycemia[3]; hence, screening using fasting blood glucose might lead to underestimation of glucocorticoid-induced hyperglycemia and glucocorticoid-induced DM. Similarly, $HbA_{1c}$, which measures control over the last 2 to 3 months, is inaccurate during initial weeks of glucocorticoid treatment when the risk of glucocorticoid-induced DM appears to be the highest. Postprandial blood glucose measurement in the afternoon or evening is advised, with a recommended goal of <180 mg/dL (10 mmol/L).[4] The criterion for diagnosis of glucocorticoid-induced DM is repeated random or postprandial glucose levels > 200 mg/dL (>11.1 mmol/L).[3] Management challenges include the ideal antidiabetic agent, with insulin the current agent of choice. There is also risk of hypoglycemia on tapering of glucocorticoids as disease control improves.

We are unable to answer whether topical steroids protect against hyperglycemic complications because of the small number of patients who did not receive glucocorticoids. Dermatologists should still be cautious of possible systemic absorption of high-potency topical steroid, although its risk might be lower. In our study there was no significant difference in the mean initiation dose of glucocorticoids between the 2 groups. Cumulative doses were not recorded. However, it has been suggested that a prednisolone equivalent dose > 40 mg/day for 2 days is sufficient to result in hyperglycemia.[5]

Our study highlighted both the burden of hyperglycemia in BP patients and potential risk factors for their development. There is an urgent need to view BP patients beyond a single-disease framework but to treat them in the context of multimorbidities with the attending interactions and complications.

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## Clinical outcome and safety of rituximab therapy for pemphigoid diseases

*To the Editor*: The term "pemphigoid" encompasses a group of subepidermal autoimmune blistering diseases, including bullous pemphigoid (BP), mucous membrane pemphigoid, epidermolysis bullosa acquisita, and others. Fatal complications can occur from the disease or its therapy. Rituximab (RTX) has been approved by the US Food and Drug Administration for pemphigus vulgaris, but its role in pemphigoid is unclear because of the relative paucity of reported cases.

This retrospective case series included all pemphigoid patients (n = 38) at the University of Pennsylvania followed at least 1 year after RTX or until death ( patient demographics can be found in Supplemental Table SI, available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). Outcomes followed consensus definitions[1,2] (Supplemental Methods and Supplemental Table SII, available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). The primary endpoint was complete remission (CR). Secondary endpoints were CR off therapy (CROT), corticosteroid dose, relapse, serious adverse events, and autoantibody titers.

RTX outcomes are detailed in Table I and Supplemental Table SIII (available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). Overall, 29 of 38 pemphigoid patients (76%) achieved CR after a median of 1 RTX cycle, with a median time to CR of 14.3 months (95% confidence interval, 9.7-44.1). Considering the more rigorous endpoint of CROT, 15 of 38 patients (39%) achieved CROT after a median of 2 RTX cycles. No substantive difference in CR/CROT rates was observed among pemphigoid subtypes. CR/CROT was achieved by 53%/27% versus 52%/9% of patients who received a rheumatoid arthritis dose (n = 15) versus a lymphoma dose (n = 23) for the first RTX cycle ($P > .99/P = .19$). The median prednisone dose decreased from 20 to 3.5 mg/day ($P < .001$) in BP patients and from 20 to 4.5 mg/day ($P = .001$) in non-BP patients (Fig 1).

Longitudinal autoantibody titers were available for 13 BP patients. Median anti-BP180 titer decreased from 100.2 to 11.9 U/mL 12 months after RTX ($P < .05$), suggesting that anti-BP180 antibodies are predominantly produced by short-lived plasma cells (Supplemental Fig S1, available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1).

Seventeen of 29 patients (59%) relapsed a median of 6.2 months after achieving CR (Supplemental Fig S2, *A*, available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). Surprisingly, BP patients exhibited a 4.8-fold hazard ratio for relapse (95% confidence interval, 1.34-17.4; $P = .007$) (Supplemental Figure S2, *B,* available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1), perhaps because minimal therapy was tapered in 67% of BP versus 17% of non-BP patients and relapses occurred in 8 of 9 pemphigoid patients (89%) who tapered doses of minimal therapy compared with 3 of 9 (33%) who maintained minimal therapy doses ($P < .05$).

Additional RTX cycles were prescribed to improve outcome or treat relapse (Supplemental Table S3 available on Mendeley at https://doi.org/10.17632/7j5vv3rryc.1). One hundred percent of patients who relapsed after achieving CR (n = 8) and 54% who received RTX to improve response (n = 13) attained CR after the second RTX cycle, indicating that outcomes are significantly different based on the indication for retreatment ($P = .02$).