

Pharmacology and therapeutics: Review

## Plasmapheresis: a feasible choice for bullous pemphigoid patients infected with SARS-CoV-2

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Conflict of interest: None.

Funding source: None.

doi: 10.1111/jid.15892

### Background

As is well known, a novel coronavirus, initially called 2019-nCoV, was reported at the end of the year 2019.<sup>1</sup> Then the coronavirus, which was named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV), has spread rapidly worldwide and caused the outbreak of COVID-19. Globally, as of 3:24 pm CEST, May 20 2021, there have been 169,118,995 confirmed cases of COVID-19, including 3,519,175 deaths, which were reported to the World Health Organization (WHO).<sup>2</sup>

The risk factors for SARS-CoV-2 infection and severe outcomes are advanced age and underlying diseases including, but not limited to, diabetes, hypertension, cardiovascular disease, and active cancer.<sup>3–5</sup> Bullous pemphigoid (BP) also occurs in these people,<sup>6</sup> and BP patients are vulnerable to cutaneous, respiratory, multi-organ, and systemic infections.<sup>7</sup> Therefore, as dermatologists, we should pay special attention to patients with BP during the epidemic.

### Introduction of treatment strategies for BP during the epidemic

Bullous pemphigoid, one of the autoimmune blistering diseases (AIBDs), typically presents with tense and mostly clear blisters

### Abstract

Bullous pemphigoid (BP) patients were vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection because they have similar risk factors, so we should pay attention to patients with BP during the epidemic of coronavirus disease-19 (COVID-19). As far as treatment is concerned, many strategies for BP were changed during the epidemic. Plasmapheresis not only has been included in the guidelines for BP but also has been used successfully to rescue COVID-19 patients, especially in severe cases. Therefore, it is a feasible choice for BP patients, especially for refractory BP patients, infected with SARS-CoV-2. Apart from these, we have reviewed some points for attention during the plasmapheresis session.

and erythema. Blisters often appear on the flexural aspects of the limbs and on the abdomen. Almost all patients have severe pruritus.<sup>6</sup>

In terms of treatment, for mild BP patients, topical corticosteroids, antibiotics, and nicotinamide are recommended. Topical and systemic corticosteroids and immunosuppressive drugs are suggested for the treatment of moderate BP patients. Meanwhile, for severe BP patients, intravenous immunoglobulin (IVIG), biologic agent, and plasmapheresis might be considered.<sup>8–10</sup>

Patients with AIBDs using immunosuppressive drugs which contain azathioprine, mycophenolate mofetil, mycophenolic acid, methotrexate, cyclosporine, cyclophosphamide, and corticosteroids (prednis[ol]one >10 mg/day) are more likely to be infected with SARS-CoV-2 and develop more severe COVID-19.<sup>11</sup> During the pandemic, these drugs should be tapered to the lowest effective dose.<sup>12</sup> However, if patients are positive for SARS-CoV-2, these drugs should be temporarily withdrawn, after considering the severity of AIBDs, past medical history, comorbidities, age, and severity of COVID-19, except corticosteroids, which should be reduced gradually to at least 7.5–10 mg/day to avoid abrupt termination or considerable dose reduction.<sup>11,13,14</sup> Moreover, some experts found that the low-dose systemic dexamethasone decreased the mortality rate in

COVID-19 patients who were receiving either invasive mechanical ventilation or oxygen alone at randomization.<sup>15</sup>

However, topical corticosteroids, dapsone, sulfapyridine, antibiotics (e.g., doxycycline, tetracycline), antihistamine, colchicine, and normal human IVIG are less likely to increase the risk for infection or more severe COVID-19.<sup>11,13</sup> Fortunately, dapsone, doxycycline, and IVIG also demonstrate beneficial effects on COVID-19.<sup>16,17</sup>

If patients using biologic agent have suspected or confirmed SARS-CoV-2 infection within 31 days, the next dose should be withdrawn or postponed (based on the potential time of viral shedding).<sup>18</sup> The biologic therapy can be recommended depending on the resolution of illness and/or confirmation of negative PCR testing manifesting no viral shedding<sup>18</sup> (Table 1).

In addition to the above treatments, plasmapheresis, which was proved effective for refractory BP (using systemic corticosteroids and immunosuppressant for 1 month failed to control the disease), has also been included in the guidelines for BP.<sup>8-10</sup>

## Plasmapheresis

### Introduction of plasmapheresis

Plasmapheresis, such as plasma exchange (PE) and double filtration plasmapheresis (DFPP), was a therapeutic option for severe or intractable cases.<sup>19</sup>

**Table 1** Changes in treatment strategies for bullous pemphigoid during the epidemic<sup>11-13,15-17</sup>

Drugs	During the epidemic	Patients are positive for SARS-CoV-2
Azathioprine	Tapered to the lowest effective dose	Temporarily withdrawn
Mycophenolate mofetil	Same as above	Same as above
Mycophenolic acid	Same as above	Same as above
Methotrexate	Same as above	Same as above
Cyclosporine	Same as above	Same as above
Cyclophosphamide	Same as above	Same as above
Systemic corticosteroids	Reduced gradually to prednis[ol]one ≤10 mg/day	Depending on the severity of COVID-19
Topical corticosteroids	Continued	Continued
Dapsone	Continued	Continued
Sulfapyridine	Continued	Continued
Antibiotics (e.g. doxycycline, tetracycline)	Continued	Continued
Antihistamine	Continued	Continued
Colchicine	Continued	Continued
IVIG	Continued	Continued
Biologic agent	Tapered to the lowest effective dose	Withdrawn or postponed

Therapeutic PE is a procedure in which blood of the patient is passed through a medical device that removes units of whole blood anticoagulated with heparin and isolates plasma from other components of blood. The plasma is removed and substituted with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution. Eventually, the cellular elements are then mixed with the replacement and reinfused.<sup>20,21</sup> DFPP is a filter-based therapeutic procedure that removes pathogenic substances from isolated plasma based on their size, which is mainly determined by molecular weight and three-dimensional configuration by plasma filters with different pore sizes.<sup>20</sup> In these ways, the pathologic substances such as pathologic autoantibodies, immune complexes, and cytokines will be removed.<sup>21</sup>

### Indications of plasmapheresis

We have used plasmapheresis along with glucocorticosteroid and/or immunosuppressive agents to treat severe BP patients, and the results were the reduction in serum levels of antiBP180, the alleviation of pruritus, and the disappearance of bulla, which were consistent with our expectations.<sup>22,23</sup> Similar outcomes were found in other studies.<sup>24,25</sup> When the clinical manifestation appears resistant to oral immunosuppression, or when additional second-line drugs produce an increasingly unfavorable side effect, it was preferable to consider a trial of plasmapheresis.<sup>24</sup>

In addition to BP, plasmapheresis was also used in some severe dermatoses, such as severe psoriasis, connective tissue diseases, pemphigus, drug eruption, and insect and animal bite diseases.<sup>26,27</sup> Similarly, in other disciplines, plasmapheresis was used in hematologic disorders, solid organ transplantation, hematopoietic stem cell transplantation, neurologic disorders, renal disorders, fulminant hepatitis, vasculitis, and so on.<sup>20,28</sup>

### Plasmapheresis and COVID-19

During the epidemic, plasmapheresis was used successfully to rescue COVID-19 patients, especially severe cases.<sup>29-34</sup>

As is known to all, the level of cytokine, coagulation agent, and viral load is the most important parameter to determine the outcome of COVID-19,<sup>31</sup> particularly the “cytokine storm” that plays an important role in the pathophysiology of the SARS-CoV-2 infection in patients.<sup>35</sup> Plasmapheresis can remove toxins and deleterious inflammatory cytokines such as IL-1, IL-6, granulocyte-colony stimulating factor, tumor necrosis factor (TNF), and other inflammatory parameters to alleviate cytokine storm.<sup>32</sup> These cytokines' levels, such as IL-1, IL-6, and TNF- $\alpha$ , were correlated with the activity of BP.<sup>36</sup> Then removing these cytokines by plasmapheresis is a good strategy not only for COVID-19 but also for BP patients. Moreover, plasmapheresis also exerts a role in reducing the abnormal coagulation agents.<sup>31</sup> In addition, plasmapheresis could reduce the viral load by eliminating SARS-CoV-2 viral particles since they have a diameter of 60–140 nm and are large enough to be eliminated

with DFPP.<sup>33</sup> Apart from these, plasmapheresis can promote the suppression of thromboinflammation and amelioration of microangiopathy, thus preventing the development of multisystem organ failure.<sup>34</sup>

Based on these reports, experts in our country have included plasmapheresis in the consensus on the diagnosis and treatment of COVID-19.<sup>37,38</sup> In view of obvious benefits for both BP patients and COVID-19 patients, plasmapheresis should be a feasible choice for BP patients infected with SARS-CoV-2. Especially for refractory BP patients infected with SARS-CoV-2, the plasmapheresis, which is cheaper than IVIG, is the preferred treatment.<sup>9</sup>

**Matters need attention**

So what should we pay attention to during the plasmapheresis session?

First, when is the appropriate time for the first plasmapheresis session? BP is a chronic disease, and the plasmapheresis usually is given a long time after onset. However, as is demonstrated in reports, the results of plasmapheresis for severe COVID-19 are highly dependent on timing. For most viral illnesses, viremia peaks in the first week of infection. The patient usually develops a primary immune response on days 10–14, which is followed by the clearance of the virus.<sup>39</sup> Symptomatic COVID-19 mainly consists of three phases. The first is a starting phase, including the acquisition of the virus and subsequent viremia; the second is the acceleration phase, that is, virus-induced secondary damage of targeting organs and

tissue including the lungs, the heart, the gastrointestinal tract, and even an overall inflammatory storm; and the third phase is the final recovery phase.<sup>40</sup> So, the strategies against COVID-19 should be given early in the course of the disease, just prior to the acceleration phase.<sup>34,40</sup> If clinical deterioration has begun, the first few days of deterioration is also a critical point.<sup>40</sup> Several studies have also shown that the administration of plasmapheresis within 7–14 days of the illness onset could be associated with better outcome.<sup>32,39</sup> Second, how much plasma volume is advised? A total of 2–3 liters of plasma is recommended in the plasmapheresis of BP patients,<sup>9</sup> and 1.5 plasma volume was suggested in the PE for severe COVID-19 patients every time.<sup>38</sup> In another study, 1.2 plasma volume also had a good effect on the condition.<sup>30</sup> In addition, we can use this formula to calculate the plasma volume, the amount of plasma replacement (l) = body weight (kg) × (1/13) × (1–hematocrit/100) and that at least 2 liters of plasma should be administered when plasma is scarce.<sup>41</sup> Third, what is the replacement solution? The choice for replacement solution includes fresh frozen plasma, 5% albumin, or 0.9% saline.<sup>29,42</sup> After plasmapheresis, the convalescent plasma from a recovered patient or IVIG could be transfused to the patient immediately.<sup>38,43,44</sup> Last, the frequency and the number of times of plasmapheresis depend on the patient’s condition. We summarized the experience in the treatment of BP and COVID-19 patients with plasmapheresis in Tables 2 and 3.<sup>22,31,44–47</sup>

**Table 2** Our experience in the treatment of bullous pemphigoid patients with plasmapheresis<sup>22</sup>

Patients' age	Time of first plasmapheresis after onset	Number of plasmapheresis	Frequency of plasmapheresis	Volume of each plasmapheresis	Outcome
72	4 months	Three	Every other day	2000 ml	Discharge
73	4 months	One	–	2000 ml	Discharge
69	20 days	Two	–	2000 ml	Discharge
67	0 day	Two	Once every three days	2000 ml	Discharge

**Table 3** The experience in the treatment of COVID-19 patients with plasmapheresis reported in the literature<sup>31,44–47</sup>

Patients' age/gender	Time of first plasmapheresis after onset (days)	Number of plasmapheresis	Frequency of plasmapheresis (days)	Volume of each plasmapheresis	Outcome
44/male	10	One	–	3020 ml	Discharge
55/male	17	One	–	3000 ml	Discharge
64/male	15	One	–	2660 ml	Discharge
65/female	6	One	–	4500 ml	Discharge
74/male	7	Four	7,9,11,13	About 6600 ml	Discharge
50/female	14	Four	14,15,16,17	6000 ml	Discharge
53/male	12	Two	–	3600 ml, 3660 ml	Discharge
71/male	9	One	–	3380 ml	Died
62/male	16	Two	–	3020 ml, 2930 ml	Discharge
76/female	17	One	–	3170 ml	Died
67/female	11	Two	–	3510 ml, 3400 ml	Discharge

Although plasmapheresis is safe and effective, special attention should be paid to its possible complications. The common complications include hypocalcemia or hypomagnesemia, hypothermia, transfusion reactions, hypotension, urticarial, infection, bleeding/hematoma, and so on.<sup>21,48,49</sup> However, after continuous observation in healthcare faculties, these side effects could be closely monitored, thus ensuring patients' safety.<sup>48</sup>

It is noteworthy that plasmapheresis merely interrupts or delays the progression of the disease. It only removes the pathogenic substances rapidly, creating opportunities for drug treatment, so in the meantime, etiological treatment should be carried out. Moreover, given that it is an invasive and expensive treatment, the indications should be clarified.<sup>50</sup>

### Questions: True or False questions (answers provided after references)

- 1 The risk factors for SARS-CoV-2 infection and BP are different.
- 2 BP typically presents with tense and mostly clear blisters and erythema.
- 3 During the pandemic, all drugs for BP should be temporarily withdrawn.
- 4 Dapsone, doxycycline, and IVIG demonstrate beneficial effects on COVID-19.
- 5 The pathologic substances such as pathologic autoantibodies, immune complexes, and cytokines will be removed by plasmapheresis.
- 6 We have used plasmapheresis along with glucocorticosteroid and/or immunosuppressive agents to treat severe BP patients successfully.
- 7 Plasmapheresis could not rescue COVID-19 patients.
- 8 Plasmapheresis can remove toxins and deleterious inflammatory cytokines to alleviate cytokine storm.
- 9 Plasmapheresis is not a feasible choice for BP patients infected with SARS-CoV-2.
- 10 The results of plasmapheresis for severe COVID-19 are highly dependent on timing.

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## Answers to Questions

- 1 False
- 2 True
- 3 False
- 4 True
- 5 True
- 6 True
- 7 False
- 8 True
- 9 False
- 10 True