How to Cite:
Alshammari, F. A. M., Alotaibi, S. O., Alrasheedi, M. K., Alsayegh, A. S., Alduaybi, M. A., Al Owias, M. I. Z., Al Rashedi, A. A., Alanizi, H. G., Aldukain, A. M., Alanezi, B. S., & Alrammaal, W. H. A. (2024). Goodpasture syndrome: An updated overview for healthcare professionals. *International Journal of Health Sciences*, *8*(S1), 1531–1543. https://doi.org/10.53730/ijhs.v8nS1.15309

Goodpasture syndrome: An updated overview for healthcare professionals

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Manuscript submitted: 18 Oct 2024, Manuscript revised: 27 Dec 2023, Accepted for publication: 05 Jan 2024

***Abstract*---Background:** Goodpasture syndrome is an autoimmune disorder characterized by the presence of anti-glomerular basement membrane (anti-GBM) antibodies, leading to significant lung and kidney complications, particularly pulmonary hemorrhage and glomerulonephritis. The disease has a poor prognosis if not promptly treated, making early identification and intervention crucial. **Aim:** This article aims to provide an updated overview of Goodpasture syndrome, highlighting its etiology, epidemiology, pathophysiology, diagnosis, and treatment approaches, to enhance healthcare professionals' understanding and management of this condition. **Methods:** A comprehensive review of current literature on Goodpasture syndrome was conducted, focusing on its clinical presentation, histopathological findings, and advancements in diagnostic techniques. The article discusses relevant immunological aspects, genetic predispositions, and the significance of serological testing in diagnosis. **Results:** The incidence of Goodpasture syndrome is estimated at 0.5 to 1.8 cases per million annually, with a bimodal age distribution. Genetic factors, particularly the presence of specific human leukocyte antigens (HLAs), play a significant role in disease susceptibility. The pathophysiology involves circulating autoantibodies targeting type IV collagen, leading to crescentic glomerulonephritis and pulmonary damage. Renal biopsy remains the gold standard for diagnosis, with immunofluorescence microscopy revealing characteristic linear immunoglobulin deposits. **Conclusion:** Goodpasture syndrome presents significant challenges in diagnosis and management due to its rare occurrence and overlapping symptoms with other rapidly progressive glomerulonephritides. Timely intervention, often requiring a multidisciplinary approach, is essential for improving patient outcomes. Further research is needed to better understand the underlying mechanisms and optimize treatment strategies.

***Keywords*---**Goodpasture syndrome, anti-GBM disease, pulmonary hemorrhage, glomerulonephritis, autoimmune disorder.

Introduction

Goodpasture syndrome is characterized as an anti-glomerular basement membrane (anti-GBM) disorder that affects both the lungs and kidneys, typically manifesting as pulmonary hemorrhage and glomerulonephritis. As one of the three primary etiologies of crescentic glomerulonephritis, Goodpasture syndrome frequently has a poor prognosis, particularly if not treated swiftly. For additional details and a classification of Goodpasture syndrome relative to other rapidly progressive glomerulonephritides, refer to our accompanying review, "Rapidly Progressive Glomerulonephritis." Some practitioners may use various terms interchangeably, such as anti-glomerular basement membrane disease, Goodpasture syndrome, and Goodpasture disease [1]. Anti-GBM disease may also denote renal pathology occurring without pulmonary complications, whereas Goodpasture disease or syndrome is invariably associated with pulmonary

manifestations. Additionally, some clinicians label any concurrent renal and pulmonary pathology as "Goodpasture Syndrome," though generally, this term pertains specifically to anti-GBM antibodies. Approximately 40% to 60% of cases are linked with alveolar hemorrhage, while less than 10% of anti-GBM disease presentations involve isolated pulmonary symptoms [2][3]. Goodpasture syndrome is named after Ernest Goodpasture, who initially detailed this condition in 1919. The advent of immunofluorescence techniques in the 1960s, alongside the identification of anti-GBM antibodies, significantly enhanced the understanding of the pathophysiology of Goodpasture syndrome [4].

Etiology:

Goodpasture syndrome is believed to arise from the interplay of environmental or infectious stimuli with an inherent genetic susceptibility. Currently, a definitive singular trigger for the development of anti-glomerular basement membrane antibodies has yet to be established; however, notable geographic and seasonal patterns have been observed. Compelling evidence supports a genetic component, as patients with specific human leukocyte antigen (HLA) types exhibit an increased vulnerability to the disease and often have a poorer prognosis. Notably, HLA-DR2 has been identified in up to 80% of individuals diagnosed with anti-GBM disease. The HLA-DR1 alleles display both beneficial and detrimental effects concerning the onset of anti-GBM disease. Specifically, HLA-DRB1*01 and HLA-DRB1*07 are associated with a protective effect against Goodpasture syndrome, whereas HLA-DRB1*1501 is linked to heightened susceptibility, particularly within Asian cohorts [1][2]. These alleles are also present in individuals with other autoimmune conditions as well as in healthy populations, which diminishes the frequency of HLA testing [3][4]. For instance, the DRB1*1501 allele is found in up to one-third of the Caucasian population, indicating that additional factors must contribute to disease manifestation.

The exposure of the alveolar capillaries to autoantibodies is likely precipitated by an initial insult to either the pulmonary alveolar or renal glomerular basement membranes. Environmental factors are thought to instigate localized inflammation, thereby exposing basement membrane antigens that are typically sequestered. Some agents implicated in the development of the disease include Smoking, Exposure to metal dust, organic solvents, or hydrocarbons, Bacteremia, Tobacco smoking, Endotoxemia, Exposure to volatile hydrocarbons, Infections, such as influenza A, Drugs, such as alemtuzumab, which lead to the depletion of regulatory T-cells, Inhalation of cocaine, Extracorporeal shock wave lithotripsy, and Higher inspired oxygen levels [1][5][6][7].

Epidemiology:

Goodpasture syndrome is an infrequent condition. The incidence of anti-GBM disease is estimated at approximately 0.5 to 1.8 cases per million individuals annually within Asian and European populations, accounting for 1% to 5% of all types of glomerulonephritis and representing 10% to 15% of cases of crescentic glomerulonephritis [8][9][10]. The syndrome is observed to be more prevalent among White individuals compared to Black individuals; however, certain ethnic groups, such as the Māori of New Zealand, may exhibit higher prevalence rates.

The condition demonstrates a bimodal age distribution, primarily affecting individuals in their third and sixth decades of life. Notably, younger patients tend to present with pulmonary involvement, while older patients are more likely to exhibit less severe renal-limited disease.

Pathophysiology:

Goodpasture syndrome arises from circulating autoantibodies that target the glomerular basement membrane. The resultant crescentic glomerulonephritis is attributable to antigen-antibody complexes that form at the basement membrane [11]. These autoantibodies activate the complement cascade, leading to tissue damage. The binding of these autoantibodies manifests as a linear deposition of immunoglobulins (primarily IgG and, rarely, IgA) along the basement membrane. The ensuing inflammatory response contributes to the characteristic presentation of glomerulonephritis. Type IV collagen constitutes a principal component of all basement membranes, which serve as specialized forms of extracellular matrix, providing structural integrity and fulfilling essential roles such as cell signaling and tissue regeneration [12]. The alveolar basement membrane shares the same collagen target as the glomerulus, with Type IV collagen containing non-collagenous domains. The non-collagenous domain of α-3 (α3NC1) is believed to be the antigen that activates the Goodpasture autoantibody. Interestingly, despite the presence of circulating antibodies, pulmonary symptoms are not always evident; an inciting lung injury appears to increase the likelihood of pulmonary manifestations [13]. In healthy individuals, the endothelium functions as a barrier against anti-basement membrane antibodies. However, if an injury increases the permeability of alveolar capillaries, it permits the entry of autoantibodies that can subsequently bind to the basement membrane. Although Goodpasture syndrome is classified as an autoantibody-mediated condition, T-cells play a crucial role in the disease's initiation and progression. T-cells stimulate B-cells to enhance antibody production and contribute directly to renal and pulmonary injury [14].

Double-Positive Antibody Disease:

Also referred to as dual antibody disease, this type of crescentic glomerulonephritis is characterized by a positive antineutrophil cytoplasmic antibody (ANCA) test alongside anti-GBM antibodies. Some studies have reported that between 10% and 50% of patients with anti-GBM disease have detectable ANCA, typically anti-MPO. Conversely, up to 10% of patients with ANCA-associated vasculitis may also present with circulating anti-GBM antibodies [15]. Generally, the presence of positive ANCA precedes the detection of anti-GBM antibodies, suggesting that ANCA exposure may lead to the formation of anti-GBM antibodies by unmasking epitopes on the GBM. Patients exhibiting double-positive disease are often older, experience longer prodromal periods, and have frequent relapses, akin to those seen in ANCA-associated vasculitis. Renal manifestations align with the anti-GBM pattern, while systemic symptoms mirror those of ANCA vasculitis [16]. This double-positive feature is significant in guiding treatment selection [17][18].

Histopathology:

For patients suspected of having Goodpasture syndrome, a renal biopsy is a pivotal diagnostic tool. This procedure is not only essential for confirming the diagnosis but also provides prognostic information regarding renal survival, based on the percentage of crescents observed in the biopsy. Lung tissue biopsies are typically avoided due to the invasive nature of the procedure and the complexities involved in immunofixation for lung samples. Light microscopy typically reveals crescentic glomerulonephritis, with lesions in anti-GBM disease generally presenting at the same nephritic stage. There is notable interstitial inflammation, particularly localized around the periglomerular area. As the condition progresses, fibrosis can develop rapidly within days to weeks, leading to glomerular sclerosis and obliteration. Immunofluorescence microscopy is more specific and diagnostic, often showing bright linear deposits of immunoglobulin G (IgG) and complement component C3 along the glomerular basement membrane, predominantly the IgG-1 subclass [19]. Staining may also extend to the renal tubular basement membrane in addition to glomerular staining [20]. Although lung biopsies are infrequently performed, if done, they can reveal similar staining patterns in the alveolar basement membrane. Furthermore, such biopsies may demonstrate extensive hemorrhage with hemosiderin-laden macrophages present within the alveolar spaces [1]. A crescent is characterized as a hyperplastic lesion encompassing more than 10% of the glomerulus. If a crescent is comprised of over 75% cells and fibrin, with less than 25% being fibrous matrix, it is classified as cellular. Conversely, if the crescent contains 25% to 75% cells/fibrin and the remainder is fibrous matrix, it is termed fibrocellular. A crescent that has less than 25% cells/fibrin and over 75% fibrous matrix is designated as a fibrous crescent [15].
Quantitative definitions are instrumental in classifying ANCA-associated lesions and include:

- **Focal:** 50% or more of glomeruli are normal.
- **Crescentic:** 50% or more of glomeruli display cellular crescents.
- **Mixed:** less than 50% normal, less than 50% crescentic, and less than 50% globally sclerotic glomeruli.
- **Sclerotic:** 50% or more of glomeruli are globally sclerotic [15][21].

History and Physical:

Patients with Goodpasture syndrome typically present with symptoms similar to other forms of rapidly progressive glomerulonephritis, including acute renal failure. There are no specific symptoms that differentiate anti-glomerular basement membrane disease from other conditions that cause similar organ dysfunction. Pulmonary symptoms often manifest at the initial presentation or shortly thereafter, with hemoptysis being a common finding. The severity of hemoptysis can vary significantly, from life-threatening bleeding to more subtle diffuse hemorrhage, which may only become evident upon thorough examination. Younger patients are more likely to present with both renal and pulmonary symptoms simultaneously (indicative of Goodpasture syndrome) and often appear critically ill at the time of diagnosis. In contrast, patients over the age of 50 typically present with renal involvement alone and tend to experience a less severe disease course.

Key physical examination findings in Goodpasture syndrome may include:

- Increased respiratory rate
- Basilar inspiratory crackles
- Cyanosis
- Hepatosplenomegaly
- Hypertension (observed in approximately 20% of cases)
- Purpuric rash
- Edema

Evaluation:

A kidney biopsy is considered the gold standard for diagnosing Goodpasture syndrome; however, it is not mandatory to initiate treatment. The biopsy, when performed, provides valuable insights regarding the activity and chronicity of renal involvement, which can inform therapeutic decisions. A kidney biopsy is generally preferred over a lung biopsy due to its higher diagnostic yield; lung biopsy may be indicated when a renal biopsy is contraindicated. The biopsy specimen should be analyzed using light microscopy, electron microscopy, and immunofluorescence microscopy. Light microscopy typically reveals proliferative or necrotizing crescentic glomerulopathy, with crescents becoming fibrotic over time, leading to glomerulosclerosis, tubular atrophy, and interstitial fibrosis [19]. Serologic testing is usually performed via enzyme-linked immunosorbent assay (ELISA) or bead-based fluorescence assays to detect circulating anti-GBM antibodies. Specifically, tests should target the α3NC1 domain of type IV collagen, as less specific assays may yield false positives [22]. Although Western blotting may offer higher specificity, it is generally available only in research settings. Additionally, if the anti-GBM antibodies are of less common types, such as IgG4 or IgA, there is a higher risk of false negatives [23]. Notably, around 10% of patients with biopsy-confirmed anti-GBM disease may not have detectable circulating antibodies using conventional assays, so a negative anti-GBM antibody test does not exclude the diagnosis [23]. Chemiluminescence immunoassay is being evaluated as a potentially more sensitive testing method [1]. Quantitative titters of antibodies are monitored during treatment to guide therapeutic decisions.

Other diagnostic tests typically include:

- **Urinalysis:** Usually reveals low-grade proteinuria, either gross or microscopic hematuria, and the presence of red blood cell casts.
- **Complete Blood Count (CBC):** May show anemia resulting from intrapulmonary hemorrhage, with leukocytosis often present.
- **Renal Function Tests:** These may indicate renal dysfunction.
- **Chest Radiograph:** Typically shows patchy parenchymal opacifications, which are generally bilateral and located in the bibasilar regions, while the apices and costophrenic angles are usually spared (refer to the image depicting pulmonary hemorrhages associated with Goodpasture syndrome).

- **Pulmonary Function Tests:** Often demonstrate an elevated diffusing capacity for carbon monoxide (DLCO), attributed to binding with intra-alveolar hemoglobin.

Treatment / Management:

Patients presenting with Goodpasture syndrome, which includes both glomerulonephritis and pulmonary hemorrhage, may be critically ill at the time of diagnosis. Urgent hemodialysis is often required for standard indications, and intubation may be necessary for those experiencing respiratory failure. When Goodpasture syndrome is suspected, a kidney biopsy should be performed as soon as the clinical situation allows. The preferred treatment regimen for anti-GBM disease involves plasmapheresis combined with immunosuppressive agents to remove circulating autoantibodies. Early initiation of treatment is crucial to prevent progressive renal failure and mitigate pulmonary damage. According to the 2012 guidelines from the Kidney Disease Improving Global Outcomes (KDIGO), immunosuppression should be initiated with a combination of cyclophosphamide and corticosteroids, along with plasma exchange, in all patients with Goodpasture syndrome, except for those who are dialysis-dependent at presentation and exhibit 100% crescents on biopsy without pulmonary hemorrhage. In cases where cyclophosphamide is contraindicated due to adverse effects or concerns regarding fertility in younger patients, rituximab can be used as an alternative [24]. The standard plasmapheresis protocol involves exchanging 4 liters of plasma over 2 to 4 weeks. Generally, 5% albumin serves as the replacement fluid; however, fresh frozen plasma (0.3-2 liters) should be administered in cases of invasive procedures or when pulmonary hemorrhage is present. Plasmapheresis typically continues daily until antibody levels are suppressed or for a maximum of 14 days. Prolonged treatment may be necessary if active pulmonary disease is evident or if antibody levels do not decline as expected. Plasmapheresis is always followed by immunosuppressive therapy, primarily glucocorticoids and cyclophosphamide. Recent research suggests that immunoadsorption agents may also provide benefits when included in the plasmapheresis treatment of anti-GBM disease [1][25].

Immunosuppressive Therapy Protocol:

- **Methylprednisolone:** Initiate treatment with 1 g daily for 3 days, followed by oral glucocorticoid therapy (prednisolone) at a dosage of 1 mg/kg/day (maximum of 60 mg). The dosage should be tapered weekly to 20 mg by week 6 and gradually reduced to cessation by 6 months [1].
- **Cyclophosphamide:** Administer 1 to 2 mg/kg/day orally, not exceeding 100 mg/day for patients older than 60. Monitor white blood cell counts to ensure they remain above 5000 cells/μL [26]. Alternative therapies, such as rituximab or mycophenolate mofetil, are recommended for patients who experience adverse effects from cyclophosphamide, including gross hematuria. It's important to note that rituximab can be removed by plasmapheresis, especially if the procedure occurs within 3 days post-infusion [27][28][29]. Emerging therapies such as the anti-lymphocytic agent alemtuzumab have been studied for their ability to halt the

progression of anti-GBM disease, although there is concern that it may also trigger the condition. Another promising agent is imlifidase, an IgG protease that has received approval for severe anti-GBM disease and has demonstrated a reduction in antibody levels, although data on its efficacy remains limited [1]. Following the remission phase, maintenance treatment with lower-risk agents, such as low-dose prednisone or azathioprine, should be considered, although the optimal duration of maintenance therapy is yet to be established. Overall, relapses are rare [26].

Double-Positive Antibody Crescentic Glomerulonephritis:

Treatment for double-positive antibody crescentic glomerulonephritis adheres to the same principles as pauci-immune glomerulonephritis, with the inclusion of plasmapheresis in the treatment regimen. Renal manifestations align with the anti-GBM pattern, while systemic symptoms resemble those seen in ANCA vasculitis [30]. Prolonged immunosuppression and diligent long-term monitoring are essential, as relapses are more common in this group compared to those with single-positive anti-GBM disease [17].

Differential Diagnosis:

In evaluating patients with pulmonary-renal syndromes, it is essential to consider a comprehensive list of differential diagnoses that affect both the lung and kidney. Among these, granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) are noteworthy. Systemic lupus erythematosus also presents with pulmonary-renal manifestations that must be considered. Additionally, some disorders mediated by immunoglobulin A (IgA), such as IgA nephropathy and IgA vasculitis (Henoch-Schönlein purpura), exhibit similar syndromic features. Other potential differential diagnoses include acute glomerulonephritis, community-acquired pneumonia complicated by infection-related glomerulonephritis, cryoglobulinemia, endocarditis, drug-induced vasculitis, and, although rarely associated with pulmonary symptoms, Alport syndrome. Each of these conditions warrants careful consideration in the differential diagnosis to ensure appropriate management and treatment strategies are implemented.

Prognosis:

Prognostic factors play a critical role in the management of patients with Goodpasture syndrome. Poor prognostic indicators include the presence of oligoanuria or anuria, globally sclerotic crescents on renal biopsy, and the need for dialysis due to kidney failure. Fortunately, relapse or recurrent disease post-kidney transplantation is relatively uncommon, occurring in less than 3% of cases. A long-term study demonstrated that patients presenting with a serum creatinine level of less than 5.7 mg/dL had excellent survival rates, with 1- and 5-year survival rates reported at 95% and 94%, respectively. In contrast, patients who required dialysis upon presentation had a significantly lower chance of recovery, with only 8% regaining renal function within one year [21]. These

findings highlight the importance of early detection and intervention in improving patient outcomes.

Complications:

Complications associated with Goodpasture syndrome can be broadly classified into two categories: disease-related complications and treatment-related complications. Disease-related complications often include pulmonary hemorrhage, which is frequently observed in cases of anti-GBM disease and may necessitate mechanical ventilation, thus introducing additional risks. Renal failure resulting from the syndrome can lead to dialysis and its associated complications, such as catheter-related infections and bleeding. Treatment-related complications predominantly arise from immunosuppressive therapy, where patients face an increased risk of opportunistic infections that can be life-threatening. Specific complications linked to cyclophosphamide include cystitis and hematuria, with older patients being particularly susceptible to infections and other complications associated with this medication. Furthermore, plasmapheresis can lead to the removal of clotting factors, thereby increasing the patient's vulnerability to bleeding complications [16]. Understanding these potential complications is crucial for effective management and monitoring during the treatment of Goodpasture syndrome.

Conclusion

In summary, Goodpasture syndrome is a serious autoimmune condition primarily affecting the lungs and kidneys through the presence of anti-glomerular basement membrane (anti-GBM) antibodies. The clinical presentation can vary significantly, with younger patients often exhibiting more severe pulmonary symptoms compared to older individuals, who may present predominantly with renal complications. The intricate interplay between environmental factors and genetic susceptibility remains a key area of research, suggesting that both external triggers and inherent predispositions contribute to the disease's onset. Diagnosis typically hinges on renal biopsy findings, which reveal crescentic glomerulonephritis and the characteristic linear deposition of immunoglobulins along the basement membrane. Serological testing for anti-GBM antibodies is crucial, but it is important to recognize that a negative result does not definitively exclude the diagnosis. This underscores the necessity for clinicians to maintain a high index of suspicion and to utilize comprehensive diagnostic approaches. Management of Goodpasture syndrome necessitates a prompt and aggressive treatment strategy, often including immunosuppressive therapy and plasmapheresis, particularly in cases with significant pulmonary involvement. The prognosis is closely linked to the timing of intervention; thus, increased awareness among healthcare professionals is critical to facilitate early diagnosis and treatment. As our understanding of the disease evolves, ongoing research is essential to refine therapeutic protocols and improve outcomes for patients affected by this complex disorder. Moreover, the emergence of dual-positive antibody disease, characterized by the presence of both anti-GBM and antineutrophil cytoplasmic antibodies (ANCA), presents an additional challenge in clinical management, highlighting the importance of tailored therapeutic strategies based on individual patient profiles. Continued exploration of the

disease's pathophysiology and advancements in immunological testing will likely enhance diagnostic accuracy and lead to more effective treatment paradigms in the future.

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متلازمة جودباستور: نظرة محدثة لمقدمي الرعاية الصحية

الملخص:

الخلفية :متلازمة جودباستور هي اضطراب مناعي ذاتي يتميز بوجود الأجسام المضادة ضد غشاء الكُبيبات القاعدي) الأجسام المضادة ضد GBM)، مما يؤدي إلى مضاعفات خطيرة في الرئتين والكلى، وخاصةً النزيف الرئوي والتهاب كُبيبات الكلى. تُظهر الحالة توقعات سيئة إذا لم يتم علاجها على الفور، مما يجعل التعرف المبكر والتدخل الفوري أمرًا بالغ الأهمية.

الهدف :يهدف هذا المقال إلى تقديم نظرة محدثة حول متلازمة جودباستور، مع تسليط الضوء على أسبابها، وعلم الأوبئة، والفيزيولوجيا المرضية، والتشخيص، وأساليب العلاج، لتعزيز فهم مقدمي الرعاية الصحية وإدارتهم لهذه الحالة.

الطرق :تم إجراء مراجعة شاملة للأدبيات الحالية المتعلقة بمتلازمة جودباستور، مع التركيز على العرض السريري، والنتائج الهيستوباثولوجية، والتقدم في تقنيات التشخيص. يناقش المقال الجوانب المناعية ذات الصلة، والاستعدادات الجينية، وأهمية الفحوصات المصلية في التشخيص.

النتائج :يُقدر حدوث متلازمة جودباستور بـ 0.5 إلى 1.8 حالة لكل مليون سنويًا، مع توزيع ثنائي النمط للعمر. تلعب العوامل الجينية، وخاصة وجود مستضدات الكريات البيضاء البشرية (HLAs) المحددة، دورًا كبيرًا في قابلية الإصابة بالمرض. تشمل الفيزيولوجيا المرضية الأجسام المضادة الذاتية المتداولة التي تستهدف الكولاجين من النوع الرابع، مما يؤدي إلى التهاب كُبيبات الكلى الحلقي وتلف الرئة. تبقى خزعة الكلى هي المعيار الذهبي للتشخيص، حيث تكشف المجهرية المناعية عن ترسبات مناعية خطية مميزة.

الخلاصة :تقدم متلازمة جودباستور تحديات كبيرة في التشخيص والإدارة بسبب ندرتها وتشابه أعراضها مع حالات التهاب كُبيبات الكلى الأخرى السريعة التقدم. التدخل الفوري، الذي غالبًا ما يتطلب نهجًا متعدد التخصصات، ضروري لتحسين نتائج المرضى. هناك حاجة لمزيد من البحث لفهم الآليات الأساسية بشكل أفضل وتحسين استراتيجيات العلاج.

الكلمات المفتاحية :متلازمة جودباستور، مرض مضادGBM ، النزيف الرئوي، التهاب كُبيبات الكلى، اضطراب مناعي ذاتي.