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CASE REPORT

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Trimethoprim-sulfamethoxazole acute respiratory distress syndrome requiring lung transplantation

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Abstract

Trimethoprim-sulfamethoxazole (TMP-SMX) acute respiratory distress syndrome (ARDS) is a rare, but severe complication of a commonly prescribed antibiotic. TMP-SMX typically affects young, otherwise well patients with a specific human leukocyte antigen type (HLA-B*07:02 and HLA-C*07:02). The condition is poorly understood with a unique pathological appearance and mechanism that remains unclear. Mortality rate is greater than one third. We describe the case of a previously well 18-year-old woman treated with a prolonged course of TMP-SMX for a complex urinary tract infection who developed rapidly progressive respiratory failure requiring prolonged intensive care admission, extra-corporeal membranous oxygenation, and eventual lung transplantation. No targeted treatment exists, further research is required to better understand disease pathogenetic mechanisms and potential therapeutic interventions.

KEYWORDS
ARDS, critical care medicine, inflammation, pathology, rare lung diseases

INTRODUCTION

Trimethoprim-sulfamethoxazole (TMP-SMX) is a widely used bactericidal antibiotic that acts via dual inhibition of the folate pathway essential for bacterial nucleic acid synthesis.[1] Serious adverse effects include Stevens–Johnson Syndrome, agranulocytosis, and myelosuppression, and a range of pulmonary manifestations including acute fibrinous organizing pneumonia, eosinophilic pneumonia, and drug-induced interstitial lung disease.[1–5] Recent case reports have described an association between TMP-SMX exposure and acute respiratory failure,[6–9] leading to the development of the clinico-pathological entity of TMP-SMX acute respiratory distress syndrome (ARDS).[10] This condition has an exceedingly high morbidity and mortality and a poorly understood pathogenesis and clinical course.

Case report

An 18-year-old woman presented to hospital with a 5-day history of lethargy, sore throat, dyspnoea, and a non-productive cough. She had been taking trimethoprim-sulfamethoxazole (TMP-SMX) for 3 weeks for an extended spectrum beta-lactamase *Klebsiella aerogenes* pyelonephritis, but otherwise had no significant past medical history or regular medications. She was a non-smoker, had no relevant home, occupational or avocational exposures, and no significant family history.

On presentation she was febrile to 38.0°C, her oxygen saturation was 88% on room air and respiratory rate was 26 breaths per minute, but she was haemodynamically stable. Examination revealed bilateral lower zone crepitations of the chest but was otherwise unremarkable. There was no rash, or features of rheumatological or connective tissue

disease. Full blood examination revealed a white cell count of 3.5 × 10^{-9}, and the C-reactive protein was 233 mg/L. Other biochemistry including liver function tests, urea, creatinine, and electrolytes were within normal limits. Chest x-ray demonstrated bilateral pulmonary infiltrates, and computed tomography pulmonary angiogram revealed no pulmonary embolism, but extensive bilateral lower zone predominant ground glass opacity and consolidation (Figure 1).

She became increasingly hypoxic and was admitted to intensive care for high flow nasal oxygen on day two of admission. The TMP-SMX was ceased, and she was treated for a severe community acquired pneumonia with meropenem, azithromycin, and intravenous hydrocortisone 100 mg three times a day. Despite this, she developed progressive hypoxaemic respiratory failure, and a spontaneous pneumomediastinum. Respiratory support was escalated to non-invasive ventilation, and subsequently invasive mechanical ventilation on day three of admission. She developed extensive bilateral subcutaneous emphysema and worsening pneumomediastinum presumed secondary to barotrauma, requiring the insertion of bilateral intercostal catheters (Figure 2).

Bronchoalveolar lavage (BAL) performed post intubation revealed a lymphocytosis (46%), neutrophil count (15%), alveolar macrophages (27%), bronchial epithelial cells (12%) and eosinophil count (0%) in the setting of systemic corticosteroids. BAL culture revealed no growth of bacterial, mycobacterial, or fungal elements, and extended respiratory pathogen polymerase chain reaction (AusDiagnostics, New South Wales) was negative for respiratory viruses, *Mycoplasma pneumoniae and Bordetella pertussis*. Autoimmune markers including anti-nuclear antibodies, extractable nuclear antigens, anti-neutrophilic cytoplasmic antibodies, and a myositis panel were negative. Plasma sulfamethoxazole levels (PathWest, Western Australia) were <5 mg/litre 1 week post final dose of TMP-SMX.

In the setting of ongoing significant air leak post pneumothoraces, poor pulmonary compliance, and worsening hypercapnic respiratory failure, she was transferred to a quaternary hospital. On day seven post presentation she underwent video-assisted thoracoscopic lung biopsy that demonstrated organizing diffuse alveolar injury with alveolar wall lined by macrophages, along with an absence of pneumocytes or hyaline membrane (Figure 3). Additionally, there were prominent peribronchiolar basaloid pods; changes in keeping with previously described cases of TMP-SMX ARDS.[10] Human leukocyte antigen (HLA) testing was positive for HLA-B*07:02 and HLA-C*07:02, a haplotype consistent with previous cases of this condition.[11] The following day due to progressive hypercapnia and acidosis she was initiated on veno-venous extracorporeal membranous oxygenation (ECMO). Over the subsequent days, in the absence of evidence of a steroid responsive condition or ongoing bacterial infection, both systemic corticosteroids and broad-spectrum antibiotics were ceased. Consideration was made of alternative therapies including high dose methylprednisolone, steroid sparing immunosuppression, intravenous immunoglobulin, and plasmapheresis, however given the lack of evidence in this area and potential adverse effects these treatments were not initiated.

Following 3 weeks on ECMO with lung protective ventilation (ultra-low tidal volume), she was able to be extubated allowing participation in physiotherapy, and discussions regarding potential lung transplantation. Serial CT-Chest imaging demonstrated improvement in pneumomediastinum and subcutaneous emphysema, but persistent widespread pulmonary infiltrates (Figure 2). She remained ECMO dependent, and in the setting of persistent bilateral pneumothoraces with ongoing air leak, a chylothorax that was conservatively managed, two bouts of clinical sepsis in 10 days, and an inability to further wean respiratory supports, she was assessed, listed,

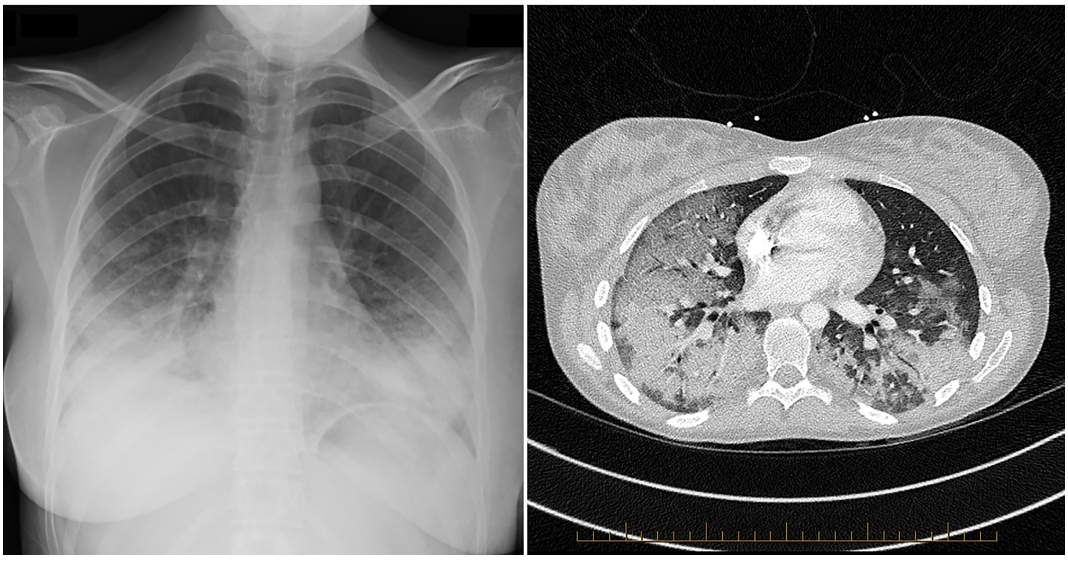

FIGURE 1 Chest x-ray (left) and computed tomography (CT) pulmonary angiogram on admission. Bilateral lower zone predominant ground-glass opacity and consolidation, distribution typical of diffuse alveolar damage.

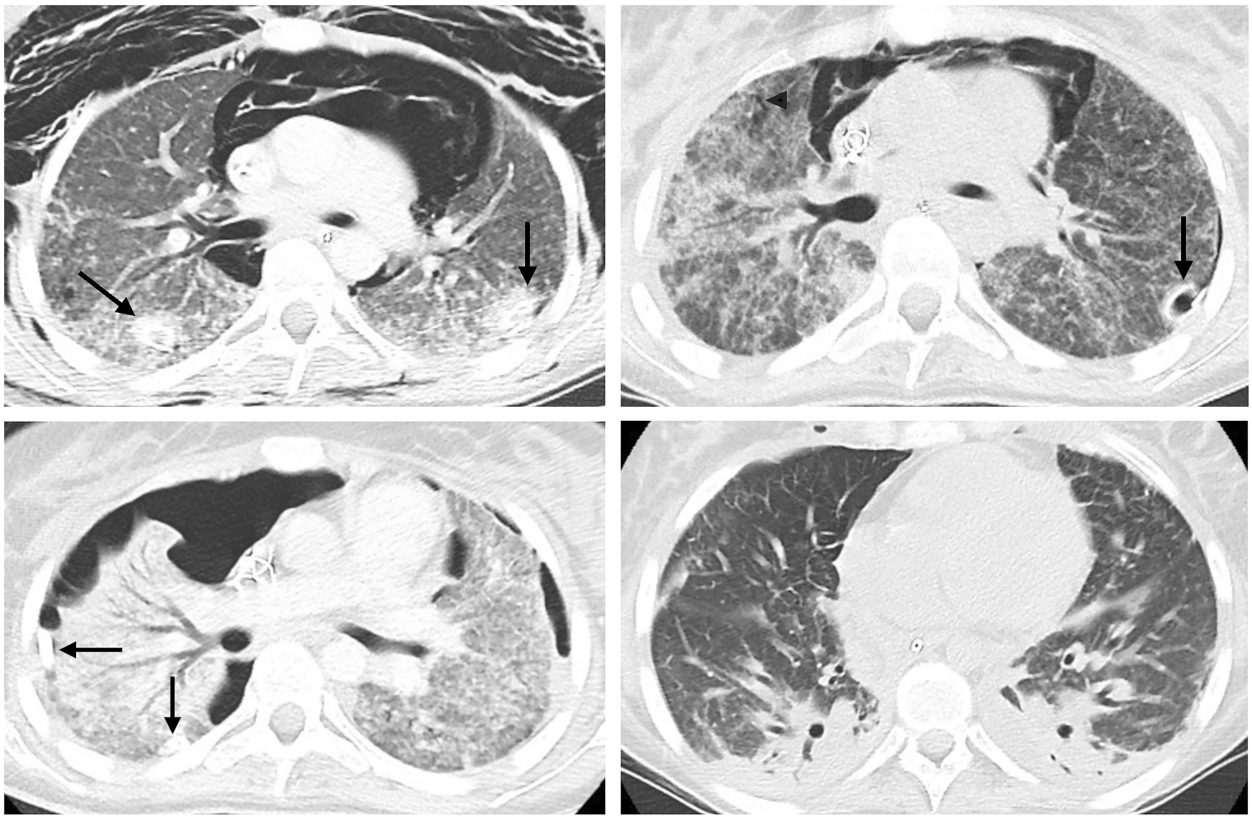

FIGURE 2 Post-contrast (A–C) and non-contrast (D) axial computed tomography (CT) of the chest. (A) (top left) Extensive subcutaneous emphysema and pneumomediastinum. Bilateral intercostal catheters are present (arrowed). Ground-glass opacity is seen posteriorly, with moderate lower zone consolidation (not pictured). (B) (top right) Subcutaneous emphysema has resolved and the pneumomediastinum is less extensive. Interstitial emphysema (arrowed) is seen as locules of gas tracking from the mediastinum along the pulmonary interstitium. Parenchymal infiltrates are more extensive. A left-sided intercostal catheter is present (arrowed), with trace pneumothorax. (C) (bottom left) The pneumomediastinum has resolved but there are now bilateral pneumothoraces. A right-sided intercostal catheter is present (arrowed). (D) (bottom right) Following bilateral sequential lung transplant. Mild post-operative posterior lung atelectasis, otherwise normal lung parenchyma.

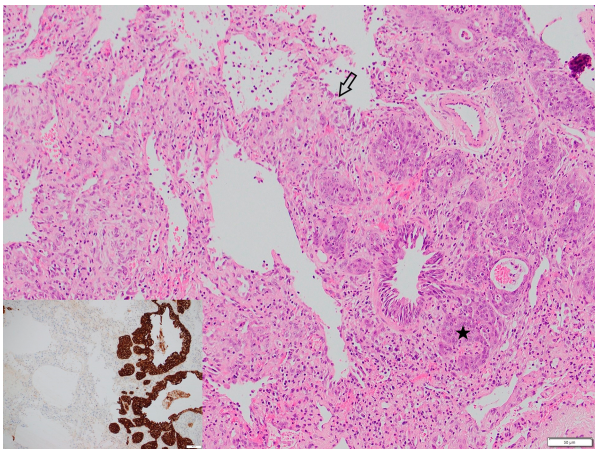

FIGURE 3 Video-assisted thoracoscopic lung biopsy on day seven of admission. Organizing diffuse alveolar injury with alveolar wall lined by macrophages (arrow), along with an absence of pneumocytes and hyaline membrane. There are prominent peribronchiolar basaloid pods (asterisk). H&E, original magnification ×100. Insert: Cytokeratin immunoperoxidase stain showing an absence of pneumocytes lining alveolar walls, adjacent to positive reactivity in peribronchiolar basaloid pods. AE1/3 immunoperoxidase stain, original magnification ×100.

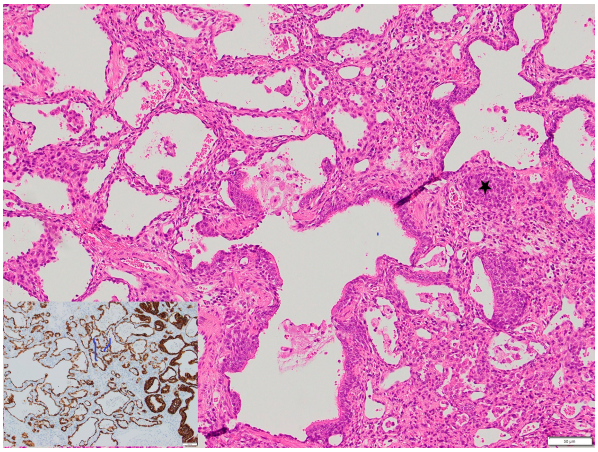

FIGURE 4 Explanted lungs on day 62 of admission. Preserved alveolar architecture lined by reactive pneumocytes. There is interstitial thickening by reactive fibroblasts. There is evidence of organization. Residual peribronchiolar basaloid pods (asterisk) are present. No hyaline membranes are seen. H&E, original magnification ×100. Inlet: Cytokeratin immunoperoxidase stain highlighted reactive pneumocytes lining alveolar walls as well as residual peribronchial basaloid pods. AE1/3 immunoperoxidase stain, original magnification ×100.

and ultimately underwent bilateral lung transplant on day 62 of admission.

The explanted lungs demonstrated interstitial thickening by fibroblasts, with reactive pneumocytes lining preserved alveolar architecture, suggesting parenchymal recovery (Figure 4). There was evidence of organization, with residual peribronchiolar basaloid pods present. No hyaline membranes were seen.

Her post-transplant course was uncomplicated, she was decannulated from VV-ECMO, and was discharged home 28 days later. Atovaquone was chosen for *Pneumocystis jirovecii* prophylaxis, and her family are undergoing genetic counselling.

DISCUSSION AND LITERATURE REVIEW

TMP-SMX ARDS is a rare, but potentially devastating complication of a frequently used antibiotic. The condition typically affects young, Caucasian, previously well females with a specific HLA genotype (HLA-B*07:02 and HLA-C*07:02). TMP-SMX ARDS is an idiosyncratic reaction resulting in a distinct pattern of pulmonary pathology characterized by diffuse alveolar injury with delayed epithelisation (DAIDE).

Miller et al 2023[10] described 19 previously well paediatric and young adult patients who developed ARDS following a median duration of 17 days exposure to treatment dose TMP-SMX. No cases have been described in those taking prophylactic dose. Patients typically present with dyspnoea, cough, and constitutional symptoms, and as seen in the present case an air leak syndrome characterized by pneumothorax and pneumomediastinum which is common even prior to intubation and positive pressure ventilation.[10] All patients were critically ill requiring intubation, with 84% requiring ECMO, for a median duration of 68 days. Mortality was high (37%), as was need for lung transplantation (32%).

Patients were treated with a range of therapies including antibiotics, corticosteroids, and corticosteroid sparing immunosuppressing agents, but no association between any of these treatments and relevant clinical outcomes were found.[10] Miller's proposed definition of TMP-SMX ARDS is; (i) unexplained severe respiratory failure in a patient receiving treatment dose TMP-SMX following the exclusion of alternative causes; (ii) positive HLA-B*07:02 and HLA-C*07:02 haplotype; and (iii) pathological findings of DAIDE on lung biopsy.[10] Outside of this series, few other cases have been reported.[7,9,12,13]

As seen in the present case, pneumocyte recovery has been described post TMP-SMX ARDS,[8,14,15] suggesting that supportive care as a bridge to recovery remains a potential therapeutic option. The early institution of ECMO, aiming to avoid the deleterious effects of barotrauma, is an important consideration. Despite this, transplant has often been required. Fortunately, there does not appear to be recurrence post-transplant, although longitudinal follow-up and the lifelong avoidance of TMP-SMX is advised.[6]

During her ICU admission, the patient's family raised the question, 'if you do not believe corticosteroids will be effective, which other anti-inflammatories might be?' Currently no targeted therapeutic interventions are available for the management of TMP-SMX ARDS.

Gene expression analysis using microarray techniques or whole exome sequencing may however be useful tools for the identification of differentially expressed genes involved in the ARDS process.[16–18] Grigoryev et al recently undertook expression-based genome-wide association studies (eGWAS) to explore the transcriptional response by lung tissue to injury, discovering 14 new differentially expressed candidate genes associated with ARDS.[17] Lu et al explored lipopolysaccharide induced ARDS in a mouse model finding the most enriched and meaningful biological process terms were mainly involved in immune-inflammation response functions and pathways linking cytokine-cytokine receptor interaction.[16]

The alveolar macrophage (AM) is recognized as a key modulator of the alveolar inflammasome[19] and AM cells critically influence the progression of ARDS through the synthesis and release of diverse inflammatory mediators.[20] AM demonstrate pyroptosis, a form of caspase-1-dependent programmed cell death triggered by proinflammatory mediators associated with increased levels of AM dependent inflammation potentially capable of influencing the progression of ARDS.[20] Emerging evidence has demonstrated that cell death and inflammation reciprocally affect each other and form an auto-amplification cycle, which then exacerbate inflammation.[19] Zhu et al explored the effects of Suramin, an antiparasitic agent, observed to inhibit sepsis associated acute lung injury in vitro.[21] These investigators identified over 500 DEGs in LPS stimulated AM cell lines, finding significant upregulation of lung inflammation, immune system signal transduction, interleukin-17 pathway and C-type lectin receptor signalling, all of which were involved in AM pyroptosis pathways and all inhibited by suramin in vitro.[21] Detailed studies of new candidate genes might lead to identification of unsuspected evolutionarily conserved mechanisms triggered by ARDS and may represent a mechanism for exploring pathogenesis and therapeutic targets in TMP-SMX ARDS.[22]

Despite increasing awareness of the condition, TMP-SMX ARDS likely remains an under-recognized entity.[10] A high degree of clinical suspicion should be held in those with unexplained respiratory failure who have been exposed to TMP-SMX. Further research is required to determine underlying pathological mechanism of injury, and to identify potential therapeutic agents.

AUTHOR CONTRIBUTIONS

All authors were involved in patient care. All authors contributed to the preparation and editing of the manuscript. All authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

No data generated.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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REFERENCES

1. Kemnic TR, Coleman M. StatPearls. Trimethoprim Sulfamethoxazole. https://www.ncbi.nlm.nih.gov/books/NBK513232/
2. Jamous F, Ayaz SZ, Choate J. Acute fibrinous organising pneumonia: a manifestation of trimethoprim-sulfamethoxazole pulmonary toxicity. BMJ Case Rep. 2014;2014(Oct):bcr2014205017.
3. Mochizuka Y, Fujisawa T, Inoue Y, Hozumi H, Suzuki Y, Karayama M, et al. Trimethoprim-sulfamethoxazole induced eosinophilic pneumonia: a case report. Respir Med Case Rep. 2022;37:101632.
4. Patel M, Gonzalez V, Hong G, Uchel T, Kulairi Z. Trimethoprim-sulfamethoxazole induced acute eosinophilic pneumonia: a common medication causing a rare fatal disease. Am J Resp Crit Care Med. 2020;201:A4941.
5. Yuzurio S, Horita N, Shiota Y, Kanehiro A, Tanimoto M. Interstitial lung disease during trimethoprim/sulfamethoxazole administration. Acta Med Okayama. 2010;64(3):181–7.
6. Miller JO, Shih AR, Mino-Kenudson M, Taylor MS, Goldman JL. Trimethoprim–sulfamethoxazole–associated fulminant respiratory failure in children and young adults. Am J Respir Crit Care Med. 2021;203(7):918–21.
7. Natterer J, Rizzati F, Perez MH, Longchamp D, Amiet V, DeHalleux Q, et al. Suspected case of drug-induced acute respiratory distress syndrome following trimethoprim-sulfamethoxazole treatment. J Pediatr Intensiv Care. 2022;11(1):67–71.
8. Rubin J, Chiu ML, Mino-Kenudson M, Sharma A, Witkin AS, Moschovis PP, et al. ARDS with pneumothorax in a young adult. Chest. 2022;161(2):e111–6.
9. Persaud PN, Chhabria MS, Manek G, Nathani AR. When treating acne goes wrong: a case of bactrim-induced ARDS in a healthy young woman. Chest. 2022;162(4):A966–7.
10. Miller J, Khan H, Mino-Kenudson M, Taylor M, Shih A, Goldman J. Definition and clinical evaluation for trimethoprim-sulfamethoxazole severe acute respiratory failure. Crit Care Med. 2023;51(12):e264–8.
11. Goldman JL, Miller JO, Miller N, Eveleigh R, Gibson A, Phillips EJ, et al. HLA-B*07:02 and HLA-C*07:02 are associated with trimethoprim-sulfamethoxazole respiratory failure. Pharmacogenomics J. 2022;22(2):124–9.
12. Jaggi KK, Corrales JCP. Trimethoprim/sulfamethoxazole-induced interstitial lung disease requiring VV-ECMO and urgent transplant evaluation. Chest. 2023;164(4):A3213–4.
13. Pysick H, Stoltz DA. Fatal lung injury secondary to trimethoprim-sulfamethoxazole. Chest. 2023;164(4):A2416.
14. Taylor MS, Chivukula RR, Myers LC, Jeck WR, Tata PR, O'Donnell WJ, et al. Delayed alveolar epithelialization: a distinct pathology in diffuse acute lung injury. Am J Respir Crit Care Med. 2018;197(4):522–4.
15. Taylor MS, Chivukula RR, Myers LC, Jeck WR, Waghray A, Tata PR, et al. A conserved distal lung regenerative pathway in acute lung injury. Am J Pathol. 2018;188(5):1149–60.
16. Lu W, Ji R. Identification of significant alteration genes, pathways and TFs induced by LPS in ARDS via bioinformatical analysis. BMC Infect Dis. 2021;21(1):852.
17. Grigoryev DN, Cheranova DI, Chaudhary S, Heruth DP, Zhang LQ, Ye SQ. Identification of new biomarkers for acute respiratory distress syndrome by expression-based genome-wide association study. BMC Pulm Med. 2015;15(1):95.
18. Xu JY, Liu AR, Wu ZS, Xie JF, Qu XX, Li CH, et al. Nucleotide polymorphism in ARDS outcome: a whole exome sequencing association study. Ann Transl Med. 2021;9(9):780.
19. He X, Qian Y, Li Z, Fan EK, Li Y, Wu L, et al. TLR4-upregulated IL-1β and IL-1RI promote alveolar macrophage pyroptosis and lung inflammation through an autocrine mechanism. Sci Rep. 2016;6(1):31663.
20. Gordon S, Plüddemann A, Estrada FM. Macrophage heterogeneity in tissues: phenotypic diversity and functions. Immunol Rev. 2014;262(1):36–55.
21. Zhu Y, Wang Z, Zheng J, Wang J, Chen Y, Huang C, et al. RNA-seq revealed the anti-pyroptotic effect of suramin by suppressing NLRP3/caspase-1/GSDMD pathway in LPS-induced MH-S alveolar macrophages. Gene. 2024;893:147888.
22. Battaglini D, Al-Husinat L, Normando AG, Leme AP, Franchini K, Morales M, et al. Personalized medicine using omics approaches in acute respiratory distress syndrome to identify biological phenotypes. Respir Res. 2022;23(1):318.

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