Acute respiratory distress syndrome (ARDS) is one of the leading death reasons in Intensive Care Unit (ICU). It is frustrating that there is no pharmacotherapy effective enough to reduce the mortality of ARDS. The most important treatment of ARDS nowadays is supportive treatment, including mechanical ventilation (MV), fluid management, and sedation. Successful trials of ARDS treatments usually aim to avoid further lung injury of ARDS patients, such as low tidal volume of MV and conservative fluid strategy. These strategies can only maintain the mortality around 40%. It is a matter of urgency to develop new methods for the treatment of ARDS. There are plenty of trials focusing on medication treatment for ARDS patients. Some medicines have been proved to be beneficial for certain kinds of ARDS including novel agents and newly developed medication. Besides, results from some early trials should be re-evaluated because of the evolution of diagnostic criteria of ARDS. Classically, ARDS is recognized to be an inflammatory lung injury. The use of corticosteroid as an anti-inflammatory agent should be a perfect match for the treatment of ARDS. However, results from randomized, placebo-controlled clinical trials (RCTs) showed that there are no benefits from corticosteroids for the improvement of ARDS survival. On the other hand, some clinical data implied that corticosteroids were able to increase oxygen level, MV-free days, and ICU-free days, which suggested that corticosteroid could play an important role during the treatment of ARDS. The problem is how and when to use it. Due to significant heterogeneity of all the trials, it is hard to come to a definitive recommendation. It is proved that low dosage of corticosteroid for ARDS patients led to better outcome. Tang et al. performed a meta-analysis consisting of five cohort studies and four trials that used 0.5–2.5 mg·kg\(^{-1}\)·d\(^{-1}\) of methylprednisolone or equivalent to treat acute lung injury (ALI)/ARDS. Both cohort studies and trials showed a trend toward mortality reduction (overall relative risk: 0.62, 95% confidence interval: 0.43–0.91, \(P = 0.01\)). Besides, methylprednisolone also improved gas exchange, MV-free days, ICU-free days, Multiple Organ Dysfunction Syndrome Score and Lung Injury Scores. Complications such as infection and neuromyopathy were not increasing in corticosteroids group. It is proved that low dosage of corticosteroid for ARDS patients led to better outcome. Tang et al. performed a meta-analysis consisting of five cohort studies and four trials that used 0.5–2.5 mg·kg\(^{-1}\)·d\(^{-1}\) of methylprednisolone or equivalent to treat acute lung injury (ALI)/ARDS. Both cohort studies and trials showed a trend toward mortality reduction (overall relative risk: 0.62, 95% confidence interval: 0.43–0.91, \(P = 0.01\)). Besides, methylprednisolone also improved gas exchange, MV-free days, ICU-free days, Multiple Organ Dysfunction Syndrome Score and Lung Injury Scores. Complications such as infection and neuromyopathy were not increasing in corticosteroids group. Another notice of corticosteroid use is timing and duration. ARDS patients may benefit from corticosteroid when initiation of the medicine at early stage of the syndrome. Meduri et al. conducted a RCT including ninety-one patients with early ARDS (<72 h) randomized (2:1 fashion) to methylprednisolone group (1 mg·kg\(^{-1}\)·d\(^{-1}\)) and placebo group. They found that corticosteroid group (63 patients) had lower ICU mortality (20.6% vs. 42.9%, \(P = 0.03\)) and better gas exchange, more ICU-free days and MV-free days without increased risk of complications. The number of the sample was too small to be convincing. Later on, Meduri et al. performed a meta-analysis of four trails investigating methylprednisolone treatment and a trial-level meta-analysis incorporating four additional RCTs investigating hydrocortisone treatment in early ARDS to support this idea. It was found that by day 28, methylprednisolone group...
had better outcome including lower mortality (20% vs. 33%;
P = 0.006), more ICU-free days and MV-free days. Another
finding of the trial-level meta-analysis was that patients who
received hydrocortisone treatment before day 14 of ARDS
onset had better survival. There are evidences supporting
this conclusion. Subgroup analysis of a large-scale RCT
also indicated 60-day (35% vs. 8%) and 180-day mortality
(44% vs. 12%) increased in corticosteroid group when
randomized after 14 days of the onset of ARDS while both
of the two time point mortality decreased when patients
were randomized between day 7 to day 13 after the onset
of ARDS, but without statistically significant. According
to these data mentioned above, corticosteroid administration
to ARDS patients is recommended at a low dosage before
day 14 of ARDS onset.

Why do the timing and duration matter during the treatment
of corticosteroid in ARDS patients? We believed that it is
because the inflammatory response of host is constantly
changing through the whole stage of ARDS. Corticosteroid
is aim to suppress the excessive reaction of immune system.
Theoretically, the high level of immune response occurs
during the early stage of inflammatory disease. However, we
do not have an effective way to test the level and duration of
immune response. The reason for why some patients of early
ARDS do not benefit from the use of corticosteroid could be
that the immune response may already be regulated to a low
level by the host system. Torres et al. used serum C-reactive
protein level >150 mg/L as a marker of high inflammatory
response of severe community-acquired pneumonia (SCAP)
patients. It turned out that corticosteroid treatment was
associated with less treatment failure among patients with
high level immune response. Although this trial was not
about ARDS, it suggested that there is certain kind of patients
who will benefit from the treatment of corticosteroid. Since
the connection of SCAP and ARDS is tight, the next stage
trials may focus on looking for a marker to label this kind
of patients who will benefit from the use of corticosteroid.

It is difficult to stop ARDS after it is fully established. It may
be wise to focus on early identification of patients at risk
and timely implementation of prevention therapy. Statins
and aspirin are the two kinds of most studied medicine
to prevent patients at high risk from turning into ARDS.
Statins are proved to have the effects of immunomodulatory
and anti-inflammatory which can be used against ARDS.
Shyamsundar et al. recruited 20 healthy volunteers
pretreated with simvastatin before lipopolysaccharide (LPS)
inhalation. After LPS challenge, cytokine levels were
significantly reduced both in bronchoalveolar lavage (BAL)
and plasma. As for critically ill patients, they were less likely
devolve ALI/ARDS if pretreated with statins. Moreover,
statin therapy might be able to reduce mortality and increase
MV-free days in ALI/ARDS patients. However, high
quality randomized controlled trial showed neither mortality
reduction nor clinical outcome improvement of statins
treatment after ARDS onset. Meta-analysis of 13 studies
also demonstrated that patients were not able to benefit
from the use of statins as preventative agent or treatment
medicine. Hence, the effects of statins on the prevention
and treatment of ALI/ARDS are still controversial.

Animal experiments revealed that platelets were essential
for the development of ALI. Aspirin, as an antiplatelet agent, was
found to be able to prevent the development of lung injury
and prevent mortality in a transfusion-related ALI mice
model. However, the Lung Injury Prevention Study With
Aspirin study, a large-scale RCT, demonstrated that use
of aspirin could not reduce the risk of ARDS among at-risk
patients. The limitation of this study was that the actual rate
of ARDS was lower than the expected rate (9.5% vs. 18%).
That might explain why no effects on the primary clinical
outcomes are noted. To date, there are inadequate evidence
for physicians to consider aspirin as a preventative therapy.

Inhalations can be an ideal way to deliver medicines
direct to lungs with less systemic side effects which are
commonly used for respiratory diseases. The most widely
used inhaled medications are beta-agonist. Alveolar-capillary
barrier is damaged during ARDS leading to the increase
of alveolar fluid. Beta-agonists are proved to have the ability
to accelerate the rate of alveolar fluid clearance in ex vivo
human lung which might be a breakthrough of ARDS
treatment. Perkins et al. evaluated inhaled short-acting
beta-agonists (salmeterol) for ARDS prevention among
patients undergoing esophagectomy. Although there was
no difference of incidence of ARDS between treatment
group and control group, salmeterol was associated with
less frequent adverse events and reduction of alveolar
inflammatory biomarkers. The latest outcome of a phase II
trial, Lung Injury Prevention Study With Budesonide and
Beta, demonstrated that the oxygen saturation benefited
from a combination of a long-acting inhaled beta-agonist
agent (formoterol) and an inhaled steroid (budesonide)
administered to adult patients at risk for ARDS. The
treatment group also showed a low incidence of developing
ARDS and requiring MV. The result supported further
study to test the efficacy of the combination of inhaled
corticosteroids and beta agonists for prevention of ARDS.

There are other agents which have been tested. The
p38 mitogen-activated phosphor kinase (MAPK) is the
key protein kinase which regulates the production of
inflammatory cytokines and chemokines. Inhibition of
p38 MAPK as a clinical treatment has been proved to be
effective to decrease inflammatory biomarkers in respiratory
diseases such as COPD. A phase IIa RCT of p38 MAPK
inhibitor has been conducted in patients with major trauma
at risk for developing ARDS. The drug was well tolerated
and capable of reducing the plasma level of inflammatory
markers. Besides, patients treated with the medicine were
less likely to develop ARDS. The p38 MAPK inhibitor
may be expectable as a pharmacal solution to ARDS.
Keratinocyte growth factor (KGF) improved ATI cell
barrier function which led to reduction of epithelial injury
and promotion of ARDS recovery. Shyamsundar et al pretreated volunteers with KGF before LPS challenge. BAL

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Investigation showed KGF improved alveolar epithelial proliferation by increasing surfactant protein D. The trial also found the influence of KGF on innate pulmonary immunity through its enhancement macrophage clearance ability, which was granulocyte-macrophage colony-stimulating factor (GM-CSF) dependent. It revealed the possibility of GM-CSF as an intervention for ARDS patients. Like other pharmacological agents, GM-CSF did not show a clinical efficacy to increase MV-free days and survival rate in a Phase II trial. Large-scale trials are needed for advanced evidence.

There are some reasons why almost every pharmacologic therapy has failed in clinical trials of ARDS despite their experimental and preclinical data were quite promising. As we all know, ARDS can be triggered by various clinical situations such as sepsis, pneumonia, aspiration, trauma, blood transfusion, and so on. The underlying pathophysiology of each disease is numerous. It is quite difficult for a single medicine to cover them all and change the outcome of all ARDS patients. Besides, ARDS patients usually have mixed conditions, most of which are extreme critical and cannot be improve by one kind of medication only. Most ARDS patients have dynamic instability, especially in lung circulation, which may cause the impediment of drug delivery to the damaged area of lungs.

After all, we believe that the most important reason is that the diagnostic tools of ARDS are still based on clinical findings and can be mistaken by many other clinical conditions. It is reported that nearly half of the ARDS patients who met the clinical criteria do not have the specific pathological changes of ARDS. Berlin definition is helping to rule out unqualified patients who used to be diagnosed as ARDS patients and were enrolled in ARDS trials. More specific markers are needed for early diagnosis of ARDS, or otherwise to distinguish the subphenotype of ARDS which might be able to benefit from certain medications. New agents are also needed to target key factors of specific pathways.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in Intensive Care Units in 50 countries. JAMA 2016;315:788-800. doi: 10.1001/jama.2016.0291.

2. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562-72. doi: 10.1056/NEJMc1711824.

3. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA 2012;307:2526-33. doi: 10.1001/jama.2012.5669.

4. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, et al. Methylprednisolone infusion in early severe ARDS: Results of a randomized controlled trial. Chest 2007;131:954-63. doi: 10.1378/ chest.06-2100.

5. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354:1671-84. doi: 10.1056/NEJMoa051693.

6. Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. Crit Care Med 2009;37:1594-603. doi: 10.1097/CCM.0b013e3181f50701.

7. Meduri GU, Bridges L, Shih MC, Marik PE, Siemieniuk RA, Kocak M, et al. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: Analysis of individual patients’ data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med 2016;42:829-40. doi: 10.1007/s00134-015-4095-4.

8. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348:138-50. doi: 10.1056/NEJMra021335.

9. Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: A randomized clinical trial. JAMA 2015;313:677-86. doi: 10.1001/jama.2015.88.

10. Shyamsundar M, McKeown ST, O’Kane CM, Craig TR, Brown V, Thickett DR, et al. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. Am J Respir Crit Care Med 2009;179:1107-14. doi: 10.1164/rcrm.200810-1540OC.

11. Koh GC, Vlaar AP, Hofstra JJ, de Jong HK, van Nierop S, Peacock SJ, et al. In the critically ill patient, diabetes predicts mortality independent of statin therapy but is not associated with acute lung injury: A cohort study. Crit Care Med 2012;40:1835-43. doi: 10.1097/ CCM.0b013e31824e1696.

12. Kor DJ, Iscimen R, Yilmaz M, Brown MJ, Brown DR, Gajic O, et al. Statin administration did not influence the progression of lung injury or associated organ failures in a cohort of patients with acute lung injury. Intensive Care Med 2009;35:1039-46. doi: 10.1007/ s00134-009-1421-8.

13. McAuley DE, Laffey JG, O’Kane CM, Perkins GD, Mullan B, Trinder TJ, et al. Simvastatin in the acute respiratory distress syndrome. N Engl J Med 2014;371:1695-703. doi: 10.1056/NEJMoa1403285.

14. Xiong B, Wang C, Tan J, Cao Y, Zou Y, Yao Y, et al. Statins for the prevention and treatment of acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. Respiratory 2016;21:1026-33. doi: 10.1111/resp.12820.

15. Chen W, Janz DR, Bastarache JA, May AK, O’Neal HR Jr, Bernard GR, et al. Prehospital aspirin use is associated with reduced risk of acute respiratory distress syndrome in critically ill patients: A propensity-adjusted analysis. Crit Care Med 2015;43:801-7. doi: 10.1097/CCM.0000000000000789.

16. Kor DJ, Carter RE, Park PK, Festic E, Banner-Goodspeed VM, Hinds R, et al. Effect of aspirin on development of ARDS in at-risk patients presenting to the emergency department: The LIPS-A randomized clinical trial. JAMA 2016;315:2406-14. doi: 10.1001/ jama.2016.6330.

17. Perkins GD, Gates S, Park D, Gao F, Knox C, Holloway B, et al. The beta agonist lung injury trial prevention. A randomized controlled trial. Am J Respir Crit Care Med 2014;189:674-83. doi: 10.1164/ rccm.201308-1549OC.

18. Festic E, Carr GE, Cartin-Ceba R, Hinds RF, Banner-Goodspeed V, Bansal V, et al. Randomized clinical trial of a combination of an inhaled corticosteroid and beta agonist in patients at risk of developing the acute respiratory distress syndrome. Crit Care Med 2017;45:798-805. doi: 10.1097/CCM.0000000000002284.

19. Watz H, Barnacle H, Hartley BF, Chan R. Efficacy and safety of the p38 MAPK inhibitor losmapimod for patients with chronic obstructive pulmonary disease: A randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2014;2:63-72. doi: 10.1016/S2213-2600(13)70200-5.

20. Christie JD, Vaslef S, Chang PK, May AK, Gunn SR, Yang S, et al. A randomized dose-escalation study of the safety and anti-inflammatory activity of the p38 mitogen-activated protein kinase inhibitor dimapimod in severe trauma subjects at risk for
acute respiratory distress syndrome. Crit Care Med 2015;43:1859-69. doi: 10.1097/CCM.0000000000001132.

21. Portnoy J, Curran-Everett D, Mason RJ. Keratinocyte growth factor stimulates alveolar type II cell proliferation through the extracellular signal-regulated kinase and phosphatidylinositol 3-OH kinase pathways. Am J Respir Cell Mol Biol 2004;30:901-7. doi: 10.1165/rcmb.2003-0406OC.

22. Shyamsundar M, McAuley DF, Ingram RJ, Gibson DS, O’Kane D, McKeown ST, et al. Keratinocyte growth factor promotes epithelial survival and resolution in a human model of lung injury. Am J Respir Crit Care Med 2014;189:1520-9. doi: 10.1164/rccm.201310-1892OC.

23. Paine R 3rd, Standiford TJ, Dechert RE, Moss M, Martin GS, Rosenberg AL, et al. A randomized trial of recombinant human granulocyte-macrophage colony stimulating factor for patients with acute lung injury. Crit Care Med 2012;40:90-7. doi: 10.1097/CCM.0b013e31822d7b0f.

24. Thille AW, Esteban A, Fernández-Segoviano P, Rodriguez JM, Aramburu JA, Peñuelas O, et al. Comparison of the berlin definition for acute respiratory distress syndrome with autopsy. Am J Respir Crit Care Med 2013;187:761-7. doi: 10.1164/rccm.201211-1981OC.

25. Wang ZY, Li T, Wang CT, Xu L, Gao XJ. Assessment of 1-year Outcomes in Survivors of Severe Acute Respiratory Distress Syndrome Receiving Extracorporeal Membrane Oxygenation or Mechanical Ventilation: A Prospective Observational Study. Chin Med J 2017; 130: 1161‑68. doi: 10.4103/0366-6999.205847.

26. Xu XF, Dai HP, Li YM, Xiao F, Wang C. Mass Spectrometry-based Proteomics in Acute Respiratory Distress Syndrome: A Powerful Modality for Pulmonary Precision Medicine. Chin Med J 2016; 129: 2357-64. doi: 10.4103/0366-6999.190669.