

BÖLÜM 9

AKUT SOLUNUM SIKINTISI SENDROMU (ARDS-ASSS)

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GİRİŞ

İlk kez 1967 yılında Ashbaugh tarafından yapılan çalışmada yetişkin solunum sıkıntısı sendromu tanımlanmıştır (1); çalışmaya dahil edilen 12 hastada tedaviye yanıtız hipoksemi ve akciğer grafisinde yaygın infiltratlar gözlenmiştir. Hastaların yedisi ölmüş ve yapılan otopsilerinde akciğerlerde inflamatuvar eksüdasyonla yoğun infiltrasyon gözlenmiştir.

Zaman içinde şok akciğeri, Da Nang akciğeri, katı akciğer sendromu, sızdıran kapiller pulmoner ödem, nonkardiyojenik pulmoner ödem, akut akciğer hasarı gibi isimler de almıştır ve son olarak akut solunum sıkıntısı sendromu (ARDS) olarak adlandırılmaktadır. Bu adlandırmaların hiçbiri akut solunum yetmezliğinin en önemli nedenlerinden biri olan ve akciğerlerde yaygın inflamatuvar hasarla seyreden bu hastalığı tarif etmede yeterli değildir.

RİSK FAKTÖRLERİ

ARDS hemen her zaman predispozan klinik risk faktörleri varlığında gelişir (Tablo 1);

çoklu risk faktörü varlığı gelişim riskini artırır (2,3). ARDS gelişiminin altta yatan sebebinden bağımsız olarak, ARDS' li hastalarda akciğerle sınırlı olmayan, inflamasyon ve organ disfonksiyonu ile seyreden sistemik hastalık tablosu görülür (4).

Sepsis indirek akciğer hasarı gelişiminin en sık nedenidir. Yoğun bakım ünitesinde (YBÜ) takip edilen, ciddi sepsisli hastalarda ARDS gelişme riski %30-40 civarındadır (2,5,6). Sepsis kaynağı pnömoni olan hastalarda ARDS gelişim riski diğer sepsis nedenlerine göre daha yüksektir (7). Şokla seyreden ciddi travma, çoklu kan ürünleri transfüzyonu gibi durumlar da indirek akciğer hasarının YBÜ'lerindeki sık sebeplerindendir. Direk akciğer hasarının en sık nedeni olan pnömoni, viral, bakteriyel veya fungal kaynaklı olabilir. Ek problemler de riski artırabilir: kronik akciğer hastalığı (6), alkol kötüye kullanımı (8,9), sigara (10-12), ileri yaş (13), kan ürünü transfüzyonu (14,15), akciğer rezeksiyonu (16), obezite (13). YBÜ'nde yatan her hastanın ARDS gelişimi açısından risk altında olduğu düşünülmeli, tanı ve tedavide ihtiyatlı yaklaşılmalıdır.

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göstermektedir; bu faktörler: yaş, APACHE skoru, PaO₂/FiO₂ ratio, organ yetmezliği, septik şok, immunsupresyon, kardiyovasküler yetmezlik ve kronik karaciğer hastalığıdır (15,128). Birçok çalışmada kısa dönem mortalitede iyileşme görülmüştür ancak 641 hastalı bir çalışmada 1 yıllık mortalite belirgin olarak yüksek bulunmuştur (%24-%41) (129). ARDS mortalitesinde kısa dönem sonuçlarda iyileşme sağlansa da uzun dönem sonuçlar açısından henüz tedavide istenilen düzeyde değiliz.

ARDS'yi atlatan hastalarda sıklıkla fonksiyonel yetersizlik, kognitif disfonksiyon ve psikososyal problemler görülür (130). İlginç olarak pulmoner fonksiyon sıklıkla normale döner. ARDS'yi atlatan 109 hastanın 1 yıllık gözleminde, akciğer volümü ve spirometrenin 6. ayda normal değerlere ulaştığı gözlenmiştir (67). Sistemik kortikosteroid ile tedavi edilmiş olmak, YBÜ' de gelişen ek hastalık, akciğer hasarı ve multiorgan disfonksiyonunun iyileşme oranı gibi faktörler fonksiyonel kapasitenin düzelmeye oranını etkileyen önemli parametrelerdir. Fiziksel ve sosyal zorluklara ek olarak, ARDS'yi atlatan hastalarda yüksek oranda depresyon ve anksiyete görülür (131).

KAYNAKLAR

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;2:319-23.
2. Pepe PE, Potkin RT, Reus DH, Hudson LD, Carrico CJ. Clinical predictors of the adult respiratory distress syndrome. *Amer J Surg* 1982;144:124-30.
3. Ferguson ND, Frutos-Vivar F, Esteban A, Gordo F, Honrubia T, Penuelas O, et al. Clinical risk conditions for acute lung injury in the intensive care unit and hospital ward: a prospective observational study. *Crit Care* 2007;11:R96.
4. Matthay MA, Zimmerman GA, Esmon C, Bhattacharya J, Coller B, Doerschuk CM, et al. Future research directions in acute lung injury: summary of a National Heart, Lung and Blood Institute working group. *Am J Respir Crit Care Med* 2003;167:1027-35.
5. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.
6. Hudson LD, Milberg JA, Anardi D, Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151:293-301.
7. Sheu CC, Gong MN, Zhai R, Bajwa EK, Chen F, Thompson BT, et al. The influence of infection sites on development and mortality of ARDS. *Intensive Care Med* 2010;36:963-70.
8. Moss M, Bucher B, Moore FA, Moore EE, Parsons PE. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. *JAMA* 1996;275:50-4.
9. Thakur L, Kojacic M, Thakur SJ, Pieper MS, Kashyap R, Trillo-Alvarez CA, et al. Alcohol consumption and development of acute respiratory distress syndrome: a population-based study. *Int J Environ Res Public Health* 2009;6:2426-35.
10. Toy P, Gajic O, Bacchetti P, Looney MR, Gropper MA, Hubmayr R, et al. Transfusion-related acute lung injury: incidence and risk factors. *Blood* 2012;119:1757-67.
11. Calfee CS, Matthay MA, Kangelaris KN, Siew ED, Janz DR, Bernard GR, et al. Cigarette smoke exposure and the acute respiratory distress syndrome. *Crit Care Med* 2015;43:1790-7.
12. Calfee CS, Matthay MA, Eisner MD, Benowitz N, Call M, Pittet JE, et al. Active and passive cigarette smoking and acute lung injury after severe blunt trauma. *Am J Respir Crit Care Med* 2011;183:1660-5.
13. Towfigh S, Peralta MV, Martin MJ, Salim A, Kelson R, Sohn H, et al. Acute respiratory distress syndrome in nontrauma surgical patients: a 6-year study. *J Trauma* 2009;67:1239-43.
14. Watson GA, Sperry JL, Rosengart MR, Minei JP, Harbrecht BG, Moore EE, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma* 2009;67:221-7; discussion 8-30.
15. Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest* 2007;131:1308-14.

16. Jeon K, Yoon JW, Suh GY, Kim J, Kim K, Yang M, et al. Risk factors for post-pneumonectomy acute-lung injury/acute respiratory distress syndrome in primary lung cancer patients. *Anaesth Intensive-Care* 2009;37:14-19.
17. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. *J Clin Invest* 2012;122:2731-40.
18. Tomashefski JF. Pulmonary pathology of acute respiratory distress syndrome. *Clin Chest Med* 2000;21:435-66.
19. Albertine KH, Soulier MF, Wang Z, Ishizaka A, Hashimoto S, Zimmerman GA, et al. Fas and fasligand are up-regulated in pulmonary edema fluid and lung tissue of patients with acute lung injury and the acute respiratory distress syndrome. *Am J Pathol* 2002;161:1783-96.
20. Lee KS, Choi YH, Kim YS, Baik SH, Oh YJ, Sheen SS, et al. Evaluation of bronchoalveolar lavage fluid from ARDS patients with regard to apoptosis. *Respir Med* 2008;102:464-9.
21. Bachofen M, Weibel ER. Structural alterations of lung parenchyma in the adult respiratory distress syndrome. *Clin Chest Med* 1982;3:35-56.
22. Bachofen M, Weibel ER. Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicemia. *Am Rev Respir Dis* 1977;116:589-615.
23. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001;163:1376-83.
24. Matthay MA, Wiener-Kronish JP. Intact epithelial barrier function is critical for the resolution of alveolar edema in humans. *Am Rev Respir Dis* 1990;142:1250-7.
25. Sprung C, Rackow E, Fein I, Jacob A, Isikoff S. The spectrum of pulmonary edema: differentiation of cardiogenic intermediate and noncardiogenic forms of pulmonary edema. *Am Rev Respir Dis* 1981;124:718-22.
26. Fein A, Grossman RF, Jones JG, Overland E, Pitts L, Murray JF, et al. The value of edema protein measurements in patients with pulmonary edema. *Am J Med* 1979;67:32-9.
27. Gregory TJ, Longmore WJ, Moxley MA, Whittsett JA, Reed CR, Fowler AAI, et al. Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. *J Clin Invest* 1991;88:1976-81.
28. Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. *Am Rev Respir Dis* 1993;147:218-33.
29. Cheng IW, Ware LB, Greene KE, Nuckton TJ, Eisner MD, Matthay MA. Prognostic value of surfactant proteins A and D in patients with acute lung injury. *Crit Care Med* 2003;31:20-7.
30. Greene KE, Wright JR, Steinberg KP, Ruzinski JT, Caldwell E, Wong WB, et al. Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. *Am J Respir Crit Care Med* 1999;160:1843-50.
31. Bastarache JA, Wang L, Geiser T, Wang Z, Albertine KH, Matthay MA, et al. The alveolar epithelium can initiate the extrinsic coagulation cascade through expression of tissue factor. *Thorax* 2007;62:608-16.
32. Bastarache JA, Fremont RD, Kropski JA, Bossert FR, Ware LB. Procoagulant alveolar microparticles in the lungs of patients with acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol* 2009;297:L1035-41.
33. Wang L, Bastarache JA, Wickersham N, Fang X, Matthay MA, Ware LB. Novel role of the human alveolar epithelium in regulating intra-alveolar coagulation. *Am J Respir Cell Mol Biol* 2007;36:497-503.
34. Prabhakaran P, Ware L, White K, Cross M, Matthay M, Olman M. Elevated levels of plasminogen activator inhibitor-1 in pulmonary edema fluid are associated with mortality in acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2003;285:L20-L8.
35. Bowler RW, Velsor LW, Duda B, Chan ED, Abraham E, Ware LB, et al. Pulmonary edema fluid anti-oxidants are depressed in acute lung injury. *Crit Care Med* 2003;31:2309-15.
36. Chabot F, Mitchell JA, Gutteridge JMC, Evans TW. Reactive oxygen species in acute lung injury. *Eur Respir J* 1998;11:745-57.
37. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end expiratory pressure. *Am Rev Respir Dis* 1974;110:556-65.
38. Determann RM, Royakkers A, Wolthuis EK, Vlaar AP, Choi G, Paulus F, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Crit Care* 2010;14:R1.
39. Dreyfuss D, Soler P, Basset G, Saumon G. High

- inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis* 1988;137:1159-64.
40. Parker JC, Townsley MI, Rippe B, Taylor AE, Thigpen J. Increased microvascular permeability in dog lungs due to high peak airway pressure. *J Appl Physiol* 1984;57:1809-16.
 41. Slutsky AS, Tremblay LN. Multiple system organ failure: is mechanical ventilation a contributing factor. *Am J Respir Crit Care Med* 1998;157:1721-5.
 42. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome. *JAMA* 1999;282:54-61.
 43. The ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
 44. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818-24.
 45. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307:2526-33.
 46. Wheeler AP, Bernard GR, Thompson BT, Schoenfeld D, Wiedemann HP, deBoisblanc B, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006;354:2213-24.
 47. Rubenfeld GD, Caldwell E, Granton J, Hudson LD, Matthay MA. Interobserver variability in applying a radiographic definition for ARDS. *Chest* 1999;116:1347-53.
 48. Meade MO, Cook RJ, Guyatt GH, Groll R, Kachura JR, Bedard M, et al. Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2000;161:85-90.
 49. Janz DR, Ware LB. Approach to the patient with the acute respiratory distress syndrome. *Clin Chest ed* 2014;35:685-96.
 50. Ferguson ND, Frutos-Vivar F, Esteban A, Fernandez-Segoviano P, Aramburu JA, Najera L, et al. Acute respiratory distress syndrome: under-recognition by clinicians and diagnostic accuracy of three clinical definitions. *Crit Care Med* 2005;33:2228-34.
 51. Mikkelsen ME, Dedhiya PM, Kalhan R, Gallop RJ, Lanken PN, Fuchs BD. Potential reasons why physicians underuse lung-protective ventilation: a retrospective cohort study using physician documentation. *Respir Care* 2008;53:455-61.
 52. Sanchez JF, Ghamande SA, Midturi JK, Arroliga AC. Invasive diagnostic strategies in immunosuppressed patients with acute respiratory distress syndrome. *Clin Chest Med* 2014;35:697-712.
 53. Libby LJ, Gelbman BD, Altorki NK, Christos PJ, Libby DM. Surgical lung biopsy in adult respiratory distress syndrome: a meta-analysis. *Ann Thorac Surg* 2014;98:1254-60.
 54. Papazian L, Doddoli C, Chetaille B, Gernez Y, Thirion X, Roch A, et al. A contributive result of open-lung biopsy improves survival in acute respiratory distress syndrome patients. *Crit Care Med* 2007;35:755-62.
 55. Wiener-Kronish JP, Matthay MA. Pleural effusions associated with hydrostatic and increased permeability pulmonary edema. *Chest* 1988;93:852-8.
 56. Gattinoni L, Bombino M, Pelosi P, Lissoni A, Peseenti A, Fumagalli R, et al. Lung structure and function in different stages of severe adult respiratory distress syndrome. *JAMA* 1994;271:1772-9.
 57. Goodman LR. Congestive heart failure and adult respiratory distress syndrome. New insights using computed tomography. *Radiol Clin N Amer* 1996;34:33-46.
 58. Maunder RJ, Shuman WP, McHugh JW, Marglin SI, Butler J. Preservation of normal lung regions in the adult respiratory distress syndrome: analysis by computed tomography. *JAMA* 1986;255: 2463-5.
 59. Pittet JF, MacKersie RC, Martin TR, Matthay MA. Biological markers of acute lung injury: prognostic and pathogenetic significance. *Am J Respir Crit Care Med* 1997;155:1187-205.
 60. Constantin JM, Grasso S, Chanques G, Aufort S, Futier E, Sebbane M, et al. Lung morphology predicts response to recruitment maneuver in patients with acute respiratory distress syndrome. *Crit Care Med* 2010;38:1108-17.
 61. Wright PE, Bernard GR. The role of airflow resistance in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1989;139:1169-74.
 62. Beiderlinden M, Kuehl H, Boes T, Peters J. Preva-

- lence of pulmonary hypertension associated with severe acute respiratory distress syndrome: predictive value of computed tomography. *Intensive Care Med* 2006;32:852-7.
63. Boissier F, Katsahian S, Razazi K, Thille AW, Roche-Campo F, Leon R, et al. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. *Intensive Care Med* 2013;39:1725-33.
64. Chesnutt AN, Matthay MA, Tibayan FA, Clark JG. Early detection of type III procollagen peptide in acute lung injury. *Am J Respir Crit Care Med* 1997;156:840-5.
65. Matthay MA, Folkesson HG, Clerici C. Lung epithelial fluid transport and the resolution of pulmonary edema. *Physiol Rev* 2002;82:569-600.
66. Folkesson HG, Matthay MA, Westrom BR, Kim KJ, Karlsson BW, Hastings RH. Alveolar epithelial clearance of protein. *J Appl Physiol* 1996;80:1431-45.
67. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Fatma A-S, et al. Oneyear outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683-93.
68. Anderson ID, Fearon KC, Grant IS. Laparotomy for abdominal sepsis in the critically ill. *Br J Surg* 1996;83:535-9.
69. Heyland DK, Cook DJ, Guyatt GH. Enteral nutrition in the critically ill patients: a critical review of the evidence. *Intens Care Med* 1993;19:435-42.
70. Cerra FB, Benitez MR, Blackburn GL, Irwin RS, Jeejeebhoy K, Katz DP, et al. Applied nutrition in ICU patients: a consensus statement of the American College of Chest Physicians. *Chest* 1997;111:769-78.
71. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;303:865-73.
72. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327-36.
73. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:637-45.
74. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:646-55.
75. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino G, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338:347-54.
76. Voggenreiter G, Aufmkolk M, Stiletto RJ, Baacke MG, Waydhas C, Ose C, et al. Prone positioning improves oxygenation in post-traumatic lung injury—a prospective randomized trial. *J Trauma* 2005;59:333-41; discussion 41-3.
77. Beuret P, Carton MJ, Nourdine K, Kaaki M, Tramon G, Ducreux JC. Prone position as prevention of lung injury in comatose patients: a prospective, randomized, controlled study. *Intensive Care Med* 2002;28:564-9.
78. Mancebo J, Fernandez R, Blanch L, Rialp G, Gordo F, Ferrer M, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;173:1233-9.
79. Guerin C, Gaillard S, Lemasson S, Ayzac L, Girard R, Beuret P, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. *JAMA* 2004;292:2379-87.
80. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001;345:568-73.
81. Taccone P, Pesenti A, Latini R, Polli F, Vagginelli F, Mietto C, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2009;302:1977-84.
82. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159-68.
83. Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. *Crit Care Med* 2009;37:2448-54.
84. Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, et al. Predictors

- of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med* 2001;27:1718-28.
85. Antonelli M, Conti G, Bui M, Costa MG, Lappa A, Rocco M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation. *JAMA* 2000;283:235-41.
 86. Hilbert G, Gruson D, Vargas F, Valentino R, Chene G, Boiron JM, et al. Noninvasive continuous positive airway pressure in neutropenic patients with acute respiratory failure requiring intensive care unit admission. *Crit Care Med* 2000;28:3185-90.
 87. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, et al. Non-invasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001;344:481-7.
 88. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185-96.
 89. Luce JM, Montgomery BA, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. *Am Rev Respir Dis* 1988;136:62-8.
 90. Bernard GR, Luce JM, Sprung CL. High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N Engl J Med* 1987;317:1565-70.
 91. Bernard GR, Wheeler AP, Arons MM, Morris PE, Paz HL, Russell JA, et al. A trial of antioxidants N-acetylcysteine and procysteine in ARDS. *Chest* 1997;112:164-72.
 92. Spragg RG, Lewis JF, Wurst W, Hafner D, Baughman RP, Wewers MD, et al. Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant. *Am J Respir Crit Care Med* 2003;167:1562-6.
 93. Anzueto A, Baughman RP, Guntupalli KK, Weg JG, Wiedemann HP, Raventos AA, et al. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. *N Engl J Med* 1996;334:1417-21.
 94. Spragg RG, Lewis JF, Walmarath H-D, Johannigman J, Bellingan G, Laterre P-F, et al. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med* 2004;351:884-92.
 95. Bernard GR, Francois B, Mira JP, Vincent JL, Delinger RP, Russell JA, et al. Evaluating the efficacy and safety of two doses of the polyclonal anti-tumor necrosis factor-alpha fragment antibody AZD9773 in adult patients with severe sepsis and/or septic shock: randomized, double-blind, placebo-controlled phase IIb study. *Crit Care Med* 2014;42:504-11.
 96. National Heart L, Blood Institute ACTN, Truwit JD, Bernard GR, Steingrub J, Matthay MA, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med* 2014;370: 2191-200.
 97. Abraham E, Baughman R, Fletcher E, Heard S, Lamberti J, Levy H, et al. Liposomal prostaglandin E1 (TLC C-53) in acute respiratory distress syndrome: a controlled, randomized, double-blind, multicenter clinical trial. *Crit Care Med* 1999;27:1478-85.
 98. Bone RC, Slotman G, Maunder R, Silverman H, Hyers TM, Kerstein M. Randomized double-blinded, multicenter study of prostaglandin E1 in patients with adult respiratory distress syndrome. *Chest* 1989;96:114-9.
 99. 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.
 100. Matthay MA, Brower RG, Carson S, Douglas IS, Eisner M, Hite D, et al. Randomized, placebo-controlled clinical trial of an aerosolized beta(2)-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med* 2011;184:561-8.
 101. Gao Smith F, Perkins GD, Gates S, Young D, McAuley DF, Tunnicliffe W, et al. Effect of intravenous beta-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet* 2012;379:229-35.
 102. The ARDS Network. Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome. *Crit Care Med* 2002;30:1-6.
 103. The Acute Respiratory Distress Syndrome Network. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2000;283: 1995-2002.
 104. Liu KD, Levitt J, Zhuo H, Kallet RH, Brady S, Steingrub J, et al. Randomized clinical trial of activated protein C for the treatment of acute lung injury. *Am J Respir Crit Care Med* 2008;178:618-23.

105. Hemmila MR, Rowe SA, Boules TN, Miskulin J, McGillicuddy JW, Schuerer DJ, et al. Extracorporeal life support for severe acute respiratory distress syndrome in adults. *Ann Surg* 2004;240:595-605; discussion 605-7.
106. Peek GJ, Moore HM, Moore N, Sosnowski AW, Firmin RK. Extracorporeal membrane oxygenation for adult respiratory failure. *Chest* 1997;112:759-64.
107. Lewandowski K, Rossaint R, Pappert D, Gerlach H, Slama KJ, Weidemann H, et al. High survival rate in 122 ARDS patients managed according to a clinical algorithm including extracorporeal membrane oxygenation. *Intensive Care Med* 1997;23:819-35.
108. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, et al. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013;368:795-805.
109. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, et al. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med* 2013;368:806-13.
110. Adhikari NK, Burns KE, Friedrich JO, Granton JT, Cook DJ, Meade MO. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ* 2007;334:779.
111. Searcy RJ, Morales JR, Ferreira JA, Johnson DW. The role of inhaled prostacyclin in treating acute respiratory distress syndrome. *Ther Adv Respir Dis* 2015;9:302-12.
112. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
113. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998;158:1831-8.
114. Boussarsar M, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L. Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. *Intensive Care Med* 2002;28:406-13.
115. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JFJ, Weaver LK, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994;149:295-305.
116. Chastre J, Trouillet JL, Vuagnat A, Joly-Guillou ML, Clavier H, Dombret MC, et al. Nosocomial pneumonia in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998;157:1165-72.
117. Sutherland KR, Steinberg KP, Maunder RJ, Milberg JA, Allen DL, Hudson LD. Pulmonary infection during the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;152:550-6.
118. Seidenfeld JJ, Pohl DF, Bell RC, Harris GD, Johanson WGJ. Incidence, site and outcome of infections in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1986;134:12-16.
119. Hudson LD, Lee CM. Neuromuscular sequelae of critical illness. *N Engl J Med* 2003;348:745-7.
120. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293-304.
121. Fletcher SN, Kennedy DD, Ghosh IR, Misra VP, Kiff K, Coakley JH, et al. Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. *Crit Care Med* 2003;31:1012-6.
122. Rosenberg AL, Dechert RE, Park PK, Bartlett RH, Network NNA. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med* 2009;24:35-46.
123. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354:2564-75.
124. Ware LB, Matthay MA. Medical progress: The acute respiratory distress syndrome. *N Engl J Med* 2000;342:1334-49.
125. Navarrete-Navarro P, Rodriguez A, Reynolds N, West R, Habashi N, Rivera R, et al. Acute respiratory distress syndrome among trauma patients: trends in ICU mortality, risk factors, complications and resource utilization. *Intensive Care Med* 2001;27:1133-40.
126. Eisner M, Thompson T, Hudson L, Luce J, Hayden D, Schoenfeld D, et al. Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute res-

- piratory distress syndrome. *Am J Respir Crit Care Med* 2001;164:231-6.
127. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012;307:795-803.
128. Roupie E, Lepage E, Wysocki M, Fagon JY, Chastre J, Dreyfuss D, et al. Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients. SRLF Collaborative Group on Mechanical Ventilation. *Society de Reanimation de Langue Francaise. Intensive Care Med* 1999;25:920-9.
129. Wang CY, Calfee CS, Paul DW, Janz DR, May AK, Zhuo H, et al. One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. *Intensive Care Med* 2014;40:388-96.
130. Wilcox ME, Patsios D, Murphy G, Kudlow P, Paul N, Tansey CM, et al. Radiologic outcomes at 5 years after severe acute respiratory distress syndrome (ARDS). *Chest* 2013;143:920-6.
131. Hopkins RO, Key CW, Suchyta MR, Weaver LK, Orme JE, Jr. Risk factors for depression and anxiety in survivors of acute respiratory distress syndrome. *Gen Hosp Psychiatry* 2010;32:147-55.