RECOMMENDATIONS

In the scope of the present study and after reviewing the previously published studies about this topic, we may recommend the following:

- Angiotensinogen could be used for predicting AKI in patients with severe sepsis.
- It should be measured multiple times during ICU stay for better prognostic accuracy.
- Multiple cut-off values should be evaluated to reach optimal threshold which could be particularly useful for screening patients who will meet the outcomes for enrollment in a clinical trial of early intervention.
- The study should be compared with other AKI biomarkers in ICU patients with other causes of AKI not only severe sepsis, but also all causes of AKI.
- Larger sample size and longer duration of study should be applied to reach optimum results.

REFERENCES

1. Roy AK, Mc Gorrian C, Treacy C, Kavanaugh E, Brennan A, Mahon NG, et al. A Comparison of Traditional and Novel Definitions (RIFLE, AKIN, and KDIGO) of Acute Kidney Injury for the Prediction of Outcomes in Acute Decompensated Heart Failure. Cardiorenal Med. Apr 2013;3(1):26-37

2. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality.Acohort analysis. *JAMA*. 1996;275(19):1489-1494.

3. Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol*. 2004;15(6):1597-1605.

4. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol*. 2005;16(11):3365-3370.

5. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med*. 2006;34(7):1913-1917.

6. Hoste EA, Kellum JA. Acute renal failure in the critically ill: impact on morbidity and mortality. *Contrib Nephrol*. 2004;144:1-11.

7. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network (AKIN): report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31.

8. Levin A,Warnock DG, Mehta RL, et al. Improving outcomes from acute kidney injury: report of an initiative. *Am J Kidney Dis*.2007;50(1):1-4.

9. Kellum JA, Bellomo R, Ronco C. The concept of acute kidney injury and the RIFLE criteria. *Contrib Nephrol*. 2007;156:10-16.

10. Uchino S. The epidemiology of acute renal failure in the world. *Curr Opin Crit Care*. 2006;12(6):538-543.

11. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury.*N Engl J Med*. 2008;359(1):7-20.

12. Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*.2009;361(17):1627-1638.

13. Mehta RL, Chertow GM. Acute renal failure definitions and classification: time for change? *JAm Soc Nephrol*. 2003;14(8):2178-2187.

14. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, and the Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fl uid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative Group. *Crit Care* 2004; 8**:** R204–R12.

15. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl.* 2012; 2:1-138.

16. Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: aprospective cohort study. J Am Soc Nephrol 2004; 15: 1597–1605.

17. Kellum JA, Bellomo R, Ronco C. The concept of acute kidney injury and the RIFLE criteria. Contrib Nephrol. 2007;156:10-16.

18. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney Int.* 2008;73(5):538-546.

19. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Metaanalysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med.* 2005;142(7):510-524.

20. Mehta RL, Pascual MT, Soroko S, Chertow GM. Diuretics, mortality, and non recovery of renal function in acute renal failure. *JAMA.* 2002;288(20):2547-2553.

21. Newsome BB, Warnock DG, McClellan WM, et al. Longterm risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. *Arch Intern Med.* 2008;168(6):609-616.

22. Coca SG, King JT Jr, Rosenthal RA, Perkal MF, Parikh CR.The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. *Kidney Int.* 2010;78(9):926-933.

23. Mehta RL, Chertow GM. Acute renal failure definitions and classification: time for change? JAm Soc Nephrol. 2003;14(8):2178-2187.

24. Liangos O, Wald R, O'Bell JW, Price L, Pereira BJ, Jaber BL.Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. *Clin J Am Soc Nephrol* 2006; **1:** 43–51.

25. Hsu CY, McCullough CE, Fan D, Ordonez JD, Cherow GM, Go AS. Community-based incidence of acute renal failure. *Kidney Int* 2007;**72:** 208–12.

26. Bagshaw SM, George C, Bellomo R, and the ANZICS Database Management Committee. Early acute kidney injury and sepsis: a multicentre evaluation. *Crit Care* 2008; **12:** R47.

27. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care* 2006; **10:** R73.

28. Ramchandra R, Wan L, Hood SG, Frithiof R, Bellomo R, May CN. Septic shock induces distinct changes in sympathetic nerve activity to the heart and kidney in conscious sheep.*Am J Physiol Regul Integr Comp Physiol* 2009; **297:** R1247–53.

29. Kourembanas S, McQuillan LP, Leung GK, Faller DV: Nitric oxide regulates the expression of vasoconstrictors and growth factors by vascular endothelium under both normoxia and hypoxia. J Clin Invest 92: 99–104, 1993

30. Loutzenhiser R, Griffi n K, Williamson G, Bidani A. Renal autoregulation: new perspectives regarding the protective and regulatory roles of the underlying mechanisms. *Am J Physiol Regul Integr Comp Physiol* 2006; **290:** R1153–67.

31. Bersten AD, Holt AW: Vasoactive drugs and the importance of renal perfusion pressure. *New Horiz* 3:650, 1995.

32. Mendonca A et al. Acute renal failure in ICU. Risk factors and outcome evaluated with SOFA score. Intensive care med 2000; 26:915-21

33. Blantz RC: Pathophysiology of prerenal azotemia. *Kidney Int* 53:512, 1998.

34. Kribben, A, Edelstein, CL, Schrier, RW. Pathophysiology of acute renal failure. J. Nephrol. 1999. 12(Suppl. 2):S142-S151.

35. Liu KD, Matthay MA, Chertow GM. Evolving practices in critical care and potential implications for management of acute kidney injury. *Clin J Am Soc Nephrol.* Jul 2006; 1:869-73.

36. Tanner, GA. Nephron obstruction and tubuloglomerular feedback. *Kidney Int. Suppl.* 1982. **12:**S213-S218.

37. Hou SH, Bushinsky DA, Wish JB, et al: Hospital acquired renal insufficiency: A prospective study. *Am J Med* 74:243, 1983.

38. Zager RA: Endotoxemia, renal hypoperfusion, and fever: interactive risk factors for aminoglycoside and sepsis-induced acute renal failure. *Am J Kidney Dis* 20:223, 1992.

39. Pannu N, Mehta RL: Mechanical ventilation and renal function: an area for concern? *Am J Kidney Dis* 39:616, 2002.

40. Murray PT,Wylam ME, Umans JG: Nitric oxide and septic vascular dysfunction. *Anesth Analg* 90:89, 2000.

41. Lieberthal W: Biology of acute renal failure: therapeutic implications *Kidney Int* 52:1102, 1997.

42. Sutton TA, Fisher CJ, Molitoris BA: Microvascular endothelial injury and dysfunction during ischemic acute renal failure. *Kidney Int* 62:1539, 2002.

43. Blantz RC: The mechanisms of acute renal failure after uranyl nitrate. *J Clin Invest* 55:621, 1975.

44. Baylis C, Rennke HG, Brenner BM: Mechanism of the defect in glomerular ultrafiltration associated with gentamicin administration. *Kidney Int* 12: 344, 1977.

45. Lameire N,Vanholder R: Pathophysiologic features and prevention of human and experimental acute tubular necrosis. *J AmSoc Nephrol* 12:S20, 2001.

46. Thurau K, Boylan JW: Acute renal success. The unexpected logic of oliguria in acute renal failure. *Am J Med* 61:308, 1976.

47. Brezis M, Rosen S: Hypoxia of the renal medulla—its implications for disease. *N Engl J Med* 332:647, 1995.

48. Brezis M, Agmon Y, Epstein FH: Determinants of intrarenal oxygenation. Effects of diuretics. *Am J Physiol* 267:F1059, 1994.

49. Moran SM, Myers BD. Pathophysiology of protracted acute renal failure in man. *J Clin Invest* 76:1440, 1985.

50. Donohoe FJ, Venkatachalam MA, Bernard DB, et al: Tubular leakage and obstruction after renal ischemia: structure-function correlations. *Kidney Int* 13:208, 1978.

51. Waikar SS, Bonventre JV: Creatinine kinetics and the definition of acute kidney injury. J Am Soc Nephrol 2009; 20: 672–679.

52. Himmelfarb J, Ikizler TA: Acute kidney injury: changing lexicography, definitions, and epidemiology. Kidney Int 2007; 71: 971–976.

53. Prowle JR, Liu YL, Licari E, Bagshaw SM, Egi M, Haase M, Haase-Fielitz A, Kellum JA, Cruz D, Ronco C, Tsutsui K, Uchino S, Bellomo R: Oliguria as predictive biomarker of acute kidney injury in critically ill patients. Crit Care 2011; 15:R172.

54. Bagshaw SM, Gibney RT. Conventional markers of kidney function. Crit Care Med. 2008;36:S152–S158.

55. Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG, Koyner JL, Wang Z, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, Krawczeski CD, Passik CS, Swaminathan M, Garg AX, for the TRIBE-AKI Consortium: Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol 2011; 22: 1748–1757.

56. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, Krawczeski CD, Koyner JL, Murray P, Zappitelli M, Goldstein SL, Makris K, Ronco C, Martensson J, Martling CR, Venge P, Siew E, Ware LB, Ikizler TA, Mertens PR: The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. J Am Coll Cardiol 2011; 57: 1752–1761.

57. Acute Dialysis Quality Initiative (ADQI): www.ADQI.org (accessed January 10, 2013).

58. Dzau VJ, Re R (1994) Tissue angiotensin system in cardiovascular medicine. A paradigm shift? Circulation 89:493–498

59. Dell'Italia LJ, Meng QC, Balcells E, Wei CC, Palmer R, Hageman GR, Durand J, Hankes GH, Oparil S (1997) Compartmentalization of angiotensin II generation in the dog heart evidence for independent mechanisms in intravascular and interstitial spaces. J Clin Invest 100:253–258

60. Katsurada A, Hagiwara Y, Miyashita K, Satou R, Miyata K, Ohashi N, Navar LG, Kobori H (2007) Novel sandwich ELISA for human angiotensinogen. Am J Physiol Renal Physiol 293:F956–F960

61. Allred AJ, Chappell MC, Ferrario CM, Diz DI: Differential actions of renal ischemic injury on the intrarenal angiotensin system. Am J Physiol Renal Physiol 2000, 279:F636-645.

62. da Silveira KD, Pompermayer Bosco KS, Diniz LR, Carmona AK, Cassali GD, Bruna-Romero O, de Sousa LP, Teixeira MM, Santos RA, Simoes e Silva AC, Ribeiro Vieira MA: ACE2-angiotensin-(1-7)-Mas axis in renal ischaemia/reperfusion injury in rats. Clin Sci (Lond) 2010, 119:385-394.

63. Kobori H, Nangaku M, Navar LG, et al. . The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev 2007;59:251-287.

64. Kobori H, Nishiyama A, Abe Y, et al. Enhancement of intrarenal angiotensinogen in Dahl salt-sensitive rats on high salt diet. Hypertension 2003;41:592-597.

65. Anderson S, Jung FF, Ingelfinger JR. Renal renin-angiotensin system in diabetes: functional, immunohistochemical, and molecular biological correlations. Am J Physiol 1993;265:F477-F486.

66. Sachetelli S, Liu Q, Zhang SL, et al. RAS blockade decreases blood pressure and proteinuria in transgenic mice overexpressing rat angiotensinogen gene in the kidney. Kidney Int 2006;69:1016-1023.

67. Liu F, Brezniceanu ML, Wei CC, et al. Overexpression of angiotensinogen increases tubular apoptosis in diabetes. J Am Soc Nephrol 2008;19:269-280.

68. Liu F, Wei CC, Wu SJ, et al. Apocynin attenuates tubular apoptosis and tubulointerstitial fibrosis in transgenic mice independent of hypertension. Kidney Int 2009;75:156-166.

69. Lo CS, Liu F, Shi Y, et al. Dual RAS blockade normalizes angiotensin-converting enzyme-2 expression, prevents hypertension and tubular apoptosis in Akita angiotensinogen-transgenic mice. Am J Physiol Renal Physiol 2012;302:F840-F852.

70. Navar LG, Prieto MC, Satou R, et al. Intrarenal angiotensin II and its contribution to the genesis of chronic hypertension. Curr Opin Pharmacol 2011;11:180-186.

71. Kobori H, Prieto-Carrasquero MC, Ozawa Y, et al. AT1 receptor mediated augmentation of intrarenal angiotensinogen in angiotensin II-dependent hypertension. Hypertension 2004;43:1126-1132.

72. Kobori H, Alper AB Jr., Shenava R, et al. Urinary angiotensinogen as a novel biomarker of the intrarenal renin-angiotensin system status in hypertensive patients. Hypertension 2009;53:344-350.

73. Kobori H, Ohashi N, Katsurada A, et al. Urinary angiotensinogen as a potential biomarker of severity of chronic kidney diseases. J Am Soc Hypertens 2008;2:349-354.

74. Aybal Kutlugun A, Altun B, Buyukasik Y, et al. Elevated urinary angiotensinogen a marker of intrarenal renin angiotensin system in ypertensive renal transplant recipients: does it play a role in development of proteinuria in hypertensive renal transplant patients? Transpl Int 2012;25:13-18.

75. Urushihara M, Kondo S, Kagami S, et al. Urinary angiotensinogen accurately reflects intrarenal Renin-Angiotensin system activity. Am J Nephrol 2010;31:318-325.

76. Yamamoto T, Nakagawa T, Suzuki H, et al. Urinary angiotensinogen as a marker of intrarenal angiotensin II activity associated with deterioration of renal function in patients with chronic kidney disease. J Am Soc Nephrol 2007;18:1558-1565.

77. Nishiyama A, Konishi Y, Ohashi N, et al. Urinary angiotensinogen reflects the activity of intrarenal renin–angiotensin system in patients with IgA nephropathy. Nephrol Dial Transplant 2011;26:170-177.

78. Jang HR, Kim SM, Lee YJ, et al. The origin and the clinical significance of urinary angiotensinogen in proteinuric IgA nephropathy patients. Ann Med 2011. epub ahead of print doi:10.3109/07853890.2011.558518.

79. Barrilli A, Molinas S, Petrini G, Menacho M, Elias MM: Losartan reverses fibrotic changes in cortical renal tissue induced by ischemia or ischemia-reperfusion without changes in renal function. Mol Cell Biochem 2004, 260:161-170.

80. Molinas SM, Cortes-Gonzalez C, Gonzalez-Bobadilla Y, Monasterolo LA, Cruz C, Elias MM, Bobadilla NA, Trumper L: Effects of losartan pretreatment in an experimental model of ischemic acute kidney injury.Nephron Exp Nephrol 2009, 112:e10-19.

81. Kobori H, Harrison-Bernard LM, Navar LG: Urinary excretion of angiotensinogen reflects intrarenal angiotensinogen production. Kidney Int 2002, 61:579-585.

82. Kim SM, Jang HR, Lee YJ, Lee JE, Huh WS, Kim DJ, Oh HY, Kim YG: Urinary angiotensinogen levels reflect the severity of renal histopathology in patients with chronic kidney disease. Clin Nephrol 2011, 76:117-123.

83. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med 29:1303, 2001.

84. Martin GS, Mannino DM, Eaton S, Moss M: The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348:1546, 2003.

85. Zeni F, Freeman B, Natanson C: Anti-inflammatory therapies to treat sepsis and septic shock: A reassessment (editorial). Crit Care Med 25:1095, 1997.

86. Angus DC, Kelley MA, Schmitz RJ, et al: Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: Can we meet the requirements of an aging population? JAMA 284:2762, 2000.

87. Levy MM, Fink MP, Marshall JC, et al: 2001SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:1250–1256

88. Bone RC, Balk RA, Cerra FB, et al, and members of the ACCP/SCCM Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992; 101:1644–1655 and Crit Care Med 1992; 20:864–874

89. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Septic acute kidney injury in critically ill patients: Clinical characteristics and outcomes. Clin J Am Soc Nephrol. 2007; 2:431–9.

90. Schrier RW, Wang W: Acute renal failure and sepsis. N Engl J Med 351: 159-169, 2004.

91. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP: The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 273: 117-123, 1995.

92. Chertow GM, Soroko SH, Paganini EP, Cho KC, Himmelfarb J, Ikizler TA, Mehta RL: Mortality after acute renal failure: models for prognostic stratification and risk adjustment. Kidney Int 70: 1120-1126, 2006.

93. Macedo E, Mehta Rl: Prerenal failure: from old concepts to new paradigms. Curr Opin Crit Care 15: 467-473, 2009.

94. Abuelo JG: Normotensive ischemic acute renal failure. N Engl J Med 357: 797-805, 2007.

95. Langenberg C, Bellomo R, May CN, Egi M, Wan l, Morgera S: Renal vascular resistance in sepsis. Nephron Physiol 104: 1-11, 2006b

96. LANGENBERG C, WAN L, EGI M, MAY CN, BELLOMO R: Renal blood flow in experimental septic acute renal failure. Kidney Int 69: 1996-2002, 2006a.

97. Langenberg C, Wan L, Egi M, May CN, Bellomo R: Renal blood flow and function during recovery from experimental septic acute kidney injury. Intensive Care Med 33: 1614-1618, 2007.

98. Damman K, Van deursen VM, Navis G, Voors AA, Van VELDHUISEN DJ, Hillege HL: Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol 53: 582-588, 2009.

99. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH: Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 53: 589-596, 2009.

100. Shear W, Rosner MH: Acute kidney dysfunction secondary to the abdominal compartment syndrome. J Nephrol 19: 556-565, 2006.

101. Chvojka J, Sýkora R, Kroužecký A, Radžj J, Varnerová V, Karvunidis T, Hes O, Novák I, Radermacher P, Matějovič M: Renal haemodynamic, microcirculatory, metabolic and histopathological responses to peritonitis-induced septic shock in pigs. Crit Care 12: R164, 2008.

102. Lugon JR, Boim MA, Ramos OL, Ajzen H, Schor N: Renal function and glomerular hemodynamics in male endotoxemic rats. Kidney Int 36: 570-575, 1989.

103. De vriese AS, Bourgeois M: Pharmacologic treatment of acute renal failure in sepsis. Curr Opin Crit Care 9:474-480, 2003.

104. Simon F, Giudici R, Scheuerle A, Groger M, Asfar P, Vogt JA, Wachter U, Ploner F, Georgieff M, Moller P, Laporte R, Radermacher P, Calzia E, Hauser B: Comparison of cardiac, hepatic, and renal effects of arginine vasopressin and noradrenaline during porcine fecal peritonitis: a randomized controlled trial. Crit Care 13: R113, 2009.

105. Gordon Ac, Russell JA, Walley KR, Singer J, Ayers D, Storms Mm, Holmes CL, Hébert PC, Cooper DJ, Mehta S, Granton JT, Cook DJ, Presneill JJ: The effects of vasopressin on acute kidney injury in septic shock. Intensive Care Med 36: 83-91, 2010.

106. YAMAGUCHI N, JESMIN S, ZAEDI S, SHIMOJO N, MAEDA S, GANDO S, KOYAMA A, MIYAUCHI T: Timedependent expression of renal vasoregulatory molecules in LPS-induced endotoxemia in rat. Peptides 27: 2258-2270, 2006.

107. Matějovič M, Radermacher P, Joannidis M: Acute kidney injury in sepsis: is renal blood flow more than just an innocent bystander? Intensive Care Med 33: 1498-1500, 2007.

108. Hotchkiss RS, Swanson PE, Freeman BD, Tinsley KW, Cobb JP, Matuschak GM, Buchman TG, Karl IE: Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med 27: 1230-1251, 1999.

109. Messmer UK, Briner VA, Pfeilschifter J: Tumor necrosis factor-alpha and lipopolysaccharide induce apoptotic cell death in bovine glomerular endothelial cells. Kidney Int 55: 2322-2337, 1999.

110. Welty-Wolf KE, Carraway MS, Ortel TL, Ghio AJ, Idell S, Egan J, Zhu X, Jiao JA, Wong HC, Piantadosi CA: Blockade of tissue factor-factor X binding attenuates sepsis-induced respiratory and renal failure. Am J Physiol 290: L21-L31, 2006.

111. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13: 818-29.

112. Vincent JL, Moreno R, Takala J, Willatts S, De Mendoca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Medicine 1996; 22:707-10.

113. Davcie JV, Lewis SM. Practical heamatology. 7th ed. London: Churchill Livingston 1991; p. 37-63.

114. Balistreri WF, Rej R. liver function. In Tietz NW, editor. Fundamentals of Clinical Chemistry. 4th ed. Philadelphia: WB Saunder's 2001; p. 543-54.

115. Whelton A, Watson AJ, Rock RC. Nitrogen metabolites and renal function. In Tietz NW, editor. Fundamentals of Clinical Chemistry. 4th ed. Philadelphia: WB Saunder's 2001; p. 575-6

116. David BS. Carbohydrates. In Tietz NW, editor. Fundamentals of Clinical Chemistry. 4th ed. Philadelphia: WB Saunder's 2001; p. 361-5.

117. Pruden EL, Anderson OS, Tietz NW. Blood gases and Ph In Tietz NW, editor. Fundamentals of Clinical Chemistry. 4th ed. Philadelphia: WB Saunder's 2001; p. 506-16.

118. Tietz NW, Pruden EL, Anderson OS. Electrolytes In Tietz NW, editor. Fundamentals of Clinical Chemistry. 4th ed. Philadelphia: WB Saunder's 2001; p. 500-2.

119. Alge JL, Karakala N, Neely BA, Janech MG, Tumlin JA, Chawla LS, et al. Urinary Angiotensinogen and Risk of Severe AKI. Clin JASN 2013; 8:184-93.

120. Kotz S, Balakrishnan N, Read CB, Vidakovic B. Encyclopedia of statistical sciences. 2nd ed. Hoboken, N.J.: Wiley-Interscience; 2006.

121. Kirkpatrick LA, Feeney BC. A simple guide to IBM SPSS statistics for version 20.0. Student ed. Belmont, Calif.: Wadsworth, Cengage Learning; 2013.

122. Honore PM, Joannes-Boyau O, Boer W, Janvier G, Gressens B. Acute kidney injury in the ICU: time has come for an early biomarker kit Acta Clin Belg Suppl 2007; 2: 318–21.

123. Koyner JL, Garg AX, Coca SG, Sint K, Thiessen-Philbrook H, Patel UD, Shlipak MG, Parikh CR, for the TRIBE-AKI Consortium: Biomarkers Predict Progression of Acute Kidney Injury after Cardiac Surgery. J Am Soc Nephrol 2012, 23:905-914.

124. Hall IE, Coca SG, Perazella MA, Eko UU, Luciano RL, Peter PR, Han WK, Parikh CR: Risk of poor outcomes with novel and traditional biomarkers at clinical AKI diagnosis. Clin J Am Soc Nephrol 2011, 6:2740-2749.

125. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992 Jun; 101(6):1644-55.

126. Martin GS, Mannino M, Moss MD. The effect of age on the development and outcome of adult sepsis. Crit Care Med 2006;34: 15-21

127. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348(16):1546-54.

128. van Gestel A, Bakker J, Veraart CP, van Hout BA. Prevalence and incidence of severe sepsis in Dutch intensive care units. Crit Care 2004 Aug;8(4):R153-62.

129. Finfer S, Bellomo R, Lipman J, French C, Dobb G, et al. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med 2004 Apr;30(4):589-96.

130. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B, Network CU-R. Current epidemiology of septic shock: the CUB-Rea Network. Am J Respir Crit Care Med 2003 Jul 15;168(2):165-72.

131. Karlsson S, Varpula M, Ruokonen E, Pettila V, Parviainen I, et al. Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study. Intensive Care Med 2007 Mar;33(3):435-43.

132. Muller LMAJ, Gorter KJ, Hake E, Goudzwaard WL, Schellevis FG, Hoepelman AIM, et al. Increased Risk of Common Infections in patients with type 1 and type2 diabetes mellitus. Clin Infect Dis 2005; 41:281-88

133. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003; 26: 510-13

134. Finfer S, Chittoc DR, Su SY-S, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009; 360: 1283-97

135. Stegenga ME, Vincent J-L, Vail GM, Xie J, Haney DJ, Williams MD, et al. Diabetes Does not Alter Mortality or Hemostatic and Inflammatory Response in Patients with Severe Sepsis. Crit Car Med 2010; 38: 539-45

136. Mayr FB, Yende S, Linde-Zwirble WT, Peck-Palmer OM, Barnato AE, Weissfeld LA, Angus DC. Infection rate and acute organ dysfunction risk as explanations for racial differences in severe sepsis. JAMA 2010; 303:2495 - 503

137. Joseph L Alge, Nithin Karakala, Benjamin A Neely, Michael G Janech, Juan Carlos Q Velez and John M Arthur. Urinary angiotensinogen predicts adverse outcomes among acute kidney injury patients in the intensive care unit. Critical Care 2013;17:R69

APPENDIX (1) [14]

RIFLE and AKIN Criteria for Diagnosis and Classification of AKI

RIFLE			AKIN	
Class	**SCr**	**Urine output (common to both)**	**Stage**	**SCr**
Risk	Increased SCr to ×1.5 baseline	Urine output <0.5 mg/kg/h, For>6 h	**1**	Increase in Cr≥0.3 mg/dL or increase in SCr to >150%-200% of baseline
Injury	Increased SCr to × 2 baseline	Urine output <0.5 mg/kg/h, For >12 hr.	**2**	Increase in SCr to >200%-300% of baseline
Failure	Increased SCr to ×3 baseline; or an increase of ≥0.5 mg/dL to a value of ≥4 mg/dL	Urine output <0.3 mg/kg/h, For>12 h or anuria for >12 h	**3**	Increase in SCr to >300% of baseline; or to ≥4 mg/dL with an acute increase of ≥0.5 mg/dL; or on RRT
loss	Need for RRT for >4 wk.			
End stage	Need for RRT for >3 mo.			

RIFLE: Risk, Injury, Failure, Loss, End stage
AKIN: Acute Kidney Injury staging
AKI: Acute Kidney Injury
SCr.: Serum Creatinine
RRT: Renal Replacement Therapy

APPENDIX (2) [14]

ACUTE KIDNEY INJURY SCORE

Stage	Serum creatinine	Urine output
1	1.5 to 1.9 times baseline *or* ≥0.3 mg/dl (≥26.5 µmol/l) increase	<0.5 ml/kg/hour for 6 to 12 hours
2	2.0 to 2.9 times baseline	<0.5 ml/kg/hour for ≥12 hours
3	3.0 times baseline *or* increase in serum creatinine to ≥4.0 mg/dl (≥353.6 µmol/l) *or* initiation of renal replacement therapy *or* in patients <18 years a decrease in e GFR to <35 ml/minute per 1.73 m^2	<0.3 ml/kg/hour for ≥24 hours *or* anuria for ≥12 hours
E GFR, estimated glomerular filtration rate		

APPENDIX (4)[111]

ACUTE PHYSIOLOGIC ASSESSMENT AND
Chronic Health Evaluation (APACHE) II Scoring System

Physiologic Variable	High Abnormal Range					Low Abnormal Range				
	+4	+3	+2	+1	0	+1	+2	+3	+4	Points
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO$_2$**or** PaO$_2$ (mm Hg) a. FIO$_2$ ≥0.5 record A-aDO2 b. FIO$_2$ <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

Interpretation of Score:

Score	DeathRate (%)
0-4	4
5-9	8
10-14	15
15-19	25
20-24	40
25-29	55
30-34	75
>34	85

APPENDIX (5) [112]

Sofa score

Organ system	1	2	3	4
Respiratory PaO_2/FiO_2, (mmHg)	<400	<300	<200	<100
Hematologic Platelets/ nl	<150	<100	<50	<20
Hepatic Bilirubin, mg/dl (µmol/l)	1,2–1,9 (20–32)	2,0–5,9 (33–101)	6,0–11,9 (102–204)	>12,0 (>204)
Cardiovascular Hypotension	MAP[2] <70 mmHG	Dopamine ≤ 5[1] or dobutamine (any dose)	Dopamine >5 or epinephrine ≤0,1[1] or Norepinephrine ≤0,1[1]	Dopamine >15 epinephrine > 0 or norepinehrine 0,1
Neurologic Glasgow Coma Score	13–14	10–12	6–9	<6
Renal Creatinine, mg/dl (µmol/l) urine output	1,2–1,9 (110–170)	2,0–3,4 (171–299)	3,5–4,9 (300–440) <500 ml/day	>5,0 (>440) <200 ml/day

Sequential Organ Failure Assessment

The SOFA score is a scoring system to determine the extent of a person's organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems.

Both the mean and highest SOFA scores being predictors of outcome. An increase in SOFA score during the first 24 to 48 hours in the ICU predicts a mortality rate of at least 50% up to 95%. Scores less than 9 give predictive mortality at 33% while above 11 can be close to or above 95%

الملخص العربي

الانجيوتينسينوجين في البول كمتنبئ محتمل للقصور الكلوي الحاد في التعفن الشديد

ان القصور الكلوي الحاد هو من المضاعفات المتكررة والخطيرة للتسمم في مرضى وحدة العناية المركزة وعلاوة على ذلك ، هناك أدلة قوية على أن التعفن والصدمة التعفنيه هي أهم أسباب القصور الكلوي الحاد في المرضى ذوي الحالات الحرجة ، مسؤولة عن ٥٠ ٪ أو أكثر من حالات القصور الكلوي الحاد في العناية المركزه .

لذلك ، فالتنبؤ المبكر بحالات القصور الكلوي لحاد في مرضي العنايه المكثفه أمر بالغ الأهمية، وذلك باستخدام المؤشرات الحيوية المبكره مثل مستوى الأنجيوتنسينوجين البولي الذي يرتبط مع مستويات الأنجيوتنسين داخل الكلية و الأنجيوتنسين٢ الذين يلعبوا دورا رئيسيا في الآليات الجزيئية للقصور الكلوي الحاد.

وكان الهدف من هذا العمل هو تقييم دور الأنجيوتنسينوجين البولي باعتباره متنبئ محتمل للقصور الكلوي الحاد في المرضى الذين يعانون من التسمم الحاد.

أجرينا دراسة وصفية مستقبلية خلال الفترة من يناير ٢٠١٤ إلى ديسمبر ٢٠١٤علي مائه(١٠٠) من المرضى البالغين من الجنسين الذين يعانون من التسمم الحاد، وتم تصنيف المرضى إلى مجموعتين وفقا لتطورالقصور الكلوي الحاد. المجموعة الغير المصابه بالقصور الكلوي الحاد التي تتألف من ٣٠ مريضا (المجموعة الأولى)، والمجموعة المصابه بالقصور الكلوي الحاد التي تتألف من ٧٠ مريضا (المجموعة الثانية). وأدرج في الدراسة المرضى الذين كان لديهم معايير تعفن الدم الحاد واستبعد الذين كان لديهم مرض مزمن في الكلى او يتلقوا استبدال العلاج الكلوي أو لديهم صدمه التعفن .

وكانت المجموعة الأولى و المجموعة الثانية متجانسة من حيث الحجم و الخصائص الديموغرافية و الظروف الموجودة مسبقا ، و موقع الإصابة مع عدم وجود فروق ذات دلالة إحصائية بينهما. و بعد أخذ الموافقة المسبقة من كل مريض أو من ذوي القربي، تم أخذ التاريخ المرضي المفصل والفحص السريري الكامل و التحاليل المعمليه الشامله لكل المرضي لتأكيد التشخيص من التعفن الشديد.

وتم سحب عينه الأنجيوتنسينوجين و الكرياتينين البولي مرة واحدة من كل مريض في يوم دخول المستشفي وذلك لحساب نسبه الأنجيوتنسينوجين البولي/ الكرياتينين البولي (نانوغرام / ملغ) و مقارنتها مع مستوي الكرياتينين في الدم التي تسحب يوميا .

وفي النهايه أثبتت نتائج هذه الدراسة أن:

- هناك ارتباط كبير بين المجموعات المدروسة ونسبه الأنجيوتنسينوجين البولي / الكرياتينين البولي ، في حين لم يكن هناك أي دلاله إحصائيه بين المجموعات المدروسه و الكرياتينين في البلازما.
- وعلاوة على ذلك ، كان هناك ارتباط إيجابي بين نسبه الأنجيوتنسينوجين البولي/ الكرياتينين البولي و تطور الاصابه بالقصور الكلوي الحاد و مستوى الكرياتينين بالبلازما لجميع المرضي في جميع في الأيام المتابعة، مع أعلى ارتباط في اليوم الخامس من متابعة .
- وعلي الصعيد الاخر بالنسبه للمجموعة الثانية (التي تطورت لقصور كلوي حاد) ، لم تتنبأ نسبه الأنجيوتنسين البولي / الكرياتينين بحاجة المرضي لعلاجات لرفع الضغط أو زيادة مدة الإقامة في المستشفى لأكثر من ٧ أيام، ولكنها تنبأت ايجابيا بحاجة المرضي لعلاج كلوي بديل و بحالات الوفاه من بين مرضي القصور الكلوي.

وبحلول نهاية هذه الدراسة، وصلنا إلى استنتاج مفاده أن الأنجيوتنسينوجين البولي ليس فقط من العلامات البيولوجية الواعدة جديدة في التنبؤ المبكر بمرضى القصور الكلوي الحاد لذوي التسمم الحاد ولكن أيضا يمكن استخدامه للتنبؤ بالنتائج بين هؤلاء المرضى .

جامعة الإسكندرية
كلية الطب
قسم الطب الحرج

الانجيوتينسينوجين في البول كمتنبئ محتمل للفشل الكلوي الحاد في التعفن الشديد

رسالة

مقدمة لقسم الطب الحرج
كلية الطب - جامعة الإسكندرية
ضمن متطلبات درجة

الماجستير فى الطب الحرج

من

محمد ابراهيم عبد الحميد محمد
بكالوريوس الطب والجراحة ، ٢٠٠٧

كلية الطب
جامعة الإسكندرية

٢٠١٥

المشــرفــون

و/ أحمد فتحي القريعي

أستاذ مساعد الامراض الباطنه
قسم الأمراض الباطنة
كلية الطب- جامعة الإسكندرية

و/تامر عبد الله حلمى

أستاذ مساعد الطب الحرج
قسم الطب الحرج
كلية الطب- جامعة الإسكندرية

المشرفان المشاركان

و/سمير محمد العوضى

مدرس الطب الحرج
قسم الطب الحرج
كلية الطب- جامعة الإسكندرية

و/ إيمان طايع السيد

مدرس الباثولوجيا الاكلينيكة والكيميائيه
قسم الباثولوجيا الاكلينيكة والكيميائيه
كلية الطب- جامعة الإسكندرية