score for the development of critical illness during hospitalization may be useful to help identify patients with severe sepsis (13). In addition, some have proposed point-of-care lactate testing to assist EMS providers in diagnosing severe sepsis (14).

Once recognized, several interventions may be effective in improving the care of patients with severe sepsis. A first step would be to institute prenotification, rapid transport, and an associated mobilization of ED resources. Although this would require further study, experience from other time-sensitive conditions strongly suggests that improved timeliness-of-care processes should be effective. Other potentially time-saving interventions may include pre-hospital intravenous access, volume resuscitation, intravenous antibiotics, and the initiation of vasopressor therapy. However, overly aggressive volume resuscitation without close hemodynamic monitoring may be harmful (15), highlighting the need to properly study pre-hospital interventions before they are routinely implemented. In addition, delay in transport for pre-hospital interventions should be closely monitored. Seymour and colleagues reported long average on-scene times (35 min), compared with just 12.6 min for scene-to-hospital times. The potential for unintended consequences, such as adverse outcomes for pre-hospital endotracheal intubation in select patients, has sometimes favored basic interventions with rapid transport over more advanced interventions, especially when scene-to-hospital times are short (16).

Because novel therapies for severe sepsis have largely been unsuccessful and in-hospital mortality remains 20–30%, our attention must continue to focus on optimizing delivery and timeliness of the basic interventions that do work. Randomized controlled trials of pre-hospital protocols and interventions would be ideal to assess potential benefits in improving outcomes, but the feasibility of such trials can be limited by time constraints, informed consent, and other logistical challenges. Alternatively, pre-hospital research might be suitable to other study designs, including quasi-experimental and natural experimental designs, and advanced analytic techniques such as propensity score matching and instrumental variable analysis.

Although the verdict is still out on whether EMS providers can reliably detect severe sepsis and which interventions may improve outcomes, Seymour and colleagues have highlighted an important issue that clearly deserves further attention.

Author disclosures are available with the text of this article at www.atsjournals.org.

Adit A. Ginde, M.D., M.P.H.
Department of Emergency Medicine
University of Colorado School of Medicine
Aurora, Colorado

Marc Moss, M.D.
Department of Medicine
University of Colorado School of Medicine
Aurora, Colorado

References

1. Eisenberg MS, Bergner L, Hallstrom A. Out-of-hospital cardiac arrest: improved survival with paramedic services. *Lancet* 1980;1:812–815.
2. Cwinn AA, Pons PT, Moore EE, Marx JA, Honigman B, Dinerman N. Prehospital advanced trauma life support for critical blunt trauma victims. *Ann Emerg Med* 1987;16:399–403.
3. Brown JP, Mahmud E, Dunford JV, Ben-Yehuda O. Effect of prehospital 12-lead electrocardiogram on activation of the cardiac catheterization laboratory and door-to-balloon time in ST-segment elevation acute myocardial infarction. *Am J Cardiol* 2008;101:158–161.
4. Lin CB, Peterson ED, Smith EE, Saver JL, Liang L, Xian Y, Olson DM, Shah BR, Hernandez AF, Schwamm LH, *et al*. Emergency medical service hospital prenotification is associated with improved evaluation and treatment of acute ischemic stroke. *Circ Cardiovasc Qual Outcomes* 2012;5:514–522.
5. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–1377.
6. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, Shofer FS, Goyal M. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010;38:1045–1053.
7. Nguyen HB, Corbett SW, Steele R, Banta J, Clark RT, Hayes SR, Edwards J, Cho TW, Wittlake WA. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 2007;35:1105–1112.
8. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, *et al*. The surviving sepsis campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010;38:367–374.
9. Seymour CW, Rea TD, Kahn JM, Walkey AJ, Yealy DM, Angus DC. Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome. *Am J Respir Crit Care Med* 2012;186:1264–1271.
10. Herlitz J, Bang A, Wireklint-Sundstrom B, Axelsson C, Bremer A, Hagiwara M, Jonsson A, Lundberg L, Suserud BO, Ljungstrom L. Suspicion and treatment of severe sepsis: an overview of the prehospital chain of care. *Scand J Trauma Resusc Emerg Med* 2012;20:42.
11. Studnek JR, Artho MR, Garner CL Jr, Jones AE. The impact of emergency medical services on the ED care of severe sepsis. *Am J Emerg Med* 2012;30:51–56.
12. Baez AA, Hanudel P, Wilcox SR, Perez MT, Giraldez EM. Prehospital sepsis project: knowledge and attitudes of United States advanced out-of-hospital care providers. *Prehosp Disaster Med* 2010;25:41–43.
13. Seymour CW, Kahn JM, Cooke CR, Watkins TR, Heckbert SR, Rea TD. Prediction of critical illness during out-of-hospital emergency care. *JAMA* 2010;304:747–754.
14. Shapiro NI, Fisher C, Donnino M, Cataldo L, Tang A, Trzeciak S, Horowitz G, Wolfe RE. The feasibility and accuracy of point-of-care lactate measurement in emergency department patients with suspected infection. *J Emerg Med* 2010;39:89–94.
15. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011;39:259–265.
16. Strote J, Roth R, Cone DC, Wang HE. Prehospital endotracheal intubation: the controversy continues (conference proceedings). *Am J Emerg Med* 2009;27:1142–1147.

DOI: 10.1164/rccm.201210-1895ED

Obesity Hypoventilation Syndrome: An Underdiagnosed and Undertreated Condition

Grenoble and Geneva groups are supported by unrestricted grants from the scientific council of AGIR à dom, a French home care provider (www.agiradom.com/), and the Pulmonary League of Geneva (www.lpge.ch).

Obesity hypoventilation syndrome (OHS) is defined as a combination of obesity (body mass index ≥ 30 kg/m^2), daytime hypercapnia ($Pa_{CO_2} \leq 45$ mm Hg) and sleep-disordered breathing after

ruling out other disorders that may cause alveolar hypoventilation. It is a chronic disease associated with respiratory and cardiometabolic impairments leading to a decrease in activities of daily life and social involvement, increased health-related costs, and higher risks of hospitalization and death (1, 2). Despite its established severity compared with eucapnic obesity, OHS is largely underrecognized, with only one-third of patients actually diagnosed when hospitalized for acute-on-chronic respiratory failure (3–6). In this issue of the *Journal*, Carrillo and colleagues (pp. 1279–1285) describe the outcomes of 173 patients treated by noninvasive ventilation (NIV) for acute hypercapnic respiratory failure (AHRF) due to obesity hypoventilation (7). Only 9% of them were chronically treated at home by continuous positive airway pressure (CPAP)/NIV prior to admission, although 65% had already been admitted to an intensive care unit (ICU), probably for similar episodes of AHRF. These data emphasize the importance of a better awareness of OHS and systematic screening for hypercapnia in patients with obesity, particularly in primary care settings and obesity clinics. A sensitive and inexpensive marker in obese patients is serum bicarbonate: a level greater than 27 mmol/L is associated with a high prevalence of OHS and should lead to the patient's referral to a respiratory physician (2). Early diagnosis is a crucial issue. Patients in whom NIV is initiated in acute conditions are more likely to have developed OHS-related cardiovascular complications, thus increasing the risk of multiple organ failure and death at the time of acute respiratory failure (5, 6).

There are no randomized controlled trials and very few well-designed studies addressing the question of efficacy of NIV in AHRF due to OHS. Available studies are retrospective and/or case studies including a limited numbers of patients. These studies, aiming to demonstrate the impact of NIV on mortality, included patients for whom NIV was initiated both in acute and chronic settings, which clearly correspond to distinct OHS phenotypes. Results cannot be extrapolated to an outcome analysis based on strict criteria of AHRF leading to ICU referral. Carrillo and colleagues prospectively assessed 716 consecutive patients (173 with OHS and 543 with chronic obstructive pulmonary disease [COPD]) with AHRF (7). NIV success was defined as avoidance of intubation and ICU survival at least 24 hours in the ward. Hospital survivors were followed for 1 year to assess hospital readmission rate and survival. This prospective study is by far the largest study in the field. Compared with COPD for whom NIV represents standard care in AHRF (8), patients with OHS exhibited less late NIV failure (7% vs. 13%, $P = 0.037$), less readmission to the ICU, and lower hospital and ICU mortality (6% vs. 18%, $P < 0.001$). Patients with OHS are thus clearly responsive to NIV. The pathophysiology of OHS results from complex interactions between various sleep breathing disorders (i.e., obstructive sleep apnea [OSA] and REM sleep hypoventilation), increased work of breathing as a result of a decreased thoracoabdominal compliance, and altered ventilatory drive. All these mechanisms are successfully addressed by NIV, and patients

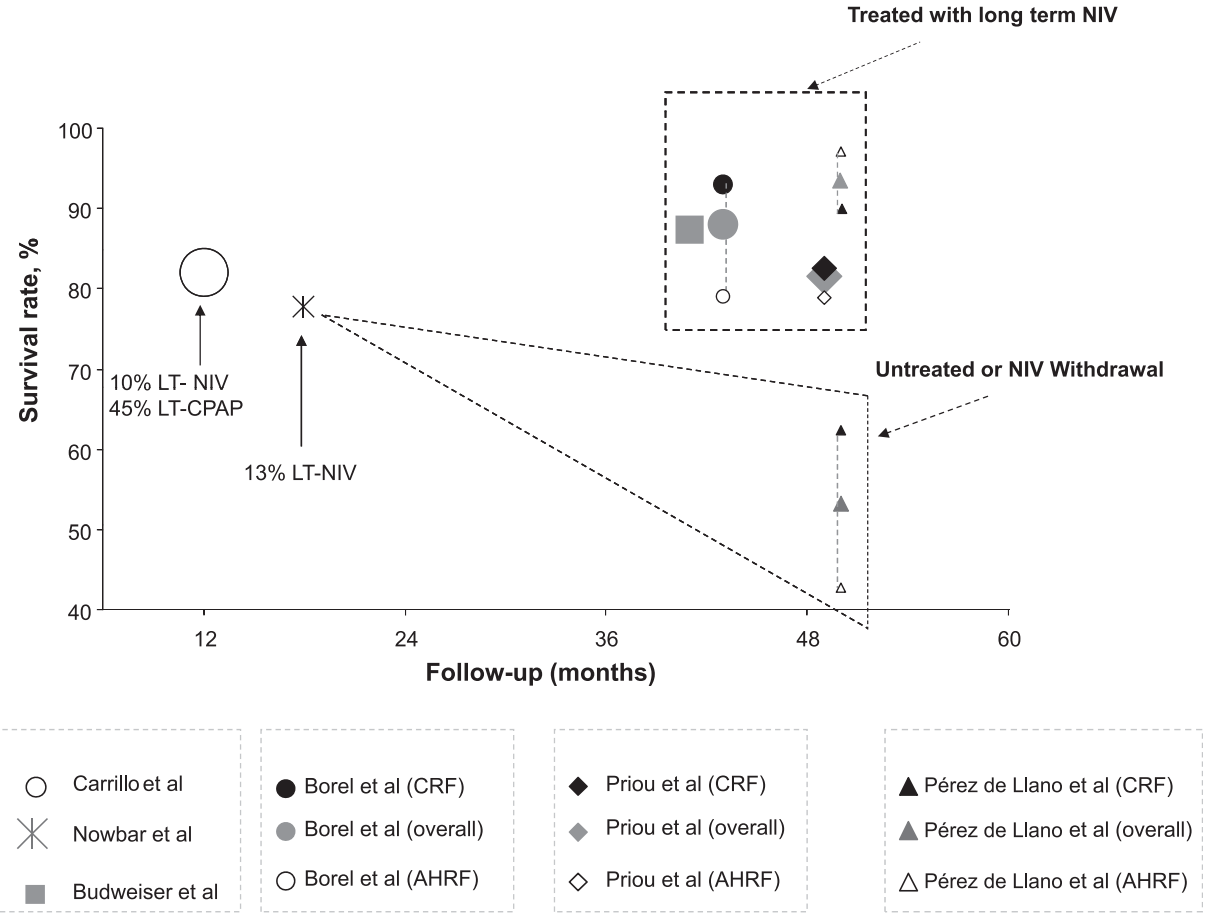

Figure 1. Survival rate in patients with obesity hypoventilation syndrome according to the condition of noninvasive ventilation (NIV) initiation and the long-term treatment with or without NIV. For the studies of Budweiser and colleagues (14), Priou and colleagues (6), Pérez de Llano and colleagues (5), and Borel and colleagues (13), survival rates are plotted at the mean observation time reported in each study. *Symbols in white*: NIV initiated in AHRF; *symbols in black*: NIV initiated in stable CRF; *symbols in gray*: NIV initiated in both conditions (AHRF + CRF). The size of the symbols is proportional to the sample size of the studies. AHRF = acute hypercapnic respiratory failure; CRF = chronic respiratory failure.

with OHS were even more effectively treated for their AHRF than are patients with COPD.

There are, however, a few unexpected findings in the study by Carrillo and coworkers. First, the investigators applied a similar protocol to titrate NIV pressure support in COPD and in patients with OHS. The bilevel positive airway pressure devices used in the study deliver adjustable inspiratory and expiratory positive airway pressure (EPAP). In OHS, 80 to 90% of the patients have associated obstructive sleep apnea, and EPAP levels are adjusted to maintain upper airway patency and to abolish obstructive events during sleep. For these patients, typical EPAP pressures range between 8 and 12 cm H_2O (9). In patients with COPD, OSA is not more frequent than in the general population, and titration of EPAP in acute conditions aims to counteract intrinsic positive end-expiratory pressure at values that do not usually exceed 6 to 8 cm H_2O (10). It is unclear, therefore, why the titration protocol was exactly the same for both groups of patients in the study by Carrillo and colleagues. Among patients with COPD included, 33.9% were obese, and 28% had associated OSA ("overlap syndrome"), which probably explains why the same titration protocol was in fact effective. Second, although in hospital mortality was lower in OHS, both 1-year adjusted survival and readmission rate following AHRF were similar to that of patients with COPD. The authors state that decisions as to long-term care were left to the attending physicians. However, only 55% of patients with OHS studied were put on a long-term positive pressure ventilatory support (CPAP or NIV) at home, and a very low 10% were treated by NIV. This is unexpected and probably not appropriate. Clinical guidelines and consensus statements recommend long-term NIV use in patients with OHS. Open studies show that long-term NIV for OHS suppresses respiratory events during sleep, normalizes sleep structure, and restores daytime vigilance (11, 12). Much higher survival rates (1-yr survival above 90%) have been reported for patients with OHS treated by NIV (4–6, 13, 14) (Figure 1), potentially explained by a decrease in incident cardiovascular events, and when comparative data were available, survival was much higher than for patients with COPD treated by NIV. Survival data from the study by Carrillo and coworkers are similar to those reported by Nowbar and colleagues (4) in untreated patients with OHS (Figure 1). This strongly suggests that long-term NIV should be systematically proposed at home after an acute-on-chronic failure in patients with OHS. Oxygen therapy alone is not appropriate when taking into account the underlying mechanisms for hypoventilation in OHS (15) but remains overused as demonstrated by the 39% of patients with OHS on long-term oxygen therapy before their admission for ARHF in the study by Carrillo and colleagues. After an acute respiratory failure, patients with OHS should be reevaluated on a regular basis. When normalization of Pa_{CO_2} and resetting of the respiratory centers is achieved by NIV, a proportion of OHS could be protected from respiratory failure by the use of simple CPAP therapy. ICU and respiratory physicians should favor the implementation of clinical pathways allowing an easy transition from ICU to home NIV treatment.

CONCLUSIONS

The study by Carrillo and colleagues shows that better screening for patients with OHS is necessary to reduce the delay of NIV initiation and avoid acute-on-chronic respiratory failure. NIV appears at least as effective in acute conditions as in COPD. A step forward would be to improve the link between the acute initiation of NIV and long-term care. OHS requires a multimodal therapeutic approach including home NIV/CPAP, rehabilitation programs with physical training, weight loss, lifestyle changes, and appropriate medication to further control cardiovascular risk factors.

Author disclosures are available with the text of this article at www.atsjournals.org.

Jean-Louis Pépin, M.D., Ph.D.
INSERM U 1042
CHU de Grenoble
Grenoble, France

Jean-Christian Borel, Ph.D.
Research and Development Department
AGIR à dom
Meylan, France

Jean-Paul Janssens, M.D.
Division of Pulmonary Diseases
Geneva University Hospitals
Geneva, Switzerland

References

1. Jennum P, Kjellberg J. Health, social and economical consequences of sleep-disordered breathing: a controlled national study. *Thorax* 2011; 66:560–566.
2. Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. *Respir Care* 2010;55:1347–1362, discussion 1363–1365.
3. BaHammam A, Syed S, Al-Mughairy A. Sleep-related breathing disorders in obese patients presenting with acute respiratory failure. *Respir Med* 2005;99: 718–725.
4. Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, Taylor MR, Zwillich CW. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *Am J Med* 2004;116:1–7.
5. Pérez de Llano LA, Golpe R, Ortiz Piquer M, Veres Racamonde A, Vazquez Caruncho M, Caballero Muinelos O, Alvarez Carro C. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. *Chest* 2005;128:587–594.
6. Priou P, Hamel JF, Person C, Meslier N, Racineux JL, Urban T, Gagnadoux F. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. *Chest* 2010;138:84–90.
7. Carrillo A, Ferrer M, Gonzalez-Diaz G, Lopez-Martinez A, Llamas N, Alcazar M, Capilla L, Torres A. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:1279–1285.
8. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ* 2003;326:185.
9. Murphy PB, Davidson C, Hind MD, Simonds A, Williams AJ, Hopkinson NS, Moxham J, Polkey M, Hart N. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. *Thorax* 2012;67:727–734.
10. Girault C, Chevron V, Richard JC, Daudenthun I, Pasquis P, Leroy J, Bonmarchand G. Physiological effects and optimisation of nasal assist-control ventilation for patients with chronic obstructive pulmonary disease in respiratory failure. *Thorax* 1997;52:690–696.
11. Borel JC, Tamisier R, Gonzalez-Bermejo J, Baguet JP, Monneret D, Arnol N, Roux-Lombard P, Wuyam B, Levy P, Pepin JL. Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. *Chest* 2012;141:692–702.
12. Chouri-Pontarollo N, Borel JC, Tamisier R, Wuyam B, Levy P, Pepin JL. Impaired objective daytime vigilance in obesity-hypoventilation syndrome: impact of noninvasive ventilation. *Chest* 2007;131:148–155.
13. Borel J, Burel B, Tamisier R, Dias-Domingos S, Baguet J, Levy P, Pépin J. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. *PLoS ONE* (In press)
14. Budweiser S, Riedl SG, Jorres RA, Heinemann F, Pfeifer M. Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. *J Intern Med* 2007;261:375–383.
15. Wijesinghe M, Williams M, Perrin K, Weatherall M, Beasley R. The effect of supplemental oxygen on hypercapnia in subjects with obesity-associated hypoventilation: a randomized, crossover, clinical study. *Chest* 2011;139:1018–1024.

DOI: 10.1164/rccm.201210-1922ED