Review

Year in review 2007: Critical Care - intensive care unit management

Clayton Barbieri¹, Shannon S Carson² and André Carlos Amaral¹

¹Critical Care Department, Hospital Brasília (ESHO), SHIS QI 15 Cj G, Brasília, DF, 71635-200, Brazil

²Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of North Carolina, 4134 Bioinformatics Building, CB# 7020, Chapel Hill, NC 27599-7020, USA

Corresponding author: André Carlos Kajdacsy-Balla Amaral, amaral@hobra.com.br

Published: 14 October 2008

This article is online at http://ccforum.com/content/12/5/229

© 2008 BioMed Central Ltd

Critical Care 2008, 12:229 (doi:10.1186/cc6951)

Abstract

With the development of new technologies and drugs, health care is becoming increasisngly complex and expensive. Governments and health care providers around the world devote a large proportion of their budgets to maintaining quality of care. During 2007, *Critical Care* published several papers that highlight important aspects of critical care management, which can be subdivided into structure, processes and outcomes, including costs. Great emphasis was given to quality of life after intensive care unit stay, especially the impact of post-traumatic stress disorder. Significant attention was also given to staffing level, optimization of intensive care unit capacity, and drug cost-effectiveness, particularly that of recombinant human activated protein C. Managing costs and providing high-quality care simultaneously are emerging challenges that we must understand and meet.

Introduction

With the development of new technologies and drugs, health care is becoming increasingly complex and expensive. Governments and health care providers around the world devote a large proportion of their budgets to maintaining quality of care. Growing concern over patient care and safety has prompted initiatives such as The 5 Million Lives Campaign, a voluntary initiative to protect patients from 5 million incidents of medical harm between December 2006 and December 2008 [1]. With the dawn of a new era focusing on quality and patient safety, the responsibility for overseeing quality is more clearly recognized as a priority for health care organizations.

One must measure to control, and one must control to manage [2]. This is the mainstay of quality, and therefore indicators (units of measurement) must be identified for each management situation. However, these indicators must be well understood and must focus on the primary outcomes of interest. If one evaluates the wrong factors along the way, then unexpected

and misleading results may emerge [3]. We therefore structured this review of last year's *Critical Care* papers related to intensive care unit (ICU) management, dividing them into the primary categories of structure and processes, naturally leading on to outcomes, including cost issues.

Structure

Structure includes the physical aspects of the ICU, biomedical equipment (beds, monitors, ventilators and other devices) and how the multidisciplinary team is organized. Organization includes both quantity and quality of staffing, and the leadership taken by the ICU medical team regarding medical decisions (for instance, open versus closed units).

Availability of technology alone does not assure quality of care. Manpower (staffing level) appears to be a fundamental component, as indicated by Hugonnet and colleagues [4]. In their prospective cohort study, the fourth quartile of nurse-to-patient ratio (>2.2) was associated with lower risk for late-onset ventilator-associated pneumonia (hazard ratio = 0.42, 95% confidence interval = 0.18 to 0.99). This observation is consistent with various adverse factors associated with reduced staffing that can lead to inadequate care in ventilated patients: multiple opportunities for cross-contamination, increased workload, low compliance with hand hygiene recommendations and a stressful environment. During the period of study, the median nurse-to-patient ratio was 1.9 (interquartile range 1.8 to 2.2) [4,5].

In general, the ideal nurse-to-patient ratio is difficult to estimate, given the heterogeneity of data reported in the literature [6-8] and wide variation in local policies and practices. There is a growing need for further research specifically examining relationships between staffing models and outcomes.

APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; LOS = length of stay; PMV = prolonged mechanical ventilation; PTSD = post-traumatic stress disorder; QoL = quality of life; RBC = red blood cell; rhAPC = recombinant human activated protein C.

An interesting safety issue in ICU care was the focus of a study by van Lieshout and colleagues [9], namely the impact of electromagnetic interference by next-generation mobile phones on critical care medical equipment. Episodes of electromagnetic interference were identified in 43% of 61 critical care medical devices, and 33% of these episodes were classified as hazardous (total switch off and restart of a mechanical ventilator, complete stop of syringe pumps without alarm, and incorrect pulsing by external pacemaker). van Lieshout and colleagues recommend a policy of keeping mobile phones at least 1 m from the critical care bedside, combined with easily accessed areas in which mobile phone use is unrestricted.

Processes

Processes may be understood as specific approaches to the delivery of health care, and these areas are important targets for quality improvement in the ICU. Approaches to process improvement include (but are not limited to) use of protocols and care bundles, and capacity optimization.

Issues related to rationing of ICU care are gaining attention in the literature [10-12]. Rationing may be defined as allocation of health care resources in the face of limited availability, which necessarily means that beneficial interventions are withheld from some individuals [11]. Some studies conducted in ICUs have documented high rates of refusal to admit because of lack of available beds [13,14]. This is a discussion that leads to numerous ethical conflicts and to a need to identify ways to optimize ICU capacity. In a retrospective study conducted at Erasmus University Medical Center, The Netherlands, Van Houdenhoven and coworkers [15] created and validated three models that incorporate characteristics of individual patients who underwent oesophagectomy for cancer to predict length of stay (LOS) in the ICU. The authors concluded that it is possible to predict LOS and optimize ICU occupancy, yielding more efficient use of ICU beds and better quality of care as a result of fewer cancellations of surgical procedures. However, the best model used data acquired during the first 72 hours of ICU admission, which limits its use before procedures have been applied.

Evidence-based protocols are known to minimize errors and adverse effects, but even simple procedures, such as taking a conservative approach to red blood cell (RBC) transfusions, are difficult to implement and strongly influenced by physicians' personal convictions [16]. Understanding the adverse effects of a procedure may be important in justifying unit protocols that restrict its use. A secondary analysis of a multicentre, prospective cohort of critically ill patients [17] indicated that RBC transfusion is associated with an increased risk for developing acute respiratory distress syndrome (ARDS), with a dose-response relationship. Among 4,730 patients without ARDS at admission, 246 (5.2%) developed ARDS in the ICU. On average, patients developing ARDS received significantly more blood than did

control patients (3.8 units versus 1.8 units per patients transfused; P < 0.0001), and there was a significant association between RBC transfusion and ARDS development (adjusted odds ratio = 2.8), with a clear dose-response relationship. The likely cause and effect relationship between RBC transfusion and ARDS is supported by the TRICC (Transfusion Requirements in Critical Care) study [18], which compared a conservative (7 g/dl) versus a liberal (10 g/dl) transfusion threshold. This study identified a 7.7% incidence of ARDS with the conservative threshold versus 11.4% with the liberal threshold (P = 0.06).

Outcomes

The final point in the quality improvement process is to describe the results, in terms of the primary outcomes. There are many important outcomes critical care, including mortality and LOS, but other factors are receiving research attention. These include quality of life (QoL) outcomes after ICU discharge (including functional and psychosocial recovery) [19] and cost. Indeed, the concept of value is related to providing the best possible quality at the lowest possible cost. Therefore, when two ICUs provide the same level of care, the most valuable one is that which is least expensive.

Modelling mortality has been used for many years in critical care [20-23] for benchmarking, process improvement and standardizing illness severity in clinical studies. An interesting report by Hofhuis and colleagues [24] explored the influence of QoL before ICU admission, assessed using the 36-item Short Form questionnaire, in terms of predicting mortality. Those investigators followed a prospective cohort in a university-affiliated teaching hospital and compared the ability of 36-item Short Form components to predict 6-month mortality as compared with that of the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system. The authors concluded that pre-admission health-related QoL in critically ill patients is as good as APACHE II scores in predicting 6-month mortality. The models studied were more specific (81% to 84%) than sensitive (44% to 56%) [24], similar to other validated scoring systems [25]. However, the models did not meet standard thresholds for discrimination, because all areas under the receiver operating characteristic curves were under 0.80. Several limitations were noted: the APACHE II system was intended for use in predicting inhospital mortality and not long-term mortality, and only patients with an ICU stay longer than 48 hours were included. Finally, it is unclear how accurate proxy assessments of preadmission health-related QoL are, especially for items relating to mental health function.

Whether advances in acute care can be translated into long-term benefits remains unclear, especially in chronically critically ill patients. In a retrospective observational study conducted in Germany, Hartl and colleagues [26] analyzed changes in acute and long-term mortality in surgical patients with an ICU stay longer than 28 days. The overall ICU survival

rate was 54%, with survival rates at 1, 3 and 5 years of 62%, 45% and 37%, respectively, among ICU survivors. This study showed that acute mortality is determined by disease severity during the ICU stay and by pre-existing illnesses, whereas long-term survival mostly depends on underlying disease. Age was a significant factor in both analyses. Interestingly, the authors were also able to demonstrate that both acute and long-term outcomes in this specific population did not differ over 2 decades in their institution, which is in contrast to several other studies that showed improved outcomes over time in populations of patients with severe sepsis [27,28].

Prolonged mechanical ventilation (PMV) is an important outcome in critical care because of the associated resource utilization. However, clear definitions for PMV and chronic critical illness have been lacking in the literature. In a prospective cohort of 817 patients mechanically ventilated for 48 hours or more, of whom 293 were PMV patients, Cox and coworkers [29] compared 1-year health outcomes (survival, functional status, QoL and hospital costs) between two common PMV definitions. These definitions were ventilation for ≥21 days in total, with ventilation discontinued for no more than 48 hours; and diagnosis-related group 541 and 542, involving mechanical ventilation for more than 96 hours and a tracheostomy. They also compared outcomes between PMV patients and those ventilated for shorter periods of time. The investigators found that PMV defined as mechanical ventilation for ≥21 days more specifically identified those who are outliers in terms of resource consumption from among ventilated patients. One-year mortality in patients ventilated for longer than 21 days was similar to that in patients receiving mechanical ventilation for shorter periods. Between the two PMV definitions, the one using diagnosis-related group 541/542 selects those patients who have lower illness severity, lower mortality and lower hospital costs, as compared with the definition involving ≥21 days of mechanical ventilation. PMV patients experienced persistent ICU-associated functional disability, at great cost.

Patients who survive critical illness often report poor QoL and exhibit symptoms of post-traumatic stress disorder (PTSD) [30]. Studies conducted in long-term survivors of ICU treatment identified clear and vivid recall of various categories of traumatic memory, such as nightmares, anxiety, respiratory distress, or pain, with little or no recall of factual events. A high number of these traumatic memories from the ICU have been shown to be a significant risk factor for later development of PTSD in long-term survivors [19]. The relationship between critical illness and PTSD has been assessed in few studies over the past decade, with reported prevalence rates ranging from 5% to 63%. The highest prevalence rates were reported in small studies, and loss to follow up ranged from 10% to 70% [31]. In a cohort of 100 patients with secondary peritonitis, of whom 61 were admitted to the ICU, the overall prevalence of long-term PTSD using Post-Traumatic Stress Syndrome-10 questionnaires was 24% [32]. ICU admission per se was significantly associated with PTSD after controlling for other factors related to PTSD (age, sex and APACHE II score). Older age and male sex were associated with a lower incidence of PTSD [32,33], whereas higher APACHE II score, mechanical ventilation [32] and administration of higher doses of lorazepam [33] were associated with a greater incidence. Although the latter could either indicate causation or simply be a marker for acute anxiety, long-term follow up of a randomized study of daily interruption to sedation [34] indicated that this strategy may decrease PTSD symptoms. In an era in which mental health professionals are beginning to recognize the significant costs [35] associated with this psychiatric syndrome, understanding the relationship between critical illness and PTSD is a challenge that demands attention and better designed studies [31].

ICU organization and pathology-specific volume of patients may influence outcome [36]. Several studies tried to identify the volume-outcome relationship in ICU patients [37,38]. Some failed to identify any such relationship [39], but others such as a retrospective cohort study from The Netherlands [40] - found important associations. They studied mortality among 4,605 patients with severe sepsis admitted to 28 different ICUs, and they found that a higher annual volume is associated with lower in-hospital mortality in this group of patients (odds ratio = 0.970, 95% confidence interval = 0.943 to 0.997; P = 0.029); the upper quartile of sepsis admissions was 96 patients/year and, compared with the lower quartile (38 patients/year), the absolute risk for inhospital mortality was 3% to 4% lower. Interestingly, this study also demonstrated a higher risk for in-hospital mortality when step-down units were present in hospitals; this finding warrants further study. Adequate structure [41] and staffing levels [4-8], and well established and understood processes [42,43] that are associated with higher volumes of specific patient types may reduce ICU and in-hospital mortality.

Another approach to improving quality of care is to reduce missed diagnoses by analyzing discrepancies between premortem and post-mortem diagnoses. A retrospective review of medical records and autopsy reports in critically ill cancer patients was undertaken in an oncologic ICU in the USA [44]. Missed diagnoses with potential impact on treatment and survival were noted in 26% of autopsies. Most discrepancies were due to opportunistic infections (viral, bacterial, fungal and parasitic) and cardiopulmonary complications. Lung infections were the most prevalent, followed by central nervous system, gastrointestinal and disseminated infectious disease. Ischaemic cardiomyopathy, thrombotic endocarditis, congestive heart failure and pulmonary embolism were identified as cardiopulmonary missed diagnoses. Another study enrolling critically ill patients [45] found that post-mortem findings were in complete agreement with premortem diagnoses in fewer than half of cases (n = 17 [45%]).

Major missed diagnoses were present in 15 cases (39%). Myocardial infarction, carcinoma and pulmonary embolism represented the most frequently missed diagnoses, which is clearly different from the former study and probably highlights differences between the two populations. These findings further confirm the importance of the post-mortem examination in determining an accurate cause of death and in continuously improving and renewing the search for alternative diagnostic hypotheses during the course of critical illness, especially in immunosuppressed patients. Autopsy remains an important tool for education and quality control.

Costs

Critical care services represent a large and growing proportion of health care expenditure [11]. It may be influenced by LOS, severity of illness, presence of sepsis, ventilator-associated pneumonia, the level of hospital care, drug costs and staffing levels. Several studies have shown that severity of illness has a large impact on ICU costs [46-50]. A German national prevalence study examining the costs of critical care [51] revealed that, in the studied population, 10% of all patients consumed about 19% of total resources. In all levels of hospital care, the most expensive patients were those who required mechanical ventilation, those with greater severity of illness and/or severe sepsis, those admitted for emergency surgical procedures and nonsurvivors.

Ventilator-associated pneumonia probably also influences costs, because it is associated with increased duration of mechanical ventilation (by 5 to 7 days) and longer hospital LOS [4]. Hospital costs in patients receiving PMV are substantially higher than in patients ventilated for shorter periods, and up to 41% of PMV patients receive potentially ineffective care [29].

Staffing levels contribute to a major proportion of ICU costs (56.1% on average overall) [51]. Neverthless, there is growing evidence that high workload and low staffing level increases the risk for negative patient outcomes such as death and nosocomial infection [4-8]. Thus, finding an adequate staff-to-patient ratio that neither increases costs nor decreases quality of assistance and patient safety is the answer to this cost-effectiveness question.

New and expensive drugs also have a major impact on ICU costs, but they are often not adequately evaluated for cost-effectiveness [52,53]. A prospective observational study was conducted in France to evaluate the cost-effectiveness of recombinant human activated protein C (rhAPC) in severe sepsis and multiple organ failure [54]. They used propensity scores to match patients before and after rhAPC was licensed for use in France, thus avoiding selection bias from the original randomized controlled trial. The study concluded that there was a 74% probability that the use of rhAPC would be cost-effective if there were willingness to pay €50,000 per life-year gained and a 64.3% probability if there were

willingness to pay €50,000 per quality-adjusted life-year gained. An important difference between this study and other studies examining the cost-effectiveness of rhAPC [55,56] is that they did not demonstrate as large an effect size in their actual practice population as was seen in the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial.

Conclusion

Last year's *Critical Care* papers dealt with several aspects of ICU management, including quality, safety and cost management. Rational use of drugs, optimization of ICU capacity, mechanical ventilation and its complications, and adequate staffing levels are important factors that should be highlighted in efforts to improve the quality of care delivered to patients during an ICU stay and after discharge. Managing costs and providing high quality of care simultaneously are emerging challenges that must be understood and met.

Competing interests

The authors declare that they have no competing interests.

References

- McCannon CJ, Hackbarth AD, Griffin, FA: Miles to go: an Introduction to the 5 million lives campaign. Jt Comm J Qual Patient Saf 2007, 33:477-484.
- Ishikawa K: Introduction to Quality Control. London: Chapman & Hall: 1990.
- Goldratt E, Cox J: The Goal: A Process of Ongoing Improvement. New Haven, CT, USA: North River Press; 1992.
- Hugonnet S, Uckay I, Pittet D: Staffing level: a determinant of late-onset ventilator-associated pneumonia. Crit Care 2007, 11:R80.
- Burchardi H, Moerer O: Twenty-four hour presence of physicians in the ICU. Crit Care 2001, 5:131-137.
- Kane RL, Shamliyan T, Mueller C, Duval S, Wilt TJ: Nurse staffing and quality of patient care. Evid Rep Technol Assess (Full Rep) 2007. 151:1-115.
- Gerdtz MF, Nelson S: 5-20: a model of minimum nurse-topatient ratios in Victoria, Australia. J Nurs Manag 2007, 15:64-71
- Hugonnet S, Chevrolet JC, Pittet D: The effect of workload on infection risk in critically ill patients. Crit Care Med 2007, 35: 76-81.
- van Lieshout EJ, van der Veer SN, Hensbroek R, Korevaar JC, Vroom MB, Schultz MJ: Interference by new-generation mobile phones on critical care medical equipment. Crit Care 2007, 11:P08
- Joynt GM, Gomersall CD, Tan P, Lee A, Cheng CA, Wong EL: Prospective evaluation of patients refused admission to an intensive care unit: triage, futility and outcome. *Intensive Care Med* 2001, 27:1459-1465.
- Truog RD, Brock DW, Cook DJ, Danis M, Luce JM, Rubenfeld GD, Levy MM: Rationing in the intensive care unit. Crit Care Med 2006, 34:958-963.
- Ward NS, Teno JM, Curtis JR, Rubenfeld GD, Levy MM: Perceptions of cost constraints, resource limitations, and rationing in United States intensive care units: results of a national survey. Crit Care Med 2008, 36:471-476.
- Duke GJ: Metropolitan audit of appropriate referrals refused admission to intensive care. Anaesth Intensive Care 2004, 32: 702-706
- Garrouste-Orgeas M, Montuclard L, Timsit JF, Reignier J, Desmettre T, Karoubi P, Moreau D, Montesino L, Duguet A, Boussat S, Ede C, Monseau Y, Paule T, Misset B, Carlet J; French ADMISSIONREA Study Group: Predictors of intensive care unit refusal in French intensive care units: a multiple-center study. Crit Care Med 2005, 33:750-755.

- Van Houdenhoven M, Nguyen DT, Eijkemans MJ, Steyerberg EW, Tilanus HW, Gommers D, Wullink G, Bakker J, Kazemier G: Optimizing intensive care capacity using individual length-of-stay prediction models. Crit Care 2007, 11:R42.
- Quenot JP, Mentec H, Feihl F, Annane D, Melot C, Vignon P, Brun-Buisson C: Bedside adherence to clinical practice guidelines in the intensive care unit: the TECLA study. *Intensive* Care Med 2008 [Epub ahead of print].
- Zilberberg MD, Carter C, Lefebvre P, Raut M, Vekeman F, Duh MS, Shorr AF: Red blood cell transfusions and the risk of acute respiratory distress syndrome among the critically ill: a cohort study. Crit Care 2007, 11:R63.
 Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C,
- Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999, 340:409-417.
- Schelling G: Post-traumatic stress disorder in somatic disease: lessons from critically ill patients. Prog Brain Res 2008. 167:229-237.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: a severity of disease classification system. Crit Care Med 1985, 13:818-829.
- Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A: The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991, 100: 1619-1636.
- Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993, 270:2957-2963.
- Lemeshow S, Teres D, Klar J, Avrunin JS, Gehlbach SH, Rapoport J: Mortality Probability Models (MPM II) based on an international cohort of intensive care unit patients. *JAMA* 1993, 270: 2478-2486.
- Hofhuis JG, Spronk PE, van Stel HF, Schrijvers AJ, Bakker J: Quality of life before intensive care unit admission is a predictor of survival. Crit Care 2007. 11:R78.
- Anonymous: Predicting outcome in ICU patients. 2nd European Consensus Conference in Intensive Care Medicine. Intensive Care Med 1994, 20:390-397.
- Hartl WH, Wolf H, Schneider CP, Kuchenhoff H, Jauch KW: Acute and long-term survival in chronically critically ill surgical patients: a retrospective observational study. Crit Care 2007, 11:R55.
- Annane D, Aegerter P, Jars-Guincestre MC, Guidet B: Current Epidemiology of Septic Shock: The CUB-Rea Network. Am J Respir Crit Care Med 2003, 168:165-172.
- 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, 348:1546-1554.
- Cox CE, Carson SS, Lindquist JH, Olsen MK, Govert JA, Chelluri L: Differences in one-year health outcomes and resource utilization by definition of prolonged mechanical ventilation: a prospective cohort study. Crit Care 2007, 11:R9.
- Capuzzo M, Valpondi V, Cingolani E, Gianstefani G, De Luca S, Grassi L, Alvisi R: Post-traumatic stress disorder-related symptoms after intensive care. *Minerva Anestesiol* 2005, 71: 167-179.
- Jackson JC, Hart RP, Gordon SM, Hopkins RO, Girard TD, Ely EW: Post-traumatic stress disorder and post-traumatic stress symptoms following critical illness in medical intensive care unit patients: assessing the magnitude of the problem. Crit Care 2007, 11:R27.
- Boer KR, Mahler CW, Unlu C, Lamme B, Vroom MB, Sprangers MA, Gouma DJ, Reitsma JB, De Borgie CA, Boermeester MA: Long-term prevalence of post-traumatic stress disorder symptoms in patients after secondary peritonitis. Crit Care 2007, 11:R30.
- Girard T, Shintan A, Jackson JC, Gordon S, Pun B, Henderson M, Dittus R, Bernard GR, Ely EW: Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. Crit Care 2007, 11:R28.
- Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB: The long-term psychological effects of daily sedative interrup-

- tion on critically ill patients. Am J Respir Crit Care Med 2003, 168:1457-1461.
- Seedat S, Lochner C, Vythilingum B, Stein DJ: Disability and quality of life in post-traumatic stress disorder: impact of drug treatment. Pharmacoeconomics 2006, 24:989-998.
- 36. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD: Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med* 2006, **355**:41-50.
- Halm EA, Lee C, Chassin MR: Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med 2002, 137:511-520.
- 38. Stone VE, Seage GR, III, Hertz T, Epstein AM: The relation between hospital experience and mortality for patients with AIDS. JAMA 1992, 268:2655-2661.
- Durairaj L, Torner JC, Chrischilles EA, Vaughan Sarrazin MS, Yankey J, Rosenthal GE: Hospital volume-outcome relationships among medical admissions to ICUs. Chest 2005, 128: 1682-1689.
- Peelen L, de Keizer NF, Peek N, Scheffer GJ, van der Voort PH, de Jonge E: The influence of volume and intensive care unit organization on hospital mortality in patients admitted with severe sepsis: a retrospective multicentre cohort study. Crit Care 2007, 11:R40.
- Wasserfallen JB, Revelly JP, Moro D, Gilliard N, Rouge J, Chiolero R: Can the impact of bed closure in intensive care units be reliably monitored? *Intensive Care Med* 2004, 30:1134-1139.
- 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.
- Resar R, Pronovost P, Haraden C, Simmonds T, Rainey T, Nolan T: Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia. *Jt Comm J Qual Patient Saf* 2005, 31:243-248.
- Pastores SM, Dulu A, Voigt L, Raoof N, Alicea M, Halpern NA: Premortem clinical diagnoses and postmortem autopsy findings: discrepancies in critically ill cancer patients. Crit Care 2007, 11:R48.
- Perkins GD, McAuley DF, Davies S, Gao F: Discrepancies between clinical and postmortem diagnoses in critically ill patients: an observational study. Crit Care 2003, 7:R129-R132.
- Teres D, Rapoport J, Lemeshow S, Kim S, Akhras K: Effects of severity of illness on resource use by survivors and nonsurvivors of severe sepsis at intensive care unit admission. Crit Care Med 2002, 30:2413-2419.
- Rapoport J, Teres D, Lemeshow S, Avrunin JS, Haber R: Explaining variability of cost using a severity-of-illness measure for ICU patients. Med Care 1990, 28:338-348.
- Moerer O, Schmid A, Hofmann M, Herklotz A, Reinhart K, Werdan K, Schneider H, Burchardi H: Direct costs of severe sepsis in three German intensive care units based on retrospective electronic patient record analysis of resource use. *Intensive Care Med* 2002, 28:1440-1446.
- Rapoport J, Teres D, Zhao Y, Lemeshow S: Length of stay data as a guide to hospital economic performance for ICU patients. Med Care 2003, 41:386-397.
- Needham DM, Pronovost PJ: The importance of understanding the costs of critical care and mechanical ventilation. Crit Care Med 2005, 33:1434-1435.
- Moerer O, Plock E, Mgbor U, Schmid A, Schneider H, Wischnewsky MB, Burchardi H: A German national prevalence study on the cost of intensive care: an evaluation from 51 intensive care units. Crit Care 2007, 11:R69.
- Conti G, Dell'Utri D, Pelaia P, Rosa G, Cogliati AA, Gasparetto A: Do we know the costs of what we prescribe? A study on awareness of the cost of drugs and devices among ICU staff. Intensive Care Med 1998, 24:1194-1198.
- Weber RJ, Kane SL, Oriolo VA, Saul M, Skledar SJ, Dasta JF: Impact of intensive care unit (ICU) drug use on hospital costs: a descriptive analysis, with recommendations for optimizing ICU pharmacotherapy. Crit Care Med 2003, 31:S17-S24.
- 54. Dhainaut JF, Payet S, Vallet B, Franca LR, Annane D, Bollaert PE, Le Tulzo Y, Runge I, Malledant Y, Guidet B, Le Lay K, Launois R; PREMISS Study Group: Cost-effectiveness of activated protein C in real-life clinical practice. Crit Care 2007, 11:R99.

- 55. Angus DC, Linde-Zwirble WT, Clermont G, Ball DE, Basson BR, Ely EW, Laterre PF, Vincent JL, Bernard G, van Hout B: Costeffectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. Crit Care Med 2003, 31:1-11.
 56. Riou FL, Launois R, Le Lay K, Aegerter P, Bouhassira M, Meshaka P, Guidet B: Cost-effectiveness of drotrecogin alfa (activated)
- in the treatment of severe sepsis with multiple organ failure. Int J Technol Assess Health Care 2006, 22:101-108.