Received July 2012; accepted October 2012

REVIEW

Treatment of the delirious critically ill patient

MMJ van Eijk

Department of Anesthesiology, Leiden University Medical Centre, Leiden, The Netherlands

Abstract - Delirium is a commonly encountered disorder in critically ill patients. As delirium is associated with more adverse events and worse outcomes when compared to non-delirious patients, prevention and treatment of delirium in Intensive Care Unit (ICU) patients is of importance to intensivists. This article presents an overview of pharmacological (for example, prophylactic administration of antipsychotics) and non-pharmacological strategies (for example, early mobilisation and daily interruption of sedation) to prevent the occurrence of delirium and reduce its burden. Furthermore, an overview of pharmacological therapies (including α2-agonists and cholinesterase inhibitors) for treating delirium in ICU patients is presented. Finally, future directions for research are discussed.

Keywords - **Intensive Care Unit; delirium; treatment**

Introduction

Since the start of Intensive Care medicine in the second half of the last century, neuropsychiatric disorders in patients admitted to the Intensive Care Unit (ICU) have been commonly seen in critically ill patients. In the past, several names have been used for these symptoms, which include the ICU syndrome or ICU psychosis [1]. In recent years, however, the term delirium has been accepted as the underlying disorder. Since the landmark publication by Ely et al. [2] scientific interest has risen for this disorder, especially in the field of detecting delirium and identifying the risk factors [3]. Delirium is characterized by agitation (which can be severe) apathy or both. The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) defines delirium as a disturbance of consciousness with cognitive changes, which has developed over a short period of time, and is caused by a medical condition [4]. Several pathways have been suggested for the pathogenesis of delirium, although scientific evidence remains unavailable. Leading theories are the cholinergic deficiency hypothesis [5] and an excess of dopamine in delirious patients [6]. Other disorders may play a role as well, these include neuro-inflammation, microthrombosis and neurologic changes associated with sepsis (septic encephalopathy) [6,7].

Delirium in the ICU

Delirium is common in critically ill patients with reported frequencies ranging from 11% to 89%, depending on the method used for detection and case-mix [2, 8-15]. In a recent study among 282 critically ill patients admitted to ten Dutch ICUs, the point prevalence of delirium (e.g. the frequency of delirium in all admitted ICU patients at one point in time, including those deeply sedated) as diagnosed by an expert group (neurologists, geriatricians and psychiatrists) was 28% [16]. The ability of the ICU care-givers to recognize delirium, however, is low, as was shown in a 2009 study among 221 adult ICU patients. In this study, expert groups (as described above), evaluated the patients for the presence or absence of delirium and found a point prevalence of 19% (deeply sedated or comatose patients were also evaluated). As a secondary outcome, ICU physicians were asked to assess the patients (as part of their daily evaluation). The specificity of the ICU physician's evaluation was high (96%), the sensitivity, however, was surprisingly low (29%), indicating that the impression of the ICU physician is not sensitive enough to identify a delirious ICU patient [17].

Identifying delirium

In order to improve the identification of delirious patients, several easy-to-use screening methods have been developed for use in clinical practice. Most methods have been developed for use in the general population (e.g. hospital ward or care-home), but two methods were specially adapted for use in non-communicative (e.g. intubated) ICU patients; the Intensive Care Delirium Screening Checklist (ICDSC) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). The latter showed better test characteristics in a mixed-type, Dutch, ICU [17] and is now the most commonly used screening method in the Netherlands. The CAM-ICU showed remarkable good test characteristics in the original validation studies (range, 97% – 100%) and specificity (range, 89% – 100%) [2,18]. In these validation studies, the CAM-ICU was administered by specially trained and designated research nurses; in a recent study, sensitivity was shown to be much lower (47%) [16] when the test was administered by bedside nurses with only a basic training in the use of the CAM-ICU. Results, however, did improve with more extensive training. These results show that the CAM-ICU might not be as useful in identifying delirium in the daily, clinical situation as previously thought, although improved implementation strategies and training might enhance the quality of this instrument.

Consequences

The impact of delirium on critically ill patients is still a matter of debate. Earlier studies showed that patients admitted to the ICU suffering from delirium during their admission remained in the ICU longer, had a longer hospital stay, had a higher in-hospital mortality

Correspondence

MMJ van Eijk

E-mail: M.M.J.van_Eijk@lumc.nl

and showed more severe cognitive impairments after discharge [10-12,19,20]. Furthermore, persistent delirium was associated with worse outcomes, as each delirious day extra was associated with a 10% increased risk of death after 6 months [14]. Although these studies were performed with large cohorts and the data were adjusted for several key confounders (for example, age, severity of illness at admission and co-morbidities), an independent association between delirium and outcome is still uncertain.

Treatment

The first step of delirium treatment is management of the underlying illness [21]. In a septic patient, for example, the focus of the medical and nursing staff should be aimed on treatment of the infection and supportive measures to counteract the effects of the sepsis. However, there are several measures aimed directly at the symptoms and onset of delirium. In this article measures for preventing the occurrence of delirium are discussed along with non-pharmacological treatment of delirium. Finally, drug therapy and future perspectives on delirium treatment are discussed.

Non-pharmacological approach

There are numerous factors thought to play a role in the development of delirium, especially in patients who are critically ill. Not only the severity of the underlying disorder, or the critical condition of the patient, but also the treatment of ICU patients (for example, polypharmacy, sedation or analgesics) can cause and provoke delirium. Furthermore, the ICU environment, with noise and continuous light, can be a stimulus for a patient to develop delirium. Although the cornerstone of delirium treatment is focused on treating the underlying disorder, it is reasonable to assume that non-pharmacological measures might help to reduce the incidence, duration and adverse effects of delirium in critically ill patients.

Measures aimed at risk factors

One of the first studies to investigate a non-pharmacological approach to delirium was performed in 1999 by Inouye et al. and published in the *New England Journal of Medicine* [22]. The investigators developed a simple, multi-component intervention for preventing delirium, targeting six risk factors for the development of delirium (cognitive impairment; sleep deprivation; immobility; visual impairment; hearing impairment and dehydration). This intervention was compared with usual care in older patients with an increased risk of delirium. The incidence of delirium was significantly lower in the intervention group as compared to the usual care group (10% versus 15%; p-value 0.02), as was the duration of delirium. Although this study did not include patients admitted to the ICU, it is reasonable to assume that these measures might, in part, be useful in critically ill patients. This assumption is further substantiated by a more recent study by Schweickert et al. in 2009 [23]. In this study, the investigators targeted one of the six risk factors identified by Inouye: immobilization. 104 patients admitted to the ICU were randomized in two groups, one receiving usual care and one received early physical and occupational therapy. In the latter group, even deeply sedated patients on mechanical ventilation were visited by a therapist and underwent passive range of motion exercise. Delirium occurred significantly less in the intervention group; median duration of delirium days 2 versus 4 in the usual care group (p-value 0,03), indicating that early mobilisation can prevent delirium and non-pharmacological measures can be useful in the ICU.

Sedation and delirium

A unique feature of the ICU population is mechanical ventilation and prolonged sedation. In 2000 Kress et al. [24] showed that daily interruption of sedation reduced ICU stay by 3.5 days. Although delirium was not investigated it is reasonable to assume that shorter duration of sedation and mechanical ventilation can result in a lower incidence of delirium. For example, benzodiazepines were shown to be associated with a higher occurrence of delirium [25], thus, if fewer benzodiazepines are used, a decline in delirium is expected. Shorter duration of sedation and mechanical ventilation might be a promising way to prevent delirium from occurring.

Preventive pharmagological measures

A number of studies that investigate ways of preventing delirium in critically ill patients have been published (see table 1). As haloperidol (a first generation or typical antipsychotic drug) is the treatment of choice for delirium, several studies used this pharmacological approach to prevent delirium from occurring.

Prophylactic antipsychotics

Kalisvaart et al.[26] investigated the prophylactic administration of haloperidol to patients at risk of delirium who were scheduled for hip surgery. Although no effect on the incidence of delirium was shown, prophylactic haloperidol did shorten the duration of delirium. This important study, however, did not include critically ill patients. The first study to investigate prophylactic antipsychotics in critically ill patients was published in 2007 by Prakanrattanna et al. [27]. In this prospective study, 126 post cardio-thoracic surgery patients admitted to the ICU received either 1 mg. risperidone (an atypical antipsychotic) or placebo directly after regaining consciousness following surgery (not blinded). Using the CAM-ICU, delirium during admission was registered. Analysis showed that the incidence of post-operative delirium was reduced (11% in placebo group versus 32% in risperidone group, p 0.009). Although post-operative patients are not completely comparable to the general ICU population (e.g. septic patients), these results were promising. In 2010 Girard and others performed the Modifying the Incidence of Delirium (MIND) Trial [28]. In this prospective, randomized, double-blind trial, 101 mechanically ventilated surgical or medical ICU patients with an abnormal level of consciousness or who were on sedative medication, were randomized to receive either haloperidol (5 mg., n = 35); ziprasidone (an a-typical antipsychotic) (40 mg.; n = 30) or placebo (equivalent volume) four times a day, for up to 14 days. The main outcome in this study was delirium or coma free days; the secondary outcomes included mortality, use of antipsychotics (in addition to the study medication) and adverse events. The results of this small, but carefully executed study showed no differences in either the primary or secondary outcomes (number of delirium or coma free days: haloperidol: 14.0; ziprasidone: 15.0; placebo: 12.5; p-value: 0.66), which questions the use of antipsychotics as prevention for delirium. Wang et al.,

however, did find a significant difference in frequency of delirium when using haloperidol [29]. In this, double-blind, randomized, placebo controlled study with 475 older (age >65 yr) non-cardiac surgery ICU patients, 229 received haloperidol (0.5 mg. bolus followed by continous infusion of 0.1 mg./hr.) for 12 hours. The remaining 228 patients received an equivalent volume of placebo. The frequency of delirium was lower in the haloperidol group (15%) when compared to the placebo group (23%) (p-value: 0.03). These remarkable results were recently repeated by Van den Boogaard et al. [30]. In this prospective case-control study 177 ICU patients, with a high probability of developing delirium (identified using the PRE-DELIRIC [31] prediction model), received haloperidol 0.5-1 mg. every 8 hours of the ICU admission. The primary and secondary outcomes (including delirium incidence, number of delirium free days and 28-day mortality) were compared to 299 historical controls. The incidence of delirium was 75% in the control group and 65% in the haloperidol group (p-value 0.01), the number of delirium free days was also lower in the haloperidol group (13 (IQR 3-27) days in the control group versus 20 (IQR 8-27) days in the haloperidol group, p-value 0.003). Although the design of this study was not perfect, this study shows that preventing delirium by giving antipsychotic drugs might be feasible, especially in high risk patients.

Cholinesterase inhibitors

Another trial, performed by Gamberini et al., studied the cholinesterase inhibitor rivastigmine as a possible prophylactic drug for delirium in ICU patients [32]. 120 patients admitted to the ICU after an elective cardio-surgical procedure received either rivastigmine (1.5 mg; n = 59) or placebo (equivalent volume; n = 61) three times a day starting on the evening before surgery and throughout six days post-operatively. The primary outcome was the occurrence of delirium. Delirium was equally frequent in both groups (rivastigmine 30%; placebo 32%; p-value 0.80). The secondary outcomes (mortality, use of sedatives, side effects and others) did not differ between both groups. This study had

Table 1. Studies on pharmacological prevention of delirium in critically ill patients

STUDY	DESIGN	POPULATION	NUMBER OF PATIENTS	INTERVENTION	RESULT
Prakanrattanna et al. 2007[27]	Prospective, randomized	Cardio-surgical patients	126	Risperidone or placebo. Duration: one dose after regaining consciousness	Lower frequency of delirium in risperidone group
Pandharipande et al. 2007[35]	Prospective, randomized, double-blind	Mechanically ventilated medical and surgical patients	106	Dexmedetomidine or lorazepam. Duration: until extubation or maximum 120 hours.	More delirium/coma free days in dexmedetomidine group
Riker et al. 2009[36]	Prospective, randomized, double-blind	Mechanically ventilated medical and surgical patients	375	Dexmedetomidine or midazolam. Duration: until extubation or until maximal 30 days.	Lower frequency of delirium in dexmedetomidine group
Maldonado et al. 2009[37]	Prospective, randomized	Cardio-surgical patients	118	Dexmedetomidine; midazolam or Propofol sedation. Duration: from surgery until extubation in the ICU	Lower frequency of delirium in dexmedetomidine group
Shehabi et al. 2009[38]	Prospective, randomized, double-blind	Cardio-surgical patients	306	Dexmedetomidine or morphine. Duration: maximum 48 hours post-operatively	No difference on frequency of delirium. Shorter duration of delirium in dexmedetomidine group
Gamberinin et al. 2009[32]	Prospective, randomized, double-blind, placebo controlled	ICU patients, post cardio-thoracic surgery	120	Rivastigmine or placebo. Duration: 6 days post-operatively	No difference on frequency of delirium between interventions
Rubino et al. 2010[33]	Prospective, randomized, placebo controlled	Patients after acute type A aortic dissection	30	Clonidine or placebo. Duration: during weaning from mechanical ventilation	No difference on frequency of delirium. Lower severity of delirium in clonidine group
Girard et al. 2010[28]	Prospective, randomized, double-blind, placebo controlled	Mechanically ventilated medical and surgical patients	101	Haloperidol, ziprasidone or placebo Duration: 14 days	No difference on duration of delirium between interventions.
Wang et al. 2012[29]	Prospective, randomized, double-blind, placebo controlled	Non-cardiac surgical ICU patients (age >65yr)	475	Haloperidol or placebo. Duration: 12 hours	Lower frequency of delirium in haloperidol group
Van den Boogaard et al. 2012[30]	Prospective case-control study	ICU patients with a high estimated risk of delirium	177 (299 historical controls)	Haloperidol (historical controls: standard care). Duration: during ICU admission	Lower frequency of delirium in haloperidol group, increase of delirium free days in haloperidol group

ICU = Intensive Care Unit.

some design failures (the use of the CAM-ICU and the low dose of rivastigmine used) and these may have caused the negative results.

α -2 agonists

The α-2 agonist clonidine was used by Rubino et al. [33] to prevent delirium in 30 post aortic dissection surgery patients after weaning from mechanical ventilation. Patients included in this study received clonidine (0.5 µg./kg. followed by continuous infusion of 1-2 µg./kg./hr.; n = 15) or placebo (NaCl 0.9%; n = 15) throughout the weaning from mechanical ventilation. Although the primary outcome did not differ between both groups (frequency of delirium 40% in clonidine group and 33% in placebo group; p-value 0.70) and the study had several limitations (small population, method of diagnosing delirium uncertain) remarkably, the severity of delirium as measured with the Delirium Detection Score (DDS) [34], was lower in the clonidine group, indicating that clonidine might be successful in preventing severe delirium in ICU patients.

Dexmedetomidine

Another and newer α-2 agonist (dexmedetomidine) has been studied more extensively with regard to preventing delirium in ICU patients. Pandharipande et al. showed in the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial [35] that sedation with dexmedetomidine resulted in more delirium/coma free days when compared to sedation with the benzodiazepine lorazepam. In this prospective, randomized, double-blinded trial, 106 mechanically ventilated ICU patients were randomized to receive either dexmedetomidine (0.15-1.5 µg./kg./hr., titrated to the desired effect; n = 54) or lorazepam (1.0-10.0 mg./hr., , titrated to the desired effect; n = 52). The sedation was continued until extubation or for a maximum of 120 hours. Results showed that although the frequency of delirium was not different between groups (dexmedetomidine 79% versus lorazepam 82%; p-value 0.65), patients in the dexemedetomidine group experienced more delirium/coma free days (7.0 days in dexemedetomidine group versus 3.0 days in lorazepam group; p-value: 0.01). Following this trial several other trials showed the similar positive effects of dexmedetomidine. Riker et al. [36], Maldonado et al. [37] and Shehabi et al. [38] investigated dexemedetomide and compared it with other medication regimes (see table 1). In conclusion: dexmedetomidine seems to be successful in reducing the frequency of delirium in ICU patients when compared to other sedatives. A large meta-analysis by Tan et al. in 2010 [39], however, showed no beneficial effect on the occurrence of delirium when using dexmedetomidine. Several drugs have been studied in attempts to reduce the frequency of delirium. Although not all evidence is conclusive, it seems that some decline in the incidence of delirium can be achieved with either prophylactic use of antipsychotics or by choosing different sedatives to sedate ICU patients on mechanical ventilation.

Pharmacological treatment of delirium

Historically, antipsychotics have been the cornerstone of delirium treatment. Haloperidol is the most frequently used antipsychotic drug for treating delirium and is recommended by several international guidelines [21,40]. The recommended (based on expert opinion) dosage of haloperidol is 2 mg. intravenously in agitated, hyperactive patients followed by repeated doses every 20 minutes until agitation is under control, followed by scheduled doses four times a day [40]. In 2005, Millbrandt et al. showed in an observational study (single centre retrospective cohort analysis) that mechanically ventilated patients who received haloperidol during their ICU stay had lower in-hospital mortality when compared with patients who had not received haloperidol treatment [41]. However, even for haloperidol, evidence on efficacy of antipsychotics for delirium treatment in the ICU is scarce. Haloperidol is used by 75%-80% of intensivists in the United States of America [42] although haloperidol is not approved by the Food and Drugs Administration (FDA) for the treatment of delirium. Haloperidol is associated with several, serious, side effects, including prolongation of QT-interval, extrapyramidal symptoms and malignant neuroleptic syndrome. Atypical (or second generation) antipsychotics (for example, olanzapine, quetiapine and rispiredone) are associated with fewer side effects than typical antipsychotics and thus might be more suitable for treating delirium in ICU patients [43]. Evidence from randomized controlled trials on delirium treatment in the ICU is lacking. There are, however, several studies comparing haloperidol to other, atypical, antipsychotics.

Treatment with antipsychotics

Olanzapine was compared to haloperidol by Skrobik et al. in 2004 [43]. In this prospective, randomized trial, patients admitted to a surgical/medical ICU were screened for delirium using the Delirium Index (DI) [44], delirious patients were randomized to receive either haloperidol (n=45), 0.5 – 5 mg every 8 hours (based on age) or olanzapine (n=28) 2.5 – 5 mg. every 8 hours (based on age) for up to 5 days. Delirium associated outcomes (DI scores, use of escape medication and sedatives) were similar in both groups. Side effects, however, especially extrapyramidal symptoms, were more frequently reported in the haloperidol group. The authors conclude that olanzapine is a safe alternative when treating delirious ICU patients; the results of this trial, however, are hampered by its size, the diagnostic tool used and the lack of a placebo group. Another atypical antipsychotic (quetiapine) was studied prospectively in ICU patients by Devlin et al. in 2009 [45] In this trial 36 delirious ICU patients (diagnosed using the ICDSC) were randomized to receive quetiapine 50 mg twice a day (n=18) or placebo 50 mg. twice a day (n=18). Furthermore, all patients received haloperidol as needed, hampering the placebo controlled design of this study. Despite this limitation, patients receiving quetiapine had a shorter duration of delirium (36 hours (IQR 12 – 87) versus 120 hours (IQR 60 – 195); p-value 0.006) when compared to the placebo group. Although the results of this study are promising, apart from the previously mentioned design limitation, this study is limited by the small number of patients and the fact that quetiapine is only available as an oral tablet – which hampers its use in the majority of ICU patients. Current studies on typical or atypical antipsychotics for treating delirium in ICU patients are rare and those published [43,45] are small and have several other limitations.

Cholinesterase inhibitors

Another approach to the treatment of delirium in ICU patients is with cholinesterase inhibitors. Antipsychotic treatment mainly

focuses on dopaminergic neurotransmitters as pathogeneses of delirium. Several studies have shown that the cholinergic pathway may also play a role in the development of delirium [46-48]. This has resulted in the hypothesis that cholinesterase inhibitors might be successful in the treatment of delirium. As described in the preventive measures section of this article, Gamberinni et al. studied rivastigmine (a cholinesterase inhibitor) for the prevention of delirium, showing no benefit. Van Eijk et al. studied rivastgimine as treatment for delirium in ICU patients [49]. 104 delirious ICU patients (diagnosed using the CAM-ICU) were randomized to receive rivastgimine (n=54) up to 6 mg twice a day or a comparable dosage of placebo (n=50). The included patients also received standard care, with haloperidol, as deemed necessary by the, blinded, treating physician. This study was terminated prematurely due to an increased mortality rate in the rivastgimine group (22% versus 8% in the placebo group; p-value 0.07). This study showed no beneficial effect of rivastigmine on important delirium associated outcomes (among others duration of delirium, severity of delirium and use of escape medication). Although the hypothesis of cholinesterase inhibitors for the treatment of delirium seemed promising, studies have not shown any beneficial effect. Evidence (other than expert opinion) on delirium treatment in ICU patients is lacking. Some attempts have been made to find new or alternative therapies, but, to date, none have been shown to be superior to haloperidol. Interestingly, even the efficacy of haloperidol has not been studied in a large, placebo controlled trial.

Future prespectives

Delirium is commonly encountered in critically ill patients and is a stressful and frightening disorder for patients and their relatives. Delirium is also associated with adverse events, for example, auto-extubation and adverse outcomes. Delirium is therefore a serious problem in ICU patients and evidence for preventive and therapeutic measures is warranted. As shown above, the standard treatment of delirium is the typical antipsychotic haloperidol. Although several studies attempted to find alternative or other treatment options, haloperidol is still the drug of first choice. Future studies are hampered both by the lack of understanding of the exact pathogeneses of delirium (making it difficult to find a suitable new drug) and difficulties in designing a delirium treatment study. As antipsychotics are the drug of choice, it is unethical to withhold delirious patients this treatment, making it difficult, if not impossible to investigate an alternative drug in a placebo controlled matter. A third difficulty encountered when trying to investigate a new drug in the treatment of delirium is the ICU population. As the occurrence and maintenance of delirium is multifactorial, large populations are necessary to account for all confounders. Large trials in critically ill patients are scarce as they are labour intensive and difficult to manage. Large international and national collaborations are necessary if new drugs for the treatment of delirium are studied. One first step towards improved collaboration is the establishment of a collaboration of Dutch ICU delirium investigators (chaired by professor Pickkers).

Pharmacological prevention

In contrast to the treatment of delirium, pharmacological strategies to prevent its occurrence seem more promising. As shown above, the α2-agonist dexmedetomidine used as an alternative sedative, resulted in less delirium and a decline in its duration and severity. Not only the sedative used but also a different practice of sedation is a promising way of preventing delirium from occurring in critically ill patients. Daily interruption of sedation resulted in a shorter duration of sedation and mechanical ventilation [24] possibly reducing the incidence of delirium. Several studies investigated prophylactic treatment with antipsychotics in ICU patients, especially those at high risk of developing delirium. These studies showed promising results, future studies using this approach are under way or being planned and may help to reduce the burden of delirium in ICU patients.

Non-pharmacological prevention

Non-pharmacological approaches for preventing delirium are particularly promising. For example, the early mobilisation of patients resulted in shorter delirium and other 'simple' measures suggested by Inouye [22], for example, the use of spectacles in visually impaired patients or frequent orientation in place and time might contribute to the reduction of delirium. Of particular interest is the restoration of day-night rhythm in ICU patients. Pharmacological and non-pharmacological approaches aimed at a 'better' sleep pattern are promising new fields for studies, as sleep disturbance in ICU patients is still a relatively unknown problem. These, and other, non-pharmacological interventions are of particular interest as they are relatively simple and cheap to implement and have been shown to result in a reduction of delirium in other populations. Furthermore, because pharmacological treatment of delirium in ICU patients is difficult to study and may be undesirable in the, already multi-medicated, ICU patient, non-pharmacologic strategies are promising new directions for future ICU delirium studies.

References

1. McGuire BE, Basten CJ, Ryan CJ, Gallagher J. Intensive care unit syndrome: a dangerous misnomer. Arch Intern Med 2000;160:906-909.

2. Ely EW, Inouye SK, Bernard GR et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286:2703-2710.

3. van Eijk MM, Slooter AJ. Delirium in intensive care unit patients. Semin Cardiothorac Vasc Anesth 2010;14:141-147.

4. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text revision. Washington, DC: American Psychiatric Association 2000.

5. van Gool WA, van de Beek D., Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet 2010;375:773-775.

6. Gunther ML, Morandi A, Ely EW. Pathophysiology of delirium in the intensive care unit. Crit Care Clin 2008;24:45-65, viii.

7. Ebersoldt M, Sharshar T, Annane D. Sepsis-associated delirium. Intensive Care Med 2007;33:941-950.

8. Peterson JF, Pun BT, Dittus RS et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. J Am Geriatr Soc 2006;54:479-484.
9. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med 2001;27:859-864.
10. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. Intensive Care Med 2001;27:1297-1304.
11. Lin SM, Liu CY, Wang CH et al. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med 2004;32:2254-2259.
12. Thomason JW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely EW. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. Crit Care 2005;9:R375-R381.
13. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc 2003;51:591-598.
14. Ely EW, Shintani A, Truman B et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004;291:1753-1762.
15. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. Intensive Care Med 2007;33:66-73.
16. van Eijk MM, van den Boogaard M, van Marum RJ et al. Routine use of the confusion assessment method for the intensive care unit: a multicenter study. Am J Respir Crit Care Med 2011;184:340-344.
17. van Eijk MM, van Marum RJ, Klijn IA, de WN, Kesecioglu J, Slooter AJ. Comparison of delirium assessment tools in a mixed intensive care unit. Crit Care Med 2009;37:1881-1885.
18. Ely EW, Margolin R, Francis J et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001;29:1370-1379.
19. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. J Gen Intern Med 1998;13:234-242.
20. Rockwood K, Cosway S, Carver D, Jarrett P, Stadnyk K, Fisk J. The risk of dementia and death after delirium. Age Ageing 1999;28:551-556.
21. van der Mast RC, Huyse FJ, Rosier PF. Richtlijn 'Delirium'. Ned Tijdschr Geneeskd 2005;149:1027-1032.
22. Inouye SK, Bogardus ST, Jr., Charpentier PA et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340:669-676.
23. Schweickert WD, Pohlman MC, Pohlman AS et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373:1874-1882.
24. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-1477.
25. Pandharipande P, Shintani A, Peterson J et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104:21-26.
26. Kalisvaart KJ, de Jonghe JF, Bogaards MJ et al. Haloperidol prophylaxis for elderly hip surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc 2005; 53(10):1658-1666.
27. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care 2007; 35(5):714-719
28. Girard TD, Pandharipande PP, Carson SS et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med 2010;38:428-437.
29. Wang W, Li HL, Wang DX et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. Crit Care Med 2012;40:731-739.
30. PhD thesis: Delirium in intensive care patients; detection, impact, prediction, prevention and biomarkers. Mark van den Boogaard. Nijmegen, the Netherlands. April 2nd 2012
31. van den Boogaard M, Pickkers P, Slooter AJ et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ 2012;344:e420.
32. Gamberini M, Bolliger D, Lurati Buse GA et al. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery--a randomized controlled trial. Crit Care Med 2009;37:1762-1768.
33. Rubino AS, Onorati F, Caroleo S et al. Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study. Interact Cardiovasc Thorac Surg 2010;10:58-62.
34. Otter H, Martin J, Basell K et al. Validity and reliability of the DDS for severity of delirium in the ICU. Neurocrit Care 2005;2:150-158.
35. Pandharipande PP, Pun BT, Herr DL et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-2653.
36. Riker RR, Shehabi Y, Bokesch PM et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-499.
37. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics 2009;50:206-217.
38. Shehabi Y, Grant P, Wolfenden H et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). Anesthesiology 2009;111:1075-1084.
39. Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis. Intensive Care Med 2010;36:926-939.
40. Practice guideline for the treatment of patients with delirium. American Psychiatric Association. Am J Psychiatry 1999;156:1-20.
41. Milbrandt EB, Kersten A, Kong L et al. Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients. Crit Care Med 2005;33:226-229.
42. Ely EW, Stephens RK, Jackson JC et al. Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: a survey of 912 healthcare professionals. Crit Care Med 2004;32:106-112.
43. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med 2004;30:444-449.
44. McCusker J, Cole M, Bellavance F, Primeau F. Reliability and validity of a new measure of severity of delirium. Int Psychogeriatr 1998;10(4):421-433.
45. Devlin JW, Roberts RJ, Fong JJ et al. Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med 2009; 38:419-427
46. Golinger RC, Peet T, Tune LE. Association of elevated plasma anticholinergic activity with delirium in surgical patients. Am J Psychiatry 1987;144:1218-1220.
47. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001;161:1099-1105.
48. Fischer P. Successful treatment of nonanticholinergic delirium with a cholinesterase inhibitor. J Clin Psychopharmacol 2001;21:118.
49. van Eijk MM, Roes KC, Honing ML et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet 2010; 376: 1829-1837

Received ; accepted

REVIEW

The consequences of treatment limitations on outcome

AME Spoelstra - de Man[1], JG van der Hoeven[2], LMA Heunks[2]

1 Department of Intensive Care, Tergooiziekenhuizen, The Netherlands

2 Radboud University Nijmegen Medical Center, Department of Intensive Care, The Netherlands

Abstract - Cardiopulmonary resuscitation and mechanical ventilation have enabled us to prolong the life of patients, although this may not always be appropriate. To avoid patients experiencing a poor functional outcome or a long process of dying, Do-Not-Resuscitate (DNR) orders have been instituted. However, several studies suggest that DNR orders independently increase mortality.

DNR orders are based on the patient's own preferences or because resuscitation is judged to be futile by the medical team. This latter assumes that the prognosis of the patient concerned is known. However, an accurate prognosis is extremely difficult, and prognostic models only show good agreement for patients in aggregate, not for individuals. These difficulties in prognostication could partly explain a potential increase in mortality due to DNR orders. Another cause may be unintentional but unjustified broadening of DNR orders by health care workers in patients with DNR orders, with the withholding of other treatments besides CPR and suboptimal care.

Physicians should be aware of the unintentional impact of DNR orders. We recommend several precautions that can be taken to reduce the risk of increasing mortality due to DNR orders. Hospitals should develop clear guidelines, which describe indications for DNR orders and which emphasize that these orders have to be viewed in isolation from other treatment decisions. DNR orders should be made, if possible, at an early time, by combining prognostic models with the physician's own estimate of prognosis, jointly with other colleagues and in concordance with the patient's preferences. Because of the large differences between physicians and hospitals regarding the institution of DNR orders, together with the uncertainty of prognosis, and the self-fulfilling prophecy of treatment limitations, we need to be very cautious in recommending limitations of care.

Keywords - **Do-Not-Resuscitate order, treatment limitations, prognostic models, code order, prediction, critical care**

Introduction

The development of cardiopulmonary resuscitation (CPR), continuous veno-venous hemofiltration and mechanical ventilation have enabled us to extend the life of patients. However, inappropriate use of these life-sustaining procedures may prolong only the process of dying or result in a life with severe neurological damage. Therefore, treatment limitation policies, including do-not-resuscitate (DNR) orders are often prescribed to avoid treatment that would not positively affect the patient's condition and distribute medical resources to patients who are most likely to benefit. However, several studies have now suggested that DNR orders are associated with increased mortality [1,2].

Treatment limitations may be instituted based on a patient's own preference, or because treatment is judged to be futile by the medical team. The latter assumes that the prognosis of the patient concerned is known, which is questionable. For instance, predicted hospital mortality for an individual patient varies considerably among physicians. O'Brien et al. showed that mortality of simulated patients with septic shock, as estimated by two independent physicians, could differ by more than 50 percent [3]. This wide range in expected mortality may be explained by physicians' characteristics, such as differences in age, level of training, religion, country (strongest determinant in the study by Yaguchi et al. [4]) and the subjective component of the analysis of each individual situation [5,6,7] (figure 1).

To aid physicians in prognostication, models have been developed for several diseases. These models demonstrated good agreement for describing patients in aggregate, but their accuracy for individual patients is substantially lower [8]. Furthermore, these models appear to underestimate the probability of a favourable outcome in non-DNR patients. This pessimism may drive the decision towards a DNR order to an individual in whom a favourable outcome may have been possible [9]. In this overview we will discuss the negative impact that DNR orders may independently have on outcome.

History

Soon after the development of CPR in the early 1960s, it became evident that routine application of resuscitation efforts resulted in prolonged suffering for many patients. Accordingly, in terminally ill patients, medical staff often choose to abandon a full resuscitation attempt [10]. There was, however, no formal process for these important decisions and no documentation of the rationale in the medical record. In 1974 the American Medical Association became the first professional organization that recommended formally documenting and communicating decisions to forego resuscitation [11]. In 1983 the autonomy of the patient was acknowledged in the report of the "President's Commission" in Washington that concluded that it was permissible for competent patients to refuse life-sustaining treatment [12]. Ever since, an increasing number of guidelines have been developed concerning

Correspondence

Angélique M.E. Spoelstra

E-mail: aspoelstra@tergooiziekenhuizen.nl

the use of DNR orders, although not adopted in all countries. There are important differences in decision making of DNR orders between North America and Europe. In North America, relatives by right, share this decision with physicians. In Europe, guidelines agree that proxies, whose preferences are to be taken into account, should be informed, but do not have the right and/or the responsibility for the final decision. European intensivists consider themselves the best decision makers, being better aware of the clinical situation and free from emotional involvement and interests [13]. Therefore, there is no international consensus with regard to DNR guidelines [13].

Epidemiology

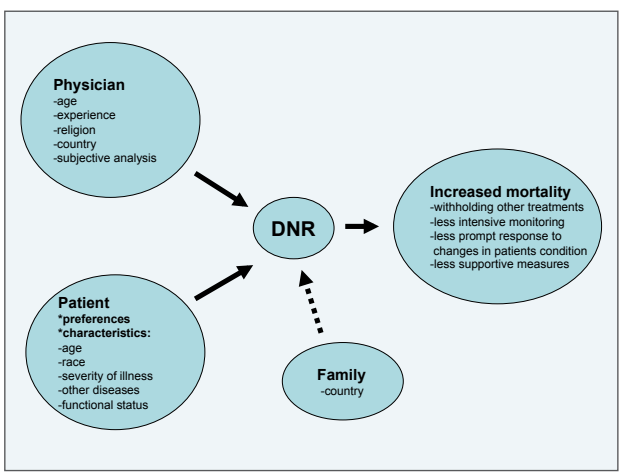
Between 18 and 28% of all hospitalized patients have a DNR order [14] and for Intensive Care Unit (ICU) patients this number varies between 1.5 and 34% [15]. Only 20% of patients who die in the ICU undergo CPR [15]. The assignment of DNR orders increases with severity of illness on admission, and most patients have experienced an acute episode of septic shock, cardiac arrest or intracranial haemorrhage before the assignment of DNR.

Certain patient characteristics are associated with higher incidence of DNR orders. For example, patients with Acquired ImmunoDeficiency Syndrome or cancer are more likely to have a DNR order than patients with cirrhosis or heart failure, despite similar prognoses [14]. Elderly patients are also more likely to have DNR orders. Furthermore, DNR orders are more frequently assigned to white Americans as compared to African Americans [14]. This may be related to the stronger spiritual belief with a reluctance for treatment limitations in African Americans [13]. Finally, educated respondents appeared to have a preference for comfort care [16].

Impact of DNR orders on mortality.

The association between DNR orders and mortality has been described in the literature since the nineteen-eighties. These earlier studies reported that mortality was 3 – 25 times higher in patients with DNR orders. However, those studies were limited to single hospitals and diadjust for severity of illness and other prognostic factors [17,18,19,20]. Later studies, also including withdrawal of vasopressors, mechanical ventilation and dialysis, showed a significantly increased mortality in patients with treatment limitations, even after adjustment for confounding variables, such as disease severity, functional impairment and comorbidities [6,21,22]. To demonstrate an independent relationship between DNR order and mortality, one would need to conduct a controlled clinical trial, randomizing patients either to receive DNR orders or full medical treatment. Ethical considerations obviously preclude such a trial. Shepardson used propensity scores to generate a matched cohort study simulating a randomized trial (1). This methodology first identifies factors related to the use of the intervention under investigation (i.e. DNR order). Then, based on these factors, estimates the likelihood (propensity) that each patient receives the DNR order. Outcomes are compared among patients with a similar propensity for the intervention. Her analysis showed, in line with earlier studies, an increased mortality in patients with a DNR order compared to patients without treatment limitations [1].

Figure 1. Factors with a potential impact on DNR decisions and possible consequences of DNR orders.



Variability in DNR policy between hospitals

The use of DNR orders varies among hospitals. Hospital rates of DNR usage range widely from 0% to 70% [23,24]. Academic medical centres appear to have lower rates of DNR orders than non-academic medical centres, even after adjusting for case mix [23]. However, even among the academic medical centres, a large variability in DNR rates (1.5 – 22%) is reported [16,25].
Mortality rates are higher in hospitals with more frequent use of DNR orders, even after adjustment for number of patients and hospital characteristics [26]. This implies that DNR is not restricted to patients with a particularly poor prognosis. The DNR rate of the hospital (case mix adjusted) may act as a proxy for overall aggressiveness of care [26]. A low threshold for the use of DNR orders may reflect an overall "nonaggressive" approach in that particular hospital. This variability in aggressiveness of care can influence patient outcome irrespective of code status (the ripple effect).

Prognostic models

To investigate the variability in hospital mortality between hospitals, prognostic models were developed to objectively quantify the risk and to evaluate the outcomes of care. These models were certainly not designed for prognostication of *individual* patients. Also, their accuracy for populations other than those used to develop the score is substantially lower [8], even after score customization [27]. A systematic review of studies comparing physician predictions of hospital survival of critically ill adults to objective scoring systems [28] did not demonstrate superiority of the scoring systems. Several explanations can be given for this unexpected finding. First, most of the prognostic models are based on data upon admission or soon thereafter. Physicians, however, will often use the clinical course in their prognostication, as the patient's prognosis becomes more evident during hospital stay. Second, physicians can use information beyond that

contained in severity of illness scores, especially factors that are difficult to quantify such as functional status and quality of life. Third, most prognostic models have been derived from cohorts that include both non-DNR and DNR patients. This results in predictions that appear to be pessimistic in patients without DNR orders, but optimistic in those with DNR orders [9]. Pessimism may result in a superfluous number of DNR orders. Fourth, when the decision is made to withdraw support this will make all previously identified clinical prognosticators of outcome worthless, because it becomes a self-fulfilling prophecy.

Prognostic models should be used to determine the prognosis of an individual patient with extreme prudence. They may have additional value in calibration, but limited value for a specific patient and should therefore not be used as a sole determinant for DNR decision making.

Patients with intracerebral haemorrhage

The effect of treatment limitations on outcome has been studied most thoroughly in patients with acute intracerebral haemorrhage (ICH). The effect of treatment limitations in this category of patients may serve as an example for other disorders.

Treatment limitation decisions are important in patients with acute stroke, since these patients may be prone to an outcome with a quality of life below patients' or relatives' expectations. However, in the last decade, both functional outcome and mortality after ICH have been improved by care in specialised neurologic ICUs, with 65% of subjects without DNR discharged home, and only 8% to a nursing home [22].

Shepardson et al. studied the use of DNR orders in 13,337 stroke patients. DNR orders were used in 22% and the mortality rate was 34 times higher in patients with DNR orders, as compared with patients without DNR orders after adjustment for propensity scores and based on nine demographic and clinical variables [1]. Hemphill et al. focused on the impact of DNR orders on outcome. In their study of 8233 patients with acute ICH, a hospital that used DNR orders 10% more often than another hospital with a similar case mix, had a 13% higher mortality rate ($p < 0.001$) [23].

The most important prognostic variables of ICH are the haematoma volume, the initial Glasgow Coma Score, the presence of intraventricular haemorrhage, hydrocephalus, an infratentorial location, age, active bleeding, the degree of midline shift, hyperglycaemia and marked hypertension [29]. Several prognostic models based on these factors have been developed. However, these models may be overly pessimistic in predicting outcome, since they have failed to account for care limitations such as DNR or withdrawal of technical support [29,9].

Most patients with ICH die soon after admission to the hospital when support is withdrawn because of presumed poor prognosis. Despite the uncertain ground on which it is based, the use of DNR orders within the first 24 hours after acute ICH is common and heterogeneous across different hospitals. Therefore, we agree with the guidelines of the American Stroke Association recommending aggressive guideline-concordant therapy in all ICH patients who do not have advanced directives. New DNR orders should be postponed until at least the second full day of hospitalization [30].

Reasons for increased mortality in DNR patients

The reasons for increased mortality in DNR patients is only partly understood; several hypothesis can, however, be formulated. First, DNR may reflect patients unwilling to undergo the burdensome care of life-sustaining interventions and have a lower "will to survive". Second, the propensity scores used to calculate the difference between the observed minus the expected mortality rate are inaccurate. More difficult to quantify covariates, such as quality of life and functional status, may be omitted from the propensity score, which may result in a too optimistic predicted survival for DNR patients. In contrast, in patients without a DNR order, prognostic models appear to be too pessimistic [31,9,29]. This may result in an inappropriate DNR order for this patient. There is no evidence what proportion of patients with a given condition will survive when support is not allowed to be withdrawn. Patients with an apparent poor prognosis would have to be randomized to continue or withdraw unrestricted treatment, which evidently would be unethical. Therefore, prognoses and prognostic models have to be made on the basis of the available evidence, derived from studies that have included patients with treatment limitations. This will certainly have an impact on outcome. In these predictions death despite treatment cannot be certain, and treatment limitations on this basis will therefore unavoidably increase mortality.

Finally and most worryingly, having a DNR order may affect that patient's penumbra of care. Although formally only interventions in the case of cardiac arrest should be withdrawn, these patients may face suboptimal care under other conditions as well. When, for example, more than one acutely ill patient needs attention at the same time, for instance during a nightshift, the doctor or nurse may give lower priority to a DNR patient. In his or her perception it may be acceptable to delay or to withhold treatments other than CPR (figure 1). This may cause a significant delay in doing diagnostic and therapeutic procedures, resulting in longer disturbance of functions of vital organs (hypotension, low urine output, deoxygenation et cetera), which may have a negative impact on the prognosis of that particular patient.

Practical recommendations

As shown earlier, several studies suggest that DNR orders are an independent risk factor for mortality. Despite this potential negative impact of DNR orders on mortality, using DNR orders is sometimes unavoidable. To completely refrain from using DNR orders may result in an increasing number of patients with a prolonged process of dying or survival with severe impairment [13].

So what can we do to decrease the risk of unwanted mortality due to the assignment of DNR orders? As explained earlier, in North America, relatives by right, share this decision with physicians, whereas in Europe, the preferences of proxies are to be taken into account, but the physician makes the final decision . We will focus on the situation in Europe.

Part of the enhanced mortality can be explained by patient preferences for limited therapy and this should be respected.

However, precautions should be taken into account when discussing DNR orders. As discussed earlier, prognostic models tend to underestimate the changes of survival in non-DNR patients. Although they may aid in calibration, they should not be used as a sole determinant for DNR decision making. Furthermore, it is important that treatment limitations are enforced only by experienced physicians, preferably intensivists [32] clinicians working in the ICU, as they are better in prognostication and can better overlook the effects of aggressive medical treatment. It is advisable to discuss treatment limitations early with the patient and family. During an emergency admission it is unlikely that there will be enough time to discuss the chances of a good functional outcome with the risk of resuscitation efforts being in vain. During evening and night shifts many senior staff members will not be available for this discussion and it turns out to be the – inexperienced house officer -- who has never seen the patient before -- who is confronted with this challenge. Whenever there is doubt about a code order, ICU attending physicians should be consulted.

When patients have already been admitted to the ICU without a code order, treatment limitations should be a multidisciplinary decision with the involvement of nurses and other colleagues.

Another important question here is how the broadening of DNR orders can be avoided? First, all hospitals should have clear guidelines about DNR orders, preferably based on national guidelines. These should state that DNR orders have to be viewed in isolation from other treatment decisions. Furthermore, treatment limitations should be specified and clearly written in the patient's medical record, by preference on specific code forms.

Conclusions

It should be remembered that having a DNR order does not only depend on patient characteristics, but on the attitude of individual doctors and the culture in a specific hospital as well. Therefore, it is extremely important that physicians are aware of the unintentional impact of DNR orders and avoid broadening the interpretations of DNR and withholding treatments other than CPR in DNR patients.

Competing interests

The authors declare that they have no competing interests.
Factors with a potential impact on DNR decisions and possible consequences of DNR orders

References

1. Shepardson LB, Youngner SJ, Speroff T, and Rosenthal GE. Increased risk of death in patients with do-not-resuscitate orders. Med Care 1999;37:727-737

2. Kroch EA, Johnson M, Martin J, and Duan M. Making hospital mortality measurement more meaningful: incorporating advance directives and palliative care designations. Am J Med Qual 2010;25:24-33

3. O'Brien JM, Jr., Aberegg SK, Ali NA, Diette GB, and Lemeshow S. Results from the national sepsis practice survey: predictions about mortality and morbidity and recommendations for limitation of care orders. Crit Care 2009;13:R96-

4. Yaguchi A, Truog RD, Curtis JR, Luce JM, Levy MM, Melot C, and Vincent JL. International differences in end-of-life attitudes in the intensive care unit: results of a survey. Arch Intern Med 2005;165:1970-1975

5. Cook DJ, Guyatt GH, Jaeschke R, Reeve J, Spanier A, King D, Molloy DW, Willan A, and Streiner DL. Determinants in Canadian health care workers of the decision to withdraw life support from the critically ill. Canadian Critical Care Trials Group. JAMA 1995;273:703-708

6. Wenger NS, Pearson ML, Desmond KA, Brook RH, and Kahn KL. Outcomes of patients with do-not-resuscitate orders. Toward an understanding of what do-not-resuscitate orders mean and how they affect patients. Arch Intern Med 1995;155:2063-2068

7. Kelly WF, Eliasson AH, Stocker DJ, and Hnatiuk OW. Do specialists differ on do-not-resuscitate decisions? Chest 2002;121:957-963

8. Lemeshow S, Klar J, and Teres D. Outcome prediction for individual intensive care patients: useful, misused, or abused? Intensive Care Med 1995;21:770-776

9. Creutzfeldt CJ, Becker KJ, Weinstein JR, Khot SP, McPharlin TO, Ton TG, Longstreth WT, Jr., and Tirschwell DL. Do-not-attempt-resuscitation orders and prognostic models for intraparenchymal hemorrhage. Crit Care Med 2011;39:158-162

10. Baker R and Strosberg MA. The legitimation and regulation of DNR orders. Legislating medical ethics: a study of the New York State do not resuscitate law 1995;33-101

11. American Heart Association. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care: medicolegal considerations and recommendations. JAMA 1974;227 (suppl):864-866

12. Keyserlingk EW. Review of report: Deciding to Forego Life-Sustaining Treatment (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, Washington, D.C., March, 1983). Health Law Can 1984;4:103-107

13. Moselli NM, Debernardi F, and Piovano F. Forgoing life sustaining treatments: differences and similarities between North America and Europe. Acta Anaesthesiol Scand 2006;50:1177-1186

14. Burns JP, Edwards J, Johnson J, Cassem NH, and Truog RD. Do-not-resuscitate order after 25 years. Crit Care Med 2003;31:1543-1550

15. Meissner A, Genga KR, Studart FS, Settmacher U, Hofmann G, Reinhart K, and Sakr Y. Epidemiology of and factors associated with end-of-life decisions in a surgical intensive care unit. Crit Care Med 2010;38:1060-1068

16. Jayes RL, Zimmerman JE, Wagner DP, and Knaus WA. Variations in the use of do-not-resuscitate orders in ICUS. Findings from a national study. Chest 1996;110:1332-1339

17. King JJ, Doukas DJ, and Gorenflo DW. Do not resuscitate orders for cerebrovascular accident patients. Stroke 1992;23:1032-1033

18. Alexandrov AV, Bladin CF, Meslin EM, and Norris JW. Do-not-resuscitate orders in acute stroke. Neurology 1995;45:634-640

19. Zimmerman JE, Knaus WA, Sharpe SM, Anderson AS, Draper EA, and Wagner DP. The use and implications of do not resuscitate orders in intensive care units. JAMA 1986;255:351-356

20. Rapaport FT, Meek AG, Arnold AN, Miura S, Hayashi R, and Strober S. Preoperative preparation of high-risk, specifically hyperimmunized canine renal allograft recipients with total-lymphoid irradiation and cyclosporine. Transplantation 1987;44:185-195

21. Azoulay E, Pochard F, Garrouste-Org, Moreau D, Montesino L, Adrie C, de LA, Cohen Y, and Timsit JF. Decisions to forgo life-sustaining therapy in ICU patients independently predict hospital death. Intensive Care Med 2003;29:1895-1901

22. Zahuranec DB, Brown DL, Lisabeth LD, Gonzales NR, Longwell PJ, Smith MA, Garcia NM, and Morgenstern LB. Early care limitations independently predict mortality after intracerebral hemorrhage. Neurology 2007;68:1651-1657

23. Hemphill JC, III, Newman J, Zhao S, and Johnston SC. Hospital usage of early do-not-resuscitate orders and outcome after intracerebral hemorrhage. Stroke 2004;35:1130-1134
24. Tabak YP, Johannes RS, Silber JH, and Kurtz SG. Should Do-Not-Resuscitate status be included as a mortality risk adjustor? The impact of DNR variations on performance reporting. Med Care 2005;43:658-666
25. Hakim RB, Teno JM, Harrell FE, Jr., Knaus WA, Wenger N, Phillips RS, Layde P, Califf R, Connors AF, Jr., and Lynn J. Factors associated with do-not-resuscitate orders: patients' preferences, prognoses, and physicians' judgments. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. Ann Intern Med 1996;125:284-293
26. Hemphill JC, III. Do-not-resuscitate orders, unintended consequences, and the ripple effect. Crit Care 2007;11:121-
27. Markgraf R, Deutschinoff G, Pientka L, Scholten T, and Lorenz C. Performance of the score systems Acute Physiology and Chronic Health Evaluation II and III at an interdisciplinary intensive care unit, after customization. Crit Care 2001;5:31-36
28. Sinuff T, Adhikari NK, Cook DJ, Schunemann HJ, Griffith LE, Rocker G, and Walter SD. Mortality predictions in the intensive care unit: comparing physicians with scoring systems. Crit Care Med 2006;34:878-885
29. Becker KJ, Baxter AB, Cohen WA, Bybee HM, Tirschwell DL, Newell DW, Winn HR, and Longstreth WT, Jr. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. Neurology 2001;56:766-772
30. Morgenstern LB, Hemphill JC, III, Anderson C, Becker K, Broderick JP, Connolly ES, Jr., Greenberg SM, Huang JN, MacDonald RL, Messe SR, Mitchell PH, Selim M, and Tamargo RJ. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2010;41:2108-2129
31. Wildman MJ, Sanderson C, Groves J, Reeves BC, Ayres J, Harrison D, Young D, and Rowan K. Implications of prognostic pessimism in patients with chronic obstructive pulmonary disease (COPD) or asthma admitted to intensive care in the UK within the COPD and asthma outcome study (CAOS): multicentre observational cohort study. BMJ 2007;335:1132-
32. Barrera R, Nygard S, Sogoloff H, Groeger J, and Wilson R. Accuracy of predictions of survival at admission to the intensive care unit. J Crit Care 2001;16:32-35