The Journal of International Medical Research
2010; 38: 1584 – 1595

Delayed Treatment of Delirium Increases Mortality Rate in Intensive Care Unit Patients

A Heymann[1]*, F Radtke[1]*, A Schiemann[1], A Lütz[1], M MacGuill[1], KD Wernecke[1,2] and C Spies[1]

[1]Department of Anaesthesiology and Intensive Care Medicine, Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]SOSTANA GmbH, Berlin, Germany

Delirium in the intensive care unit (ICU) is a serious complication associated with a poor outcome in critically ill patients. In this prospective observational study of the effect of a delay in delirium therapy on mortality rate, 418 ICU patients were regularly assessed using the Delirium Detection Score (DDS). The departmental standard required that if delirium was diagnosed (DDS > 7), therapy should be started within 24 h. In total, 204 patients (48.8%) were delirious during their ICU stay. In 184 of the delirious patients (90.2%), therapy was started within 24 h; in 20 patients (9.8%), therapy was delayed. During their ICU stay, patients whose delirium treatment was delayed were more frequently mechanically ventilated, had more nosocomial infections (including pneumonia) and had a higher mortality rate than patients whose treatment was not delayed. Thus, it would appear that a delay in initiating delirium therapy in ICU patients was associated with increased mortality.

KEY WORDS: Therapy; Delirium; Intensive care unit; Therapy delay; Outcome

Introduction

Delirium is a common and serious complication in critically ill patients, with a reported prevalence reaching 82% in some intensive care units (ICU).[1,2] Research has shown that the development of delirium is associated with multiple complications and poor outcome.[1,3] For example, delirium is an independent predictor of an increase in the duration of mechanical ventilation, length of stay in the ICU, total length of in-patient stay,[4 – 6] and overall hospital costs.[7] More alarmingly, delirium is also associated with a three-fold increase in the frequency of death at 6 months following ICU admission.[8]

Little evidence about the therapeutic management of delirium in critically ill patients is available. The Society of Critical Care Medicine[9] and the American Psychiatric Association[10] recommend haloperidol for the treatment of delirium in the ICU: doses ranging from 4 to 20 mg/day are commonly used. Alternatively, atypical antipsychotics including olanzapine or risperidone may be administered. Benzodiazepines and α-agonists, such as

*A Heymann and F Radtke contributed equally to this article.

clonidine, have been used successfully for treating alcohol withdrawal syndrome[11] or agitated delirium of other origin.[12]

Delirium is often considered to be an unavoidable side-effect of severe illness. In such cases, it is likely that the patient will not receive adequate therapy for delirium in a timely manner. The aim of this prospective, observational study was to clarify the effect of a delay in receiving delirium-specific therapy on the patients' outcome. The primary outcome measure was the mortality rate due to delayed treatment of delirium. Secondary outcome measures were the need for mechanical ventilation, the incidence of pneumonia and the length of stay in both the ICU and hospital.

Patients and methods

PATIENTS

Adult patients, consecutively admitted to one of three anaesthesiological ICUs or the intermediate care unit (a subsection of the ICUs) of the tertiary care university hospital of Charité – Universitätsmedizin Berlin, Berlin, Germany, between mid-August and mid-November 2006 or between mid-February and mid-May 2007, were screened for inclusion in this study. Patients were admitted following surgery (cardiac, general trauma or other), because of post-surgical complications, or for the management of respiratory failure, including adult respiratory distress syndrome. Data for all patients admitted were documented in a patient management system (MedVision®; MedVision AG, Unna, Germany and Copra®; Copra Systems, Sasbachwalden, Germany) from the day of admission until discharge. Apart from age (≥ 18 years) and a minimum length of ICU stay (72 h), there were no special inclusion criteria. Moribund patients and patients with coma or severe neurological impairment due to brain injury were excluded. The study received approval from the Ethics Committee of Charité-Universitätsmedizin Berlin (approval No. EA1/132/07). All patients participating in the study provided written informed consent related to the treatment contract; additional consent was waived by the Ethics Committee.

ASSESSMENT OF DELIRIUM AND TREATMENT

Each patient's level of sedation was evaluated every 8 h using the Richmond Agitation – Sedation Scale (RASS).[13] If the level of sedation permitted delirium screening (RASS ≥ –2), the bedside nurse documented the score in the patient management data system. For the diagnosis of delirium, the Delirium Detection Score (DDS) was used.[14] This five-item score addresses disorientation, hallucinations, agitation, fear and vegetative symptoms such as sweating and hypertension; for each item the patient is given one of four severity scores (0, 1, 4 and 7). The precondition for analysis was that a DDS applied on three consecutive days, regardless of severity. On any one day, patients with a DDS > 7 were considered as being delirious and a treatment scheme[15] was recommended, according to the current standard procedures of the university hospital (stored at the database of The German Society of Anaesthesiology and Intensive Care Medicine; www.dgai.de). Patients with hallucinations received neuroleptics: 0.5 – 5 mg haloperidol given intravenously (i.v.) two to three times a day was recommended until delirium was no longer detected or hallucinations no longer occurred according to the DDS; 75 – 150 µg bolus i.v. or 60 – 180 µg/h continuous i.v. infusion of the α_2-agonist, clonidine, was the treatment suggested for autonomic signs and was given until the DDS and/or autonomic signs were negative; benzodiazepines were

advised for the adjunctive therapy of agitated and anxiety states (typically, 7.5 mg/day lorazepam given orally or midazolam given i.v. either as a 2 mg bolus or as a 0.03 – 0.2 mg/kg per h continuous infusion until delirium detection was negative and/or agitation or anxiety were not noticeable).

To assess the effect of delayed therapy for delirium, patients were assigned to two groups: immediate therapy, in which therapy was initiated within 24 h after delirium was diagnosed; or delayed therapy, in which therapy was not started until at least 24 h after the diagnosis of delirium.

To compare the outcome of all patients in the ICU, three well-established scores were used: the Acute Physiologic and Chronic Health Evaluation II [APACHE II], the Simplified Organ Failure Assessment [SOFA] and the 28-item Therapeutic Intervention Scoring System [TISS-28].[16 – 18]

PATIENT OUTCOME

Nosocomial infections including pneumonia, the need for mechanical ventilation, mortality and length of ICU stay were recorded. Hospital-acquired pneumonia was diagnosed according to published guidelines;[19] other nosocomial infections were diagnosed according to the criteria of the Centers for Disease Control and Prevention.[20]

STATISTICAL ANALYSES

Results are expressed as arithmetic mean ± SD, median (interquartile range) or frequency. After verifying a normal distribution of the data, differences between groups in terms of clinical parameters of interest were tested using non-parametric tests: the Wilcoxon test and McNemar's test were used for paired observations, and the Kruskal–Wallis test, the Mann–Whitney *U*-test and Fisher's exact test were used for independent groups. Kaplan–Meier curves were estimated and tested using the non-parametric log rank test and Breslow test (generalized Wilcoxon test). Where there were small sample sizes, relatively large differences in sample size, large but unbalanced groups, data sets containing ties or sparse data, tests were carried out using an exact version.

Differences in mortality, pneumonia and infection rates (yes/no) were tested by univariate and multivariate analyses, using logistic regression analysis. Differences in mortality and changes over time in the occurrence of pneumonia and infection were described by Kaplan–Meier curves and subjected to multivariate analysis using the Cox proportional hazards regression model. Hazard ratios (HR) with 95% confidence intervals (CI) and the corresponding *P*-values were calculated for each risk factor. Changes in interesting clinical outcomes with respect to time were analysed using non-parametric analysis of longitudinal data in a two-factorial design (first independent factor, group; second dependent factor, repetitions in time) according to Brunner *et al.*[21] Thus, all time points were compared simultaneously on the corresponding response curves.

Two-tailed P-values < 0.05 were considered to be statistically significant. All tests should be understood as constituting exploratory data analysis; consequently, no adjustments for multiple testing were made. All numerical calculations were performed using the SPSS® Statistical Package version 16.0 (SPSS Inc., Chicago, IL, USA), SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA) and S-PLUS 2000® (Professional Release 2®, 1988 – 1999, MathSoft, Cambridge, MA, USA) for Windows®.

Results

PATIENTS

In total, 2640 consecutive patients admitted

to the ICU over a 6-month period were screened for study inclusion; patient disposition is shown in Fig. 1. Of the 418 patients regularly assessed for delirium using the DDS, 214 (51.2%) never had a DDS ≥ 7 during their ICU stay (descriptive control group). The remaining 204 patients (48.8%) were positive for delirium, i.e. they had at least one documented DDS ≥ 7, and were included in the study. Most of the patients with delirium were male (n = 135; 66.2%, P = 0.001) versus the descriptive control group (total n = 214; male 106, 49.5%). There was no significant difference in age between the groups of patients with and without delirium (total median age 62 years; range 18 – 95 years): delirious patients, median age 63 years (range 18 – 95 years); non-delirious patients, median age 60 years (range 19 – 95 years). All ICU scores (APACHE II, SOFA and TISS-28) on admission were significantly higher in delirious than in non-delirious patients (all P < 0.001). The duration of mechanical ventilation and length of stay in the ICU and in hospital were also significantly longer in delirious than in non-delirious patients (all P < 0.001). Delirious patients had a higher incidence of pneumonia (P < 0.001) and a higher mortality rate (P = 0.017) than non-delirious patients.

TREATMENT OF DELIRIUM

In 184/204 (90.2%) of the delirious patients, therapy for delirium commenced within 24 h of diagnosis, whereas in 20/204 patients (9.8%) treatment was initiated > 24 h after diagnosis. Admission diagnoses and baseline characteristics for the delirious patients are

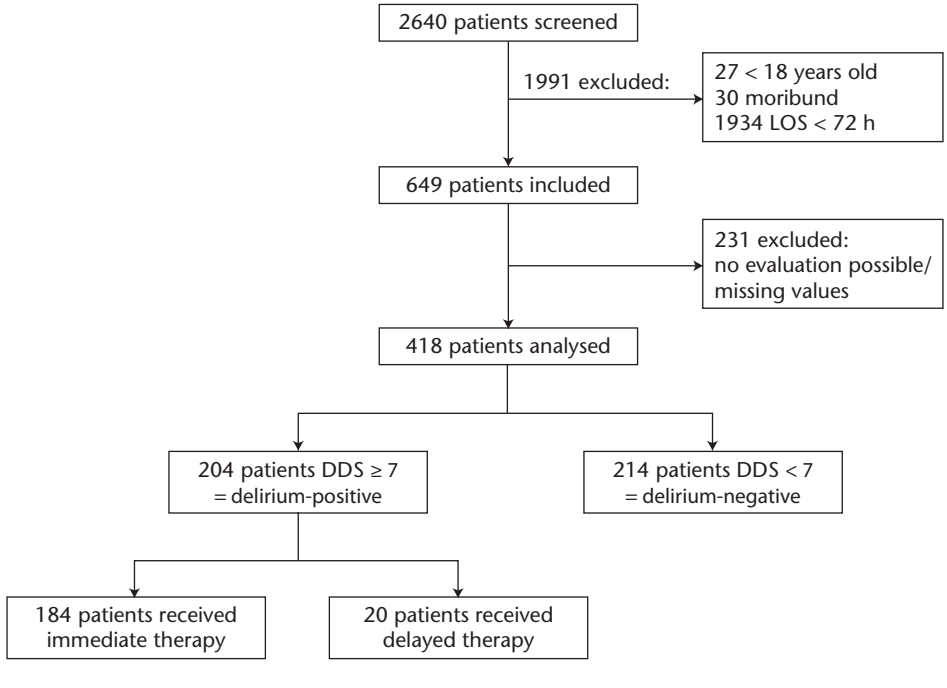

FIGURE 1: Patient disposition for a study of intensive care unit (ICU) patients, comparing the outcome of those receiving immediate or delayed therapy for delirium (DDS, Delirium Detection Score; LOS, length of stay in the ICU)

summarized in Table 1. Thirty-five per cent (n = 7) of patients in the delayed therapy group received neuroleptics at the time that treatment began, compared with 78% (n = 143) of patients in the immediate therapy group. α_2-Agonists, such as clonidine, were used in 55% (n = 11) in the delayed therapy group compared with 77% (n = 141) of patients in the immediate therapy group, and benzodiazepines were used in 85% (n = 17) and 92% (n = 169) of patients in the delayed and immediate therapy groups, respectively. The treatments used were in close accordance with the standard scheme of therapy at the Department of Anaesthesiology and Intensive Care Medicine, Charité – Universitätsmedizin Berlin: of all 204 delirious patients, neuroleptics were given in 78% (n = 158), benzodiazepines in 94% (n = 192) and clonidine in 81% (n = 166).

DURATION AND NUMBER OF EPISODES OF DELIRIUM

On average, an elevated DDS was measurable for a mean ± SD of 4.35 ± 3.69 days in patients with delirium. Patients in the delayed therapy group had significantly more recurrent delirium episodes compared with those in the immediate therapy group (2.9 ± 1.7 versus 2.2 ± 1.6 episodes; P = 0.036).

SEVERITY

At the time of diagnosis, delirium severity (DDS of 8 – 35) was significantly higher in the immediate therapy than in the delayed therapy group (mean ± SD DDS of 13.9 ± 5.6 versus 10.2 ± 3.3, respectively; P = 0.001).

TABLE 1:
Admission diagnosis and baseline characteristics of delirious patients in the intensive care unit whose delirium treatment began within 24 h (immediate therapy) or > 24 h (delayed therapy) after delirium diagnosis

Characteristic	Immediate therapy n = 184	Delayed therapy n = 20	Statistical significance[a]
Age (years)	62.5 (18 – 95)	69.4 (42 – 90)	NS
Gender (male)	124 (67)	11 (55)	NS
APACHE II score	20.2 (5 – 38)	24.7 (18 – 36)	P = 0.005
SOFA score	5.7 (0 – 14)	7.1 (3 – 18)	NS
TISS-28 score	33.3 (11 – 62)	36.7 (19 – 57)	NS
Admission diagnosis			
Trauma surgery	27 (15)	2 (10)	
General surgery	43 (23)	8 (40)	
Cardiac surgery	34 (18)	0 (0)	
Other surgery[b]	23 (13)	2 (10)	
Neurological[c]	30 (16)	5 (25)	
Pulmonary[d]	14 (8)	3 (15)	
Sepsis	13 (7)	0 (0)	

Data are median (interquartile range) or n (%).
[a]Fisher's exact test was used for comparisons of age and gender; Mann–Whitney U-test used for comparisons of APACHE II, SOFA and TISS-28.
[b]Ear, nose and throat, gynaecological or urological surgery.
[c]Neurological trauma and diseases, neurosurgery.
[d]Respiratory failure, including adult respiratory distress syndrome.
APACHE II, Acute Physiologic and Chronic Health Evaluation II; SOFA, Simplified Organ Failure Assessment; TISS-28, 28-item Therapeutic Intervention Scoring System; NS, not statistically significant (P > 0.05).

During the course of the ICU stay, the reduction in DDS was significantly greater in the immediate than in the delayed therapy group (P = 0.004). Brunner analysis demonstrated a significant correlation between the time of delirium therapy onset and the rate of the DDS reduction (P = 0.014; Fig. 2). During the first 24 h after the diagnosis of delirium, patients in the delayed therapy group showed a hypoactive form of delirium more often than those in the immediate therapy group (40% versus 14%, respectively; P = 0.041); this form of delirium was intermittently associated with RASS scores ≤ 0.

On the last day of ICU stay, the DDS was significantly lower than the score recorded on the first day of delirium in the immediate therapy group (5.5 ± 5.7 versus 13.9 ± 5.6, respectively; P < 0.001) but was not significantly lower in the delayed therapy group (7.3 ± 4.9 versus 10.2 ± 3.3, respectively).

MECHANICAL VENTILATION

The duration of mechanical ventilation was 9.5 ± 14.5 days in the immediate and 14.5 ± 15.5 days in the delayed therapy group; this difference was not statistically significant. The percentage of mechanically ventilated patients was not significantly different between the groups on the day of delirium diagnosis (immediate therapy, 41.8%; delayed therapy, 50.0%, Fig. 3A). However, at the end of the ICU stay, the percentage of mechanically ventilated patients was significantly lower in the immediate therapy

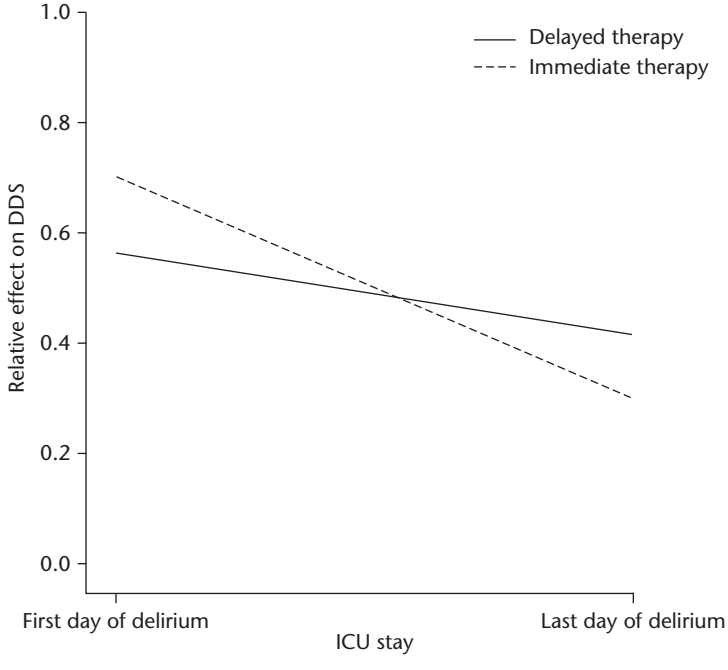

FIGURE 2: Comparison of delirium severity in intensive care unit (ICU) patients receiving delirium therapy within 24 h (n = 184, immediate therapy group) or > 24 h after delirium diagnosis (n = 20, delayed therapy group). Compared with the delayed therapy group, patients in the immediate therapy group had relatively higher severity scores (Delirium Detection Score [DDS]) on the first day of delirium, and a significantly greater rate of reduction in DDS during their ICU stay (P = 0.014)

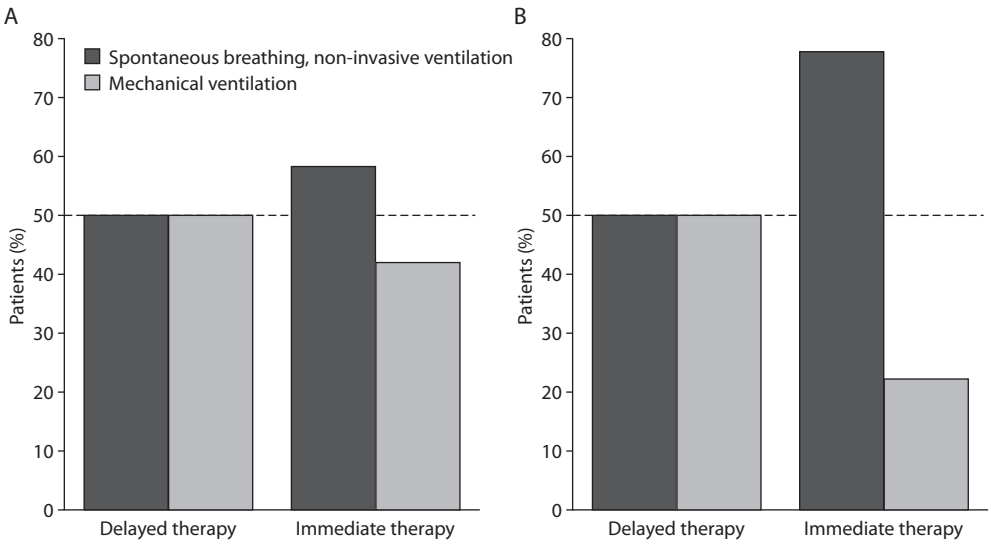

FIGURE 3: Percentages of spontaneously breathing and mechanically ventilated intensive care unit (ICU) patients with delirium, treated within 24 h of delirium diagnosis (n = 184, immediate therapy group) or > 24 h after diagnosis (n = 20, delayed therapy group): (A) on the day of delirium diagnosis, no significant between-group differences in mechanical ventilation were observed (delayed therapy group, 50.0%; immediate therapy group, 41.8%); (B) on the last day in the ICU, significantly fewer patients in the immediate therapy group needed to be mechanically ventilated, compared with the delayed therapy group (22.3% versus 50.0%, respectively; P = 0.012)

group than in the delayed therapy group (22.3% versus 50.0%, respectively; P = 0.012; Fig. 3B). During the ICU stay, patients in the immediate therapy group, therefore, showed significant improvement in their respiratory condition (P < 0.001), unlike those in the delayed therapy group.

NOSOCOMIAL INFECTIONS

Patients in the delayed therapy group experienced nosocomial infections or hospital-acquired pneumonia significantly more frequently than those in the immediate therapy group (P < 0.05; Table 2). Kaplan–Meier estimates for pneumonia (yes/no) revealed significant differences between the patient groups (log rank test, P = 0.002; Breslow test, P = 0.014; Fig. 4) following the first occurrence of delirium. Multivariate analysis by Cox regression with time-dependent covariates confirmed a significantly higher probability of developing pneumonia (HR 1.850; 95% CI 1.023 – 3.343; P = 0.042) in the delayed therapy compared with the immediate therapy group. The effect was independent of the covariates age, DDS, SAPS, SOFA, TISS-28 and APACHE II.

MORTALITY

The mortality rate was significantly higher in the delayed therapy group than in the immediate therapy group (P = 0.003; Table 2). Kaplan–Meier survival analysis revealed a significantly higher risk of death in the delayed therapy group (log rank test, P < 0.001; Breslow test, P = 0.013; Fig. 5). Cox regression analysis with time-dependent

TABLE 2:
Main outcomes in patients with delirium in the intensive care unit whose delirium treatment began within 24 h (immediate therapy) or > 24 h (delayed therapy) after delirium diagnosis

Outcome	Immediate therapy *n* = 184	Delayed therapy *n* = 20	Statistical significance[a]
Mortality	16 (8.7)	7 (35.0)	*P* = 0.003
Nosocomial infections	134 (72.8)	19 (95.0)	*P* = 0.029
Pneumonia	92 (50.0)	16 (80.0)	*P* = 0.017
Mechanical ventilation (days)	8.5 (0 – 90)	12.8 (0 – 41)	NS
Length of ICU stay (days)	17.2 (3 – 90)	20.0 (3 – 42)	NS
APACHE II score at discharge	16.9 (6 – 43)	24.1 (7 – 45)	*P* = 0.002
SOFA score at discharge	3.9 (0 – 18)	7.5 (1 – 19)	*P* = 0.005
TISS-28 score at discharge	27.3 (3 – 66)	36.9 (13 –60)	*P* = 0.001

Data are median (interquartile range) or *n* (%).
[a]Fisher's exact test used for comparisons of mortality, nosocomial infections and pneumonia; Mann–Whitney *U*-test used for comparisons of mechanical ventilation, length of stay, APACHE II, SOFA and TISS-28.
ICU, intensive care unit; APACHE II, Acute Physiologic and Chronic Health Evaluation II; SOFA, Simplified Organ Failure Assessment; TISS-28, 28-item Therapeutic Intervention Scoring System; NS, not statistically significant (*P* > 0.05).

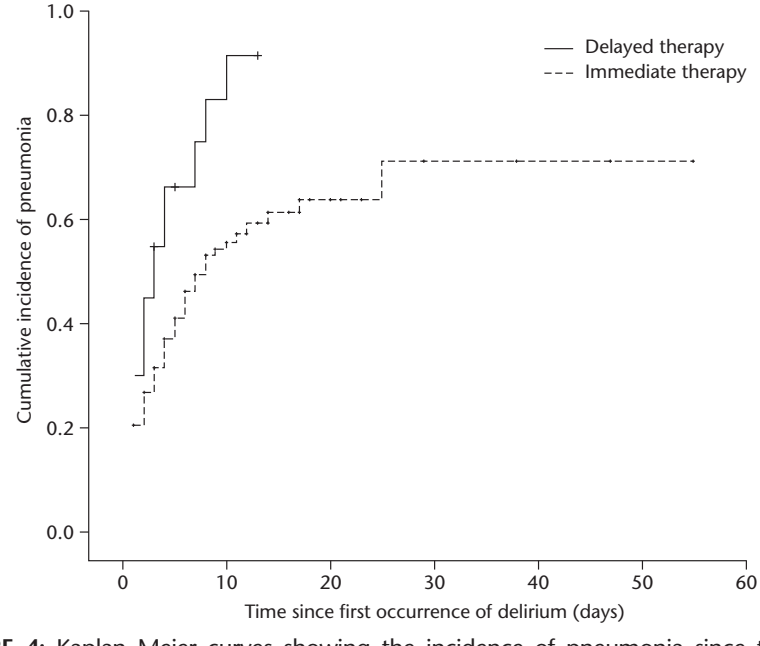

FIGURE 4: Kaplan–Meier curves showing the incidence of pneumonia since the first occurrence of delirium in 184 intensive care unit (ICU) patients receiving delirium treatment within 24 h of diagnosis (immediate therapy group) and 20 ICU patients in whom delirium treatment started > 24 h after diagnosis (delayed therapy group); the delayed therapy group had a higher probability of developing pneumonia than the immediate therapy group (vertical markers show censorship points). A significant between-group difference was observed (log rank test, *P* = 0.002; Breslow test, *P* = 0.014)

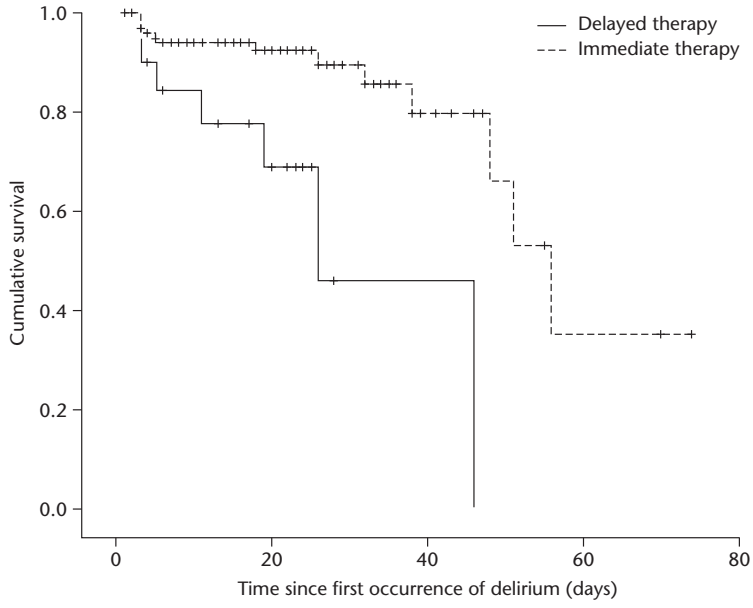

FIGURE 5: Kaplan–Meier survival estimates for 184 intensive care unit (ICU) patients with delirium treated within 24 h of diagnosis (immediate therapy group) and 20 patients in whom delirium treatment started > 24 h after diagnosis (delayed therapy group); the delayed therapy group showed a lower probability of surviving until ICU discharge than the immediate therapy group (vertical markers show censorship points). There was a significantly higher risk of death in the delayed therapy group versus the immediate therapy group (log rank test, $P < 0.001$; Breslow test, $P = 0.013$)

covariates confirmed that patients in the delayed therapy group had a three-fold higher likelihood of dying, compared with those in the immediate therapy group (HR 3.023; 95% CI 1.056 – 8.656; $P = 0.039$). This effect was significant for age (HR 1.035; 95% CI 1.002–1.070; $P = 0.038$) but not for the covariates DDS, SAPS, SOFA, TISS-28 and APACHE II.

ICU SCORES AND LENGTH OF ICU STAY

At the beginning of delirium, patients in the delayed therapy group showed significantly higher APACHE II scores in comparison with the immediate therapy group ($P = 0.005$), whereas there were no significant between-group differences in SOFA or TISS-28 scores (Table 1). On the last ICU day, APACHE II ($P = 0.002$), SOFA ($P = 0.005$), and TISS-28 ($P = 0.001$) scores were significantly higher in the delayed therapy group than in the immediate therapy group (Table 2). APACHE II, SOFA and TISS-28 scores decreased between the first day of delirium and discharge from the ICU in the immediate therapy group ($P \leq 0.001$, all scores) but not in the delayed therapy group. The two groups did not differ significantly in the length of ICU stay (Table 2).

Discussion

The most important result of the present study was the finding that a delay in starting delirium therapy was associated with an elevated mortality risk in critically ill ICU patients. Several publications have demonstrated that delirium is an independent risk factor for a variety of

complications and increased mortality rate in the ICU, but to the best of the authors' knowledge the effect of delayed therapy has not been addressed previously. In sepsis, for example, early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock:[22] the early identification of insidious illness allowed early implementation of goal-directed therapy and reduced the subsequent need for treatments such as vasopressors and mechanical ventilation.[22] In addition, inflammation-induced cytokine production occurs in several transmitter imbalances associated with delirium.[23,24]

All ICU scores (APACHE, SOFA and TISS-28) decreased significantly ($P \leq 0.001$) during the course of the ICU stay in the immediate therapy but not in the delayed therapy group. This finding supports the idea that a delay in therapy for delirium leads to aggravation of illness, and that delirium is not improved when delayed treatment starts. Elevated SOFA scores in the delayed therapy group indicated a progression of organ insufficiency over the course of the ICU stay, whereas the immediate therapy group showed a lower SOFA at discharge than at ICU entry. The continuously high TISS-28 scores seen in the delayed therapy group reflect an ongoing high requirement for care, which is characteristic of delirious patients.

The APACHE II score was higher in the delayed therapy group than in the immediate therapy group on the day of delirium diagnosis. It could be argued that the patients in the delayed therapy group were more severely ill and that this contributed to their worse outcome. Regression analysis revealed, however, that age was a relevant cofactor but APACHE II, SOFA or TISS-28 were not, i.e. that the range of scores in this observational study was very broad. Interestingly, in the present study, the DSS at the beginning of delirium was lower in patients with delayed treatment than in those treated immediately. In other settings, such as alcohol withdrawal syndrome, a delay in therapy initiation increased the severity of the syndrome.[25] The absence of an urgently required treatment could be a result of relatively low severity and late recognition of delirium. Certainly, at the point of diagnosis, the severity of delirium in the present study was higher in the immediate therapy than in the delayed therapy group. During the first 24 h after delirium diagnosis, patients in the delayed group more often showed a hypoactive form of delirium than those who received delirium treatment immediately; hypoactive states are often misdiagnosed as sedation or depression.[26] As a consequence, in the delayed therapy group the severity of delirium was not reduced to the same extent as in the immediate therapy group.

Implementation rates are often inadequate. Considering that 10% of the patients did not receive prompt treatment for delirium – and an implementation rate of 70% is usually considered sufficient for quality management[27] – there should be different implementation rates for different ICU treatments, because an elevated mortality risk was observed in the 10% of patients who were not treated immediately.

There were some limitations to the present study. Although 2640 patients were screened, the number of final evaluations in each group was small. This was because the precondition for analysis was a minimum length of ICU stay of 3 days and a minimum of at least one DDS for 3 consecutive days. The delayed therapy group was also very small (20 patients). These considerations should be taken into account when interpreting our study findings.

An incidence of delirium of 48.8% was

recorded among patients analysed in the present cohort. Other studies in ICU patients report higher incidences of delirium.[1,2] The difference in the present study may be related to the use of the DDS to identify delirium. A recent validation study in ICU patients showed that the DDS had high specificity (91%) but low sensitivity (30%).[28] With a cut-off of 7 points, the DDS probably does not detect all types of delirium and it is likely, therefore, that some delirious patients were missed in the present study. A further validation study of the DDS revealed a sensitivity of 78% and a specificity of 81% for a cut-off of 3 points.[28] It is possible that, in some patients in the present study, delirium started earlier but was not diagnosed because of the low sensitivity of the score. Thus, there might have been an unknown delay in therapy which could have contributed to the high APACHE II scores in the delayed therapy group at the time of delirium diagnosis.

Fewer patients in the delayed therapy group received neuroleptic treatment, compared with the immediate therapy group (35% versus 78% of patients, respectively). The possibility that this difference had an influence on outcome cannot be excluded. There is some evidence that haloperidol or other neuroleptics can be used as first-line medications in hypoactive forms of delirium.[29]

In conclusion, an early start to therapy is essential in the treatment of delirium in critically ill patients. Treatment delays may increase the mortality rate, whereas early treatment may decrease progression to multiorgan failure. Sustainable implementation of delirium monitoring is a potentially important aid in the provision of early diagnosis and treatment.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

• Received for publication 8 February 2010 • Accepted subject to revision 4 May 2010
• Revised accepted 1 September 2010

References

1 Dubois MJ, Bergeron N, Dumont M, *et al*: Delirium in an intensive care unit: a study of risk factors. *Intensive Care Med* 2001; **27:** 1297 – 1304.
2 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.
3 Spies CD, Neuner B, Neumann T, *et al*: Intercurrent complications in chronic alcoholic men admitted to the intensive care unit following trauma. *Intensive Care Med* 1996; **22:** 286 – 293.
4 Ely EW, Gautam S, Margolin R, *et al*: The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med* 2001; **27:** 1892 – 1900.
5 Ouimet S, Riker R, Bergeron N, *et al*: Subsyndromal delirium in the ICU: evidence for a disease spectrum. *Intensive Care Med* 2007; **33:** 1007 – 1013.
6 Salam A, Tilluckdharry L, Amoateng-Adjepong Y, *et al*: Neurologic status, cough, secretions and extubation outcomes. *Intensive Care Med* 2004; **30:** 1334 – 1339.
7 Milbrandt EB, Deppen S, Harrison PL, *et al*: Costs associated with delirium in mechanically ventilated patients. *Crit Care Med* 2004; **32:** 955 – 962.
8 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.
9 Jacobi J, Fraser GL, Coursin DB, *et al*: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; **30:** 119 – 141.
10 American Psychiatric Association: Practice guideline for the treatment of patients with delirium. American Psychiatric Association. *Am J Psychiatry* 1999; **156(5 suppl):** 1 – 20.
11 Spies C, Rommelspacher H: Alcohol withdrawal in the surgical patient: prevention and treatment. *Anesth Analg* 1999; **88:** 946 – 954.

12 Attard A, Ranjith G, Taylor D: Delirium and its treatment. *CNS Drugs* 2008; **22:** 631 – 644.
13 Ely EW, Truman B, Shintani A, *et al:* Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation–Sedation Scale (RASS). *JAMA* 2003; **289:** 2983 – 2991.
14 Otter H, Martin J, Bäsell K, *et al*: Validity and reliability of the DDS for severity of delirium in the ICU. *Neurocrit Care* 2005; **2:** 150 – 158.
15 Krahne D, Heymann A, Spies C: How to monitor delirium in the ICU and why it is important. *Clin Effect Nurs* 2006; **9(suppl 3):** e269 – e297.
16 Vincent JL, De Mendonça A, Cantraine F, *et al:* Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. *Crit Care Med* 1998; **26:** 1793 – 1800.
17 Miranda DR, de Rijk A, Schaufeli W: Simplified Therapeutic Intervention Scoring System: the TISS-28 items – results from a multicenter study. *Crit Care Med* 1996; **24:** 64 – 73.
18 Knaus WA, Draper EA, Wagner DP, *et al:* APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13:** 818 – 829.
19 American Thoracic Society, Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; **171:** 388 – 416.
20 Garner JS, Jarvis WR, Emori TG, *et al*: CDC definitions for nosocomial infections 1988. *Am J Infect Control* 1988; **16:** 128 – 140.
21 Brunner E, Domhof S, Langer F (eds): *Nonparametric Analysis of Longitudinal Data in Factorial Experiments*. New York: John Wiley & Sons, 2002.
22 Rivers E, Nguyen B, Havstad S, *et al*: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345:** 1368 – 1377.
23 Rosas-Ballina M, Tracey KJ: Cholinergic control of inflammation. *J Intern Med* 2009; **265:** 663 – 679.
24 Tracey KJ: Physiology and immunology of the cholinergic antiinflammatory pathway. *J Clin Invest* 2007; **117:** 289 – 296.
25 Spies CD, Otter HE, Huske B, *et al*: Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. *Intensive Care Med* 2003; **29:** 2230 – 2238.
26 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.
27 Nachtigall I, Tamarkin A, Tafelski S, *et al*: Impact of adherence to standard operating procedures for pneumonia on outcome of intensive care unit patients. *Crit Care Med* 2009; **37:** 159 – 166.
28 Luetz A, Heymann A, Radtke FM, *et al*: Different assessment tools for ICU delirium. Which score to use? *Crit Care Med* 2010; **38:** 409 – 418.
29 Lonergan E, Britton AM, Luxenberg J, *et al*: Antipsychotics for delirium. *Cochrane Database Syst Rev* 2007 **2:** CD005594.

Author's address for correspondence
Professor Claudia Spies
Department of Anaesthesiology and Intensive Care Medicine, Campus Virchow-Klinikum/ Campus Charité Mitte, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany.
E-mail: claudia.spies@charite.de