

Introduction

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Delirium – or: acute confusion – is a common syndrome among adults admitted at an intensive care unit (ICU). For a long time, delirium in critically ill patients has been regarded an unavoidable symptom of the critical illness, and was assumed to be reversible when the underlying disease was cured. This view has shifted, however; delirium is now seen as a form of vital organ failure, or 'brain failure', which should be prevented whenever possible, because it is strongly associated with mortality and long-term cognitive decline. Although guidelines for the management of delirium at the ICU have been issued, in clinical practice the recommendations of those guidelines are often moderately adhered to. To improve health professionals' adherence to these recommendations, we first need to identify possible factors influencing adherence and next optimize the implementation of guidelines for the management of delirium in daily practice.

What is delirium, and how does it impact patient outcomes?

Delirium is a neuropsychiatric syndrome that often afflicts hospitalized persons, especially the elderly and those treated in an intensive care unit (ICU)¹. Different terms have been used to describe delirium (e.g. acute encephalopathy, acute confusional state, postoperative confusion, intensive unit psychosis), and case descriptions of delirium have been documented since antiquity^{2,3}. In 1850, Salter proposed that delirium is "always a matter of serious consideration to the medical practitioner and the subject of diagnosis is of primary importance"⁴. As early as in the 1950s, delirium was described as a syndrome of cerebral insufficiency, and considered a form of vital organ failure or 'brain failure' that should be more frequently recognized and managed⁵. Over time, definition for this condition has evolved from 'acute encephalopathy', to cover mental alterations, to delirium – as is now mostly used. In the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), delirium is defined as a disturbance in attention and awareness and a change in cognition that develops rapidly over a short period of time⁶. To distinguish delirium from other psychiatric disorders, there must always be an organic disease as underlying cause⁶. Delirium in itself is not a disease, but rather a syndrome that has to be studied as a "final common pathway of symptomatology"³.

The pathophysiology of delirium is not well understood and a variety of etiological factors may contribute to delirium in critically ill patients. Three major hypotheses for the pathogenesis of delirium have been proposed: the immune activation hypothesis, the oxidative stress hypothesis, and the cerebral neurotransmitters disturbances hypothesis^{7,8}. The wide variation in the occurrence of delirium in ICU patients is depending on the case mix; rates from 26% to 45% in a general ICU population^{9,10}; 28% in a surgical ICU unit¹¹; and up to 78% in ventilated ICU patients have been reported^{12,13}. Contributing

factors to delirium are distinguished into predisposing factors (e.g. age, cognitive and pre-morbid functional status etc.) and precipitating factors (e.g. drugs use, infections, pain).¹ The mnemonic acronym "I Watch Death", which refers to factors such as infection, withdrawal of benzodiazepines, and hypoxia, can be used to make a differential diagnosis and detect factors which may have triggered the delirium in a specific patient¹⁴.

Over the two past decades, we have learned that delirium is independently associated with poor outcomes for elderly patients in general and ICU patients in particular^{12,15}. Furthermore, prolonged duration of ventilation, longer ICU stay and, consequently, increased healthcare costs are related to delirium in ICU patients^{16,17}. Delirium is not only related to higher mortality during the ICU stay and six months after discharge¹², but also with significant cognitive impairment months after ICU stay and long-term psychological problems^{18,19}.

Not only the patients, but also the ICU professionals and a critically ill patient's family members consider delirium a very worrisome condition. ICU nurses characterize delirium as one of the most vexing problems due to communication difficulties²⁰, restless behavior and the danger of self-injury, which is associated with an increased workload²¹. And family and friends struggle to achieve contact with the patient who is mechanically ventilated and whose level of consciousness is often low^{22,23}. Psychological recovery of ICU patients can improve if family participation at the ICU is facilitated by nurses, for example²⁴⁻²⁶.

Delirium management: screening, prevention and treatment

To alleviate the adverse clinical outcomes associated with ICU delirium, professionals need to manage delirium in the best way possible. First, by applying validated bedside delirium-screening tools, like the Confusion Assessment Method-ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC)^{27,28}, implementation of delirium screening is feasible^{29,30}. The routine screening of mechanically ventilated patients may have positive effects³¹. Second, non-pharmacological prevention strategies such as orientation, environment interventions (e.g. providing glasses and hearing aids, etc.), and early therapeutic interventions (e.g. early mobilization and pain control) can reduce delirium rates³². Third, applying pharmacological strategies to treat delirium according to the 'ICU triad' concept, based on the idea that pain, agitation, and delirium are intertwined, may be useful³³.

Guidelines and implementation

Clinical practice guidelines are systematically developed evidence-based statements to assist healthcare professionals and patients in the decision-making about appropriate health care in specific clinical circumstances³⁴. The adherence to guideline recommendations in clinical practice in general is poor and needs to be improved³⁵. In other

words: "We know what we have to do, but in daily practice we do not do what we know that has to be done" (Prof. Takala, ESICM congress, 2014). On the other hand, many different recommendations have been proposed and it is challenging for staff to adhere to all of these³⁵. ICU guidelines reflect the medical and nursing professional standard in intensive care medicine and can be processed into local protocols.

The Netherlands Society of Intensive Care (NVIC) has issued the "NVIC Delirium Guideline on Intensive Care" guideline³⁶. The Pain, Agitation and Delirium (PAD) guidelines of the international Society of Critical Care Medicine are mostly in line with the Dutch guideline but is more updated and integrates pain, agitation and delirium better^{36,37}. The most recent update is coined the PADIS (Prevention and Management of Pain, Agitation / Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU) guidelines. It includes new recommendations on sleep and immobility, but was published after the studies described in this thesis had been conducted. Screening for delirium, preventive measures and therapeutic management are the cornerstones for optimal ICU delirium management by ICU nurses and physicians, as recommended in the national and international guidelines. For unclear reasons, however, and as already stated before, the management of delirium strongly depends on local policy, individual professionals, and is often not in line with current guideline recommendations³⁵.

One of the most important challenges in improving the quality of care is achieving behavioral change of healthcare professionals³⁸. The first step would be to identify the relevant barriers to and facilitators of delirium guidelines, professionals' knowledge about and attitude to delirium guidelines, and organizational, and patient level barriers for delirium guideline adherence. Implementation interventions tailored to identified barriers for guideline adherence seem to be more effective in improving professional practice than a "one size fits all" approach. Implementation models are helpful and necessary to develop a tailored implementation strategy based on the analysis of the context and the target group, such as the Implementation Model of Change developed by Grol and Wensing³⁹.

Identifying barriers to execution of ICU delirium guideline recommendations is essential⁴⁰ to develop an implementation plan that will successfully improve execution of those recommendations^{41,42}. Only by merging implementation science with clinicians' knowledge and insight can the best possible outcomes for critically ill patients with delirium be achieved^{43,44}.

Aims and outline of the thesis

This thesis contains the reports of our studies on the implementation of delirium guidelines in daily critical care practice. For this multicenter, prospective implementation project we followed these steps: first, determining the level of guideline adherence (baseline measurement); second, describing the barriers to and facilitating factors for

adherence to the guidelines; third, developing and executing a 'tailor-made' implementation strategy; and finally, studying the effects of the implementation on compliance with the guideline and on patient outcomes before versus after the implementation. The general aims were to assess factors that influence ICU delirium guideline compliance, to develop a tailored implementation program, and to study effects of the implementation interventions on adherence to the guideline and on clinical outcomes. The above aims have been substantiated in the various studies with the following research questions:

1. What are the barriers and facilitators for implementation of delirium guidelines?
2. What is the best way to implement the ICU delirium guideline recommendations and what factors are associated with outcome improvements?
3. What is the effect of implementation on guideline adherence and clinical outcomes?
4. What is the compliance with the guideline at site level, and what are the possible explanations for the implementation effectiveness, and what are the experiences with the implementation?
5. What are the trough levels of haloperidol when haloperidol was dosed according to a protocol using a low-dose regimen; are those trough levels associated with a decrease of delirium symptoms; and what is the influence of CYP3A4 and CYP2D6 genotype on haloperidol serum levels?

Chapter two describes the original study protocol and a letter to the editor about ICU delirium. **Chapter three** describes the barriers and facilitators based on a survey among ICU healthcare professionals about delirium, attitudes, knowledge and guideline adherence. **Chapter four** describes a systematic review of the literature on delirium guideline implementation studies. An implementation strategy based on literature review and analysis of barriers was executed and the effects were measured. **Chapter five** describes the effects of implementation on process of care and patient outcomes. **Chapter six** focuses on the evaluation of the implementation process on ICU level. **Chapter seven** describes a study on haloperidol serum concentrations and clinical response. Lastly, in **Chapter 8** the main findings of our research, are presented, the clinical implications are discussed and conclusions are drawn.

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