

# Delirium in children – new research directions

Aleksandra Gózdź

Department of Clinical Pharmacy and Biopharmacy,  
Poznan University of Medical Sciences, Poznan, Poland



Corresponding author: amgozdz@gmail.com

Agnieszka Bienert

Department of Clinical Pharmacy and Biopharmacy,  
Poznan University of Medical Sciences, Poznan, Poland

<https://orcid.org/0000-0001-7272-5738>

Alicja Bartkowska-Śniatkowska

Department of Pediatric Anesthesiology and Intensive Therapy,  
Poznań University of Medical Sciences, Poznań, Poland

<https://orcid.org/0000-0003-4950-2346>

Justyna Alicja Ber

Department of Clinical Pharmacy and Biopharmacy,  
Poznan University of Medical Sciences. Poznan, Poland

<https://orcid.org/0000-0003-2270-4386>

Erwin Ista

Pediatric Intensive Care Unit, Department of  
Paediatric Surgery, Erasmus Medical Center –  
Sophia Children's Hospital, The Netherlands

Nursing Science, Department of Internal Medicine,  
Erasmus Medical Center, Rotterdam, The Netherlands

<https://orcid.org/0000-0003-1257-3108>

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## ABSTRACT

One of the problems associated with a patient's stay in the hospital and the procedures they undergo is delirium, the occurrence of which is associated with numerous complications, longer stay in the ward, higher risk of death and increased healthcare costs. Scientists are continuing to search for effective methods to minimise the risk of its occurrence, as well as to develop effective therapeutic procedures. One such area of the research is the identification of delirium biomarkers, which would allow further PK/PD (pharmacokinetic/pharmacodynamic) modelling. This article focuses on the emergence delirium, which occurs in patients recovering from general anaesthesia.

## Definition and risk factors

Delirium is an acute and rapidly changing disorder of consciousness characterised by a decrease in the ability to focus, maintain or switch attention, accompanied by disorders of cognitive functions (memory deficit, disorientation, language disorders, hallucinations) and perception, which can be diagnosed based on medical history, clinical symptoms, physical examination or laboratory

tests. According to the International Classification of Diseases ICD-10, delirium also includes emotional, psychomotor, and sleep-wake cycle disorders [1,2]. Delirium can occur in any setting, but is more common in a hospital setting, mainly in Intensive Care Units (ICU), due to associated clinical deterioration and/or pharmacological agents, such as benzodiazepines, opioids or anticholinergics, which may cause or exacerbate delirium [3-5]. Additionally, a hospital stay can

contribute to an increased risk of delirium due to exposure to stress, noise, excessive stimulation and the resulting disturbances of sleep and wake rhythm, diagnostic procedures, pain and fear related to a stay in the ward [6-12]. Injury, sepsis, any kind of shock, heart failure and respiratory failure have been associated with tissue hypoperfusion and development of inflammation, which may contribute to delirium [9,13].

## Postoperative delirium (POD)

One form of delirium is postoperative delirium (POD), which can occur in patients who have undergone general anaesthesia for surgery, most often within three days of surgery. The development of POD is associated with a higher risk of death, a longer stay in the ICU and hospital, as well as cognitive impairment and the development of long-term psychiatric disorders, including symptoms of post-traumatic stress disorder [14-18].

## Delirium in children

Children are particularly vulnerable to the occurrence of delirium, due to the dynamic development of their central nervous system, which may be disturbed under the influence of anaesthesia, and the consequences of this process may affect its further functioning. This is important because delirium can affect memory disorders in children, thus learning and intellectual development, even leading to sleep disorders, anxiety, and depression. Children's delirium significantly contributes to the increase in morbidity, mortality, and the costs of hospital care for sick children and adolescents. The current knowledge regarding the occurrence of this phenomenon in children is based mainly on extrapolation of the literature describing delirium in adults and on a few studies conducted in paediatric patients. Therefore, studies to assess the long-term impact of delirium on the development of children are necessary. Despite numerous evidence of a negative impact of delirium in paediatric patients, there are no standardised preventive, diagnostic and therapeutic measures [19]. Developing such rules could reduce the incidence of delirium among children, the length of their hospital stay and the associated costs; inva-

sive interventions, such as prolonged mechanical ventilation or prolonged sedation, would be less necessary; ultimately improving the quality of life and the patient's condition [20].

Delirium in newborns and infants is especially difficult to diagnose due to communication limitations. In those age groups, symptoms of delirium include non-purposefulness, difficulty in engaging, agitation, restlessness and difficulty in calming the child [21-23]. Preschool children are most likely to develop delirium, which may be caused by their constant need for stimulation, the lack of which is due to immobilisation during the ICU stay and their increased sensitivity to disturbances in the sleep-wake rhythm [24]. Symptoms of delirium in schoolchildren and adolescents are easier to observe and are similar to those in adult patients [25].

Scales used to assess delirium in children include The Paediatric Anaesthesia Emergence Delirium (PAED) scale, which is used in children >2 yrs of age [26] and Cornell Assessment of Paediatric Delirium [27], a rapid observational screening tool to assess delirium in infants. The Cravero and Watcha scales are based on the assessment of levels of consciousness or arousal [28,29].

## The importance of delirium prevention and current treatment

The importance of delirium for healthcare systems around the world is emphasised by LaHue et al. in relation to the COVID-19 pandemic caused by the SARS-CoV-2 coronavirus. The authors argue that in the face of a pandemic, there is a need to focus even more on preventing the occurrence of delirium, which is associated with an increased length of stay in the intensive care unit. They suggest that doubling the existing protocols for the prevention and management of delirium could significantly reduce the shortage of hospital beds and ventilators, essential in the fight against COVID-19 [30].

## Prevention

To minimise the incidence of side effects of premedication drugs such as benzodiazepines, including the increased risk of delirium, non-

pharmacological methods of reducing preoperative anxiety are being sought. West et al. examined 59 children aged 3 to 10 years without coexisting anxiety disorders undergoing elective surgery. Some children were prepared for treatments according to standard procedures that included the use of a local anaesthetic prior to insertion of the needle, a brief consultation with an anesthesiologist and surgeon, and possible administration of anxiolytic drugs. For other children, in addition to the activities covered by standard procedures, "Child life preparation" was used, which consisted of role-playing with dolls and medical equipment, presenting children books and pictures showing activities related to the operating room as well as teaching them to cope with stress and finally translating planned activities according to the patient's age. The study showed a positive effect of additional preoperative activities in reducing the anxiety associated with the procedures by 13.8 points compared to the control group [31]. Another method of reducing preoperative stress in children was investigated by Dwairej et al., who used a combination of gradual accustoming children to the mask used to induce anaesthesia and distracting the child with video games, showing that such methods reduced anxiety during induction of anaesthesia compared to the control group [32].

## Treatment

For the treatment of delirium, neuroleptic and antipsychotic drugs such as haloperidol, olanzapine, quetiapine or risperidone are used [33-36]. POD usually does not require the administration of drugs because it is short-lived, only non-pharmacological methods are used. Delirium in ICU patients lasts longer and very often requires medication, with haloperidol currently recognised as the gold standard delirium treatment. One of the other medicines used to prevent delirium in children is dexmedetomidine, a selective  $\alpha_2$ -adrenergic agonist in certain parts of the brain, which has a sympathetic, anaesthetic, anxiolytic, sedative and analgesic effect. Studies show that in ICU patients after surgery, dexmedetomidine reduces the need for midazolam, propofol and opioids both on an emergency basis and during

sedation. The incidence of delirium measured on the CAM-ICU (Confusion Assessment Method for the ICU) scale after administration of dexmedetomidine was lower compared to midazolam. However, there is a need for further studies on the use of this drug, as there are no unambiguous data on the time of administration and optimal doses in the prevention of delirium [37].

## Biomarkers

To evaluate the risk of developing postoperative delirium, the effectiveness of treatment and disease prognosis, it is necessary to select specific pharmacodynamic and disease progression biomarkers, which requires research and verifying which of them correlate well with the disease and treatment effectiveness. The most frequently mentioned in the context of delirium are: CRP (C-reactive protein), IL-6 (interleukin 6), IL-10, IL-8, PLR (platelet-to-lymphocyte ratio), PWR (platelet-to-white blood cell ratio), NLR (neutrophil-to-lymphocyte ratio), BUN/Cre (blood urea nitrogen / creatinine ratio), TNF- $\alpha$  (tumour necrosis factor  $\alpha$ ), as well as blood cortisol levels [37-49]. Some of the mentioned biomarkers, such as IL-6 and TNF- $\alpha$ , are also typical for the inflammatory response in the postoperative period, therefore it is necessary to specify the biomarkers most specific to delirium [50]. Genetic biomarkers such as the presence of the Apo-E4 alleles seem to be more exact [51].

## Mathematical modelling

Dynamically developing mathematical modelling in medical sciences and population-based approach to data analysis is becoming more widely recommended for determining optimal pharmacotherapy protocols, especially in infants and children [52]. In July 2019, the FDA (Food and Drug Administration) published a new document on the significance and indications for population PK modelling in the pharmaceutical industry and clinical trials [53]. Modern mathematical modelling is not only used in the PK/PD drug analysis, but also in creating disease progression models and evaluating the influence of drugs on the course of disease [54].

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