Paediatric delirium: where do we go from here? 
An update on key issues and research questions

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Introduction

Eugen Bleuler (1857 – 1939) - the famous Swiss psychiatrist, who coined the term “Schizophrenia” - considered paediatric delirium (PD) to be unimportant because children get delirious so easily and so often [1]. Nowadays, opinions have changed. Therefore the aim of this paper is to present the key issues regarding PD anno 2010 and to address questions for further research.

Delirium in adults is a serious neuropsychiatric disorder. It is considered a sign of acute brain dysfunction leading to end-organ failure. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) characterizes delirium by four features: (i) disturbance of consciousness with inattention, (ii) change in cognition or disorder of perception, (iii) acute onset and fluctuating course, and (iv) pathophysiological cause [2]. The prevalence in a general hospital is 10–30%, rising to more than 50% in an intensive care unit (ICU), and around 80% in the terminally ill [3]. Research in adults indicates that delirium is associated with a worse functional outcome, longer hospital stay and higher mortality rates [3,4]. Taking this into consideration, systematic monitoring for delirium and appropriate treatment with haloperidol in critically ill adult patients were included in the 2002 clinical practice guidelines for sedatives and analgesia of the Society of Critical Care Medicine [5].

In oncological and geriatric patients, delirium is often the single most important predictor of imminent death [3]. It is therefore vitally important to assess all critically ill patients on not five, but six basic signs: pulse rate, temperature, respiratory rate, blood pressure, pain and mental status [6].

Perhaps the most important step in delirium management is early recognition. After all, if delirium is not diagnosed, it is unlikely that any effort will be made to reverse it. Once delirium is detected, the first aim is to identify the underlying aetiology. Often this can be achieved by a systematic assessment of the presence of known risk factors, and every adult ICU patient has at least 13 separate risk factors for delirium (oral communication Wes Ely, Helsinki, 2008). So minimization and/or elimination of predisposing and precipitating factors are the main strategy in treating and preventing delirium. Therefore, management should focus on improving the patient’s cognitive and emotional status and reducing the risk of adverse outcomes such as aspiration, prolonged immobility, increased length of acute care, institutionalization and death.

Despite the high incidence of delirium, medical staff have difficulties in diagnosing delirium. In 2008, Cheung and colleagues concluded that Canadian intensive care unit (ICU) intensivists diagnosed delirium merely upon the presence or absence of an obvious medical aetiology [7]. In a recent editorial regarding paediatric delirium in ICUs, the issue of diagnosing PD was referred to as “the big challenge” [8]. Diagnosing delirium in an ICU is difficult due to the presence of critical illness, high levels of sedation and frequently mechanical ventilation, all of which complicate mental state assessment.

Paediatric delirium

There is a dearth of literature on paediatric delirium, especially in relation to critical illness, which is probably due to unawareness of the clinical entity [9]. A PubMed search conducted in November 2009 using the MESH headings “paediatric delirium” and “critical illness” yielded only seven English language papers between 1993 and 2007. The MESH headings “paediatric delirium” and “PICU (Pediatric Intensive Care Unit)” revealed just five English language papers between 2005 and 2009.

Also in the textbooks little has been written about PD. The DSM-IV section on child psychiatry does not mention delirium, although the chapter “Delirium, Dementia, and Amnestic and Other Cognitive Disorders” devotes six lines to delirium in children [2]. Only four major textbooks contain chapters or sections on paediatric delirium: “Handbook of Pediatric Emergencies” [10], “Child and Adolescent Psychiatry - A Comprehensive Textbook” [11], “Clinical Manual of Pediatric Psychosomatic Medicine” [12] and “Rutter’s Child and Adolescent Psychiatry” [13].

An update on PD: the four most recent findings since 2008

A study in 2008 found that three months after discharge 33% of PICU patients reported memories of having psychotic features during their admission, including delusions and disturbing hallucinations [14], which is suggestive for high rates of delirium. However, two studies in paediatric ICUs (PICUs) reported detected rates that did not exceed 5% [15,16]. Smeets et al [17], showed that PD in critically ill children prolongs PICU stay by 2.4 days, resulting in a cost increase of 1.5% (Euro 4,780). In one of
the other recent PD papers, Smith et al presented a thorough overview and they concluded: “Delirium is a syndrome of acute brain dysfunction that commonly occurs in critically ill adults and most certainly is prevalent in critically ill children all over the world. The dearth of information regarding the incidence, prevalence and severity of PD stems mainly from the fact that there is no validated tool yet for daily routine use at the bedside at the PICU” [18]. Next they proposed a possible partial solution to this problem by introducing the paediatric Confusion Assessment Method-ICU (pCAM-ICU). This is an age-adapted, easier version for use in children, which is now in its pilot phase of validation (personal communication, Dr. Heidi Smith and Dr Wes Ely, Vanderbilt University, Nashville, TN, U.S.A., October, 2008). Their first paper regarding the psychometric qualities is now in preparation. It evaluates 1) whether there is an acute change and/or fluctuating course in the mental status of the child, 2) inattention (acoustic and visual), 3) level of consciousness, and 4) disorganized thinking. There are two major adaptations regarding 1) the pictures assessing visual attention which are now more vividly coloured and cute, and 2) the questions which assess logical thinking which are now much simpler. The a priori limitation is that it is considered to be only suitable for children aged 5 years and older. However, since the majority of PICU patients are aged under 3 years, varying from 50% - 80% depending on geographical location, and 50% are even younger than 1 year, the p-CAM-ICU often cannot be applied. We present a possible solution to this diagnostic problem in the form of a flowchart and diagnostic algorithm [19].

The first step is the evaluation of the sedation-agitation level with the Richmond Agitation-Sedation Scale (RASS). The second is the psychometric assessment of behaviour using the PAED scale (Paediatric Anaesthesia Emergence Delirium) and the evaluation of the opinion of the caregivers. The third is the identification and management of somatic and pharmacological causes, the fourth and fifth are the assessment and management of discomfort as well as assessment of possible moderating qualities of the psychosocial environment. The last step represents the treatment of delirium with medication. The two scales (RASS and PAED) are completed by the nursing staff.

**RASS**

It takes 20 seconds to score. It is a 10-point rating scale with 4 levels for agitation, 5 for sedation, and 1 for calm, awake patients. Ratings are anchored according to a patient’s responses to verbal and then to physical stimulation. The RASS is the starting point of the flow chart, as the evaluation of consciousness is always the first step in a neuropsychiatric examination. Second, it is important to start the evaluation of mental status with an objective rating that may identify both hyperactive and hypoactive presentations.

**PAED**

The PAED [20] is a promising, easy tool with no a priori exclusion criteria, that measures behavioural features which reflect disturbance of consciousness, inattention, emotional and cognitive changes and psychomotor disturbances. Rating, by only observing the child, takes 1 minute and only minimal training is required. It is a 5-point scale with clear anchors:
1. The child makes eye contact with the caregiver
2. The child’s actions are purposeful
3. The child is aware of his/her surroundings
4. The child is restless
5. The child is inconsolable

Items 1, 2, and 3 are reversed scored as follows: 4= not at all, 3=just a little, 2= quite a bit, 1=very much, 0=extremely. Items 4 and 5 are scored as follows: 0=not at all, 1=just a little, 2= quite a bit, 3=very much, 4=extremely.

The scores of each item are added up to obtain a total Pediatric Anesthesia Emergence Delirium (PAED) scale score. A score of 0 to 6 suggests that no further evaluation is required. A score of 7 to 9 indicates that the patient may be subsyndromal; it is therefore very important to re-evaluate clinical state after 1 hour. A score ≥10 is compatible with delirium.

Up to now the PAED has only been validated in children in the age range of 19 months – 6 years in the post anaesthesia phase. Its criteria are clinically justified and elegant, but rather subjective. Nevertheless, it would not come as a surprise that one day it will be proved that these criteria can be generalized to all ages. The flow chart is based more on behavioural and phenomenological criteria and the opinion of the dedicated caregivers (nurses and parents), than on neuropsychological criteria of the pCAM-ICU for example.
The algorithm is also initiated by completing the RASS. The next step is the PAED and the opinion of the caregivers about critical alterations in behaviour and/or thinking of the child. Clinical anecdotal evidence indicates that their opinion is very important at least as an entry cue; it may even be considered diagnostic provided other causes have been excluded (see flow chart) in suspecting and diagnosing delirium. Some caregiver observations will coincide with items of the PAED discussed above. This paper has tried to further lower the PD diagnostic age to approximately 1 year.

Where do we go from here? There are shortcomings in our understanding and knowledge of all aspects of PD particularly regarding, 1) the awareness amongst clinicians of its existence, 2) the pathophysiology and its biomarkers, 3) risk factors, prevention and early detection, 4) clinical presentations, diagnosis and treatment, and 5) outcome.

### Research Questions

To be able to further clarify PD in the PICU the following topics first need to be addressed regarding the domains: 1) conceptualization, 2) risk factors and prediction, 3) diagnosis and 4) treatment, and outcome.

#### 1. Conceptualization

How to tackle the stratification issue? And how to value properly the temporal aspects between the dynamics of the disease process and the time of onset of PD?

One of the fundamental questions in clarifying delirium is the problem of stratification: how to construct homogenous groups of critically ill children at the PICU in order to perform sound scientific research so one can compare rightly and diagnose justly?

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**Figure 2. Algorithm: Diagnostic algorithm for paediatric delirium on the PICU [19]**

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STEP 1) Observe patient.
If patient is alert and calm, score 0. If patient is restless or agitated, score +1 to +4 (+1= Restless: anxious but movements not aggressive vigorous; +2= Agitated: frequent non-purposeful movement, fights ventilator; +3= Very agitated: pulls or removes tube(s) or catheter(s), is aggressive; +4= Combative: overtly combative, violent, immediate danger to staff)
STEP 2) If not alert, state patient’s name and ask them to open their eyes and look at speaker.
If patient awakens with sustained eye opening and eye contact, score -1; if patient awakens with eye opening and eye contact, but not sustained, score -2;
If patient has any movement in response to voice but no eye contact, score -3.
STEP 3) When no response to verbal stimulation, stimulate patient physically by shaking shoulder and/or rubbing sternum.
If patient has any movement to physical stimulation, score -4; if patient has no response to any stimulation, score -5.

*Procedure for RASS assessment*
After all, there are often so many variables all at once and/or long-itudinal in action: e.g. an endangered child arrives at a PICU with critical illness A (meningitis), and he/she develops complication B (diffuse intravasal coagulation and necrosis), next he/she undergoes surgery C (amputation) and somewhere along the line the child develops PD. In this way a medical patient can become a surgical patient and vice versa. Thus quite often the main diagnosis on admission is no longer the main diagnosis at the time of PD onset. And so to which of the somatic causes and complications are correlated with PD? These answers are of importance regarding 1) a possible causal treatment, 2) the understanding of the pathophysiology, 3) the possible prevention and 4) the early detection.

Additionally, some patients are delirious right from the start, and others only develop the disorder after a few days or weeks on ICU or have a relapse. The Pediatric Index of Mortality (PIM) and Pediatric Risk of Mortality (PRISM II) scores in critically ill children, which are only scored on admission, have been correlated with the onset of PD [21,22]. But one can question whether it is not much more logical to start the tackling of the stratification issue by scoring these tools daily in order to correlate the onset of PD with the actual clinical, medical, and surgical situation.

2. Risk factors and prediction
Multiple risk factors play a role in the development of delirium in critical illness. These comprise three main groups: 1) predispos- ing factors correlating with the patient, 2) precipitating factors in relation to the type of disorder and its severity, and 3) iatrogenic factors and PICU-related aspects. In adults and the elderly the most important risk factors are old age, premorbid cognitive de- cline, severity of illness and sedatives. In children we know almost nothing about the risk factors except for: very young age, infectious diseases and post-anæsthesia, especially withdrawal of benzodiazepines and opioids. The group of Gillian Colville re- ported a significant positive correlation between the duration of benzodiazepine and opioid use and post-PICU stay on the one hand, and the remembering of delusional memories in 33% of the children and the consecutive occurrence of PTSD (Post Trau- matic Stress Disorder) on the other hand [14].

Regarding the possible prediction of delirium: there is a quest going on for the pathophysiology of delirium and for its biomark- ers. Candidate markers include haemoglobin-beta, S100B and IL- 6, “however the causal relationships remain to be investigat- ed” [23]. The groups of Ely et al and Leung et al have found a correlation between Apo E4 polymorphism and the occurrence or duration of delirium [24,25]. However, in children all these studies have yet to be performed. Finally, the role of EEG in the diagnosis of delirium in critically ill adults and children is limited [26].

3. Diagnosis
3.1 How can PD be easily diagnosed at the bedside?
First of all one has to realize that the problem of PD is part of the broader problem of how to tackle emotional and behavioural problems in critically ill children of all ages in the PICU. The value of both the published flow charts, which deal with the diagnostics and management of these emotional and behavioural disturbances, and of the algorithm which deals more specifically with the diagnostics of PD, need to be assessed. A diagnostic bedside tool that can be easily used by non-mental-health professionals is needed. So fur- ther evaluation of the usefulness of both the pCAM- ICU (Pediatric Confusion Assessment Method at the Intensive Care Unit) and of the PAED (Pediatric Anaesthesiology Emergence Delirium) is needed [18,19].

3.2 How many forms of PD presentation are there?
There are several classification schemes of delirium, which prob- ably also have different prognostic values. Regarding motor fea- tures there are the hyperactive, hypoactive and mixed types; and regarding clinical expression there exists the subsyndromal and/or prodromal types [15,18,27]. Moreover, if it is taken for granted that delirium is “Acute brain failure in man - “and also in a child” - other clinical phenomena might be also expected to occur. For example, “brain failure” of other parts of the nervous system leading to: 1) autonomic dysregulations (intermittent tachycardia- tachypnoea- hypertensive episodes - loss of bowel and/or bladder control e.g. “regression”), 2) catatonic features and/or 3) higher cortical dys- functions dysphasia- dyspraxia - dyscalculia etc. This has to be studied much more in depth, but will probably lead to adaptations in the diagnostic tools for delirium in adults and the elderly as well as in children.

3.3 Where does withdrawal stop and delirium start?
In every day clinical practice this is a source of confusion and mis- understandings. Refractory agitation in critically ill children below 3 years of age (e.g. “fighting the ventilator”) is a common clinical problem. Given the facts that 1) children develop PD very easily and especially in the context of illness and 2) there is no lower age boundary for the onset of PD, we have to further explore the presumably high prevalence of PD in these cases. According to the DSM- IV- TR, the difference between withdrawal and delirium can also be just a quantitative one. Or in particular: symptoms in excess of what might be expected (more, more intense, non-responding or longer-lasting symptoms) are an indication of delirium [26]. Or in other words: one end of the withdrawal spectrum is refractory agita- tion i.e. delirium. But it would certainly be of great help if one could be more specific about a cut-off point.

4. Treatment and outcome
4.1 Does the treatment of PD and of its subsyndromal presentation, really improve the somatic and mental health outcomes?
There is no evidence for the fact that the treatment of PD improves outcome. But given the aforementioned risks and sequelae in adults, the high level of discomfort and suffering in adult delirious patients, combined with a lack of knowledge on these issues in critic- ically ill children, it is necessary to reduce any risk at PD by trying to detect and treat PD as much as possible until proven otherwise.

4.2 Treatment of hypoactive PD in particular
There is still no consensus on how to treat hypoactive delirium in adults and the elderly. Findings regarding the use of antipsy-
chotics (classical or atypical), benzodiazepines or other strategies (e.g., just TLC = Tender Loving Care) are inconsistent. This is worrying given the fact that it is the most prevalent variant of delirium, probably also in children. There is worldwide consensus regarding the treatment strategy of hyperactive delirium with antipsychotics, but also the unequivocal evidence of several RCTs (Randomized Controlled Trials) is missing.

Closing remarks

Although there is a large and rapidly growing body of scientific knowledge regarding delirium in adults and the elderly, there are still a lot of unsolved issues. This especially concerns questions dealing with the pathophysiology and biomarkers, risk factors, early detection and the right treatment. Our concepts and acts regarding PD are mainly derived in analogy of what are considered scientific truth and clinical wisdom in adults and the elderly.

However, infants and children are not small adults; they differ especially regarding aspects of growth, development and resilience. On the other hand, by nature they are also very similar to adults. This awareness of this requires some prudence and caution as well regarding generalizations about delirium to PD in relation to our daily work at the PICU.

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References

23. van Munster BC. Pathophysiological studies in delirium, a focus on genetics [Ph.D thesis]: University of Amsterdam; 2009.

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