

## GUIDELINES

## European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium

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The purpose of this guideline is to present evidence-based and consensus-based recommendations for the prevention and treatment of postoperative delirium. The cornerstones of the guideline are the preoperative identification and handling of patients at risk, adequate intraoperative care, postoperative detection of delirium and management of delirious patients. The scope of this guideline is not to cover ICU delirium. Considering that many medical disciplines are involved in

the treatment of surgical patients, a team-based approach should be implemented into daily practice. This guideline is aimed to promote knowledge and education in the preoperative, intraoperative and postoperative setting not only among anaesthesiologists but also among all other healthcare professionals involved in the care of surgical patients.

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### Introduction

The European Society of Anaesthesiology (ESA) is committed to develop evidence-based clinical guidelines of high quality. The ESA Guidelines Committee selected the 'Reduction of Postoperative Delirium' as a topic of interest and dedicated a Task Force – established in March 2013 – to cover this matter. The ESA Guidelines

Committee chose the members of the Task Force (CDS, CA, GB, FB and RDS) based on their clinical and methodological expertise. The Task Force elected its chairperson, by common consent, at their first telephone conference on 15 March 2013, and the ESA formally confirmed this election during the first constitutional meeting at the European Anaesthesiology Congress in Barcelona on 2 June 2013. Following the first Task Force meeting, members of the Advisory Board were chosen by the Guidelines Committee and the Task Force based on their clinical and methodological expertise in regard to the key questions as agreed by the Task Force in Barcelona in June 2013 (Table 1). The Task Force received its entire financial support from the ESA, without any

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<sup>2</sup> Claudia D. Spies was the elected chair of the Task Force.

**Table 1** Key questions as agreed by the Task Force in Barcelona, June 2013

Key question	Statements
What is postoperative and what is postinterventional delirium	7/7
What is emergence delirium (inadequate emergence)?	7/7
• What are risk factors for POD?	6/8
○ Predisposing (pre-intra-postoperative)	
○ Precipitating (pre-intra-postoperative)	
What measures can be taken to determine the individual risk of patients?	6/8
When should a risk evaluation be performed?	8/8
• Preoperative phase	7/8
○ Which pharmacological interventions can be recommended for which subgroup of patients?	
○ Which medication/actions should be avoided?	
○ Which nonpharmacological interventions can be recommended?	
■ Which supportive strategies are beneficial?	
■ Is the use of checklists/algorithms useful and does it affect incidence, severity or duration of POD?	
• Intraoperative phase	8/8
○ Which pharmacological interventions can be recommended for which subgroup of patients?	
○ Which medication/actions should be avoided?	
○ Which nonpharmacological interventions can be recommended?	
■ Which supportive strategies are beneficial?	
■ How should anaesthesia be conducted to avoid POD?	
• Postoperative phase	8/8
○ Which pharmacological interventions can be recommended for which subgroup of patients?	
■ Which medication/actions should be avoided?	
○ How should pain management be conducted in the postoperative phase to prevent delirium?	
○ Is there evidence for an algorithm (like the Pain-Agitation-Delirium Management on ICUs) that can be applied?	
Which tools should be used to monitor for POD?	8/8
Which tool should be used to monitor postoperative pain?	7/8
When should POD be monitored?	7/8
How often should POD be monitored?	8/8
What are reversible causes of POD?	7/8
How can symptoms be evaluated objectively?	8/8
When should pharmacological interventions be conducted?	8/8
Which pharmacological treatment can be used?	7/7
Where should POD be treated?	7/7
Which nonpharmacological treatment can be conducted?	7/7
■ Geriatric patients	
Are there differences in the management of POD in geriatric patients?	8/8
Is there evidence for a beneficial pre-, peri-, and postoperative treatment algorithm regarding POD?	7/7
How to manage delirium superimposed on a preexisting dementia/cognitive disorder?	8/8

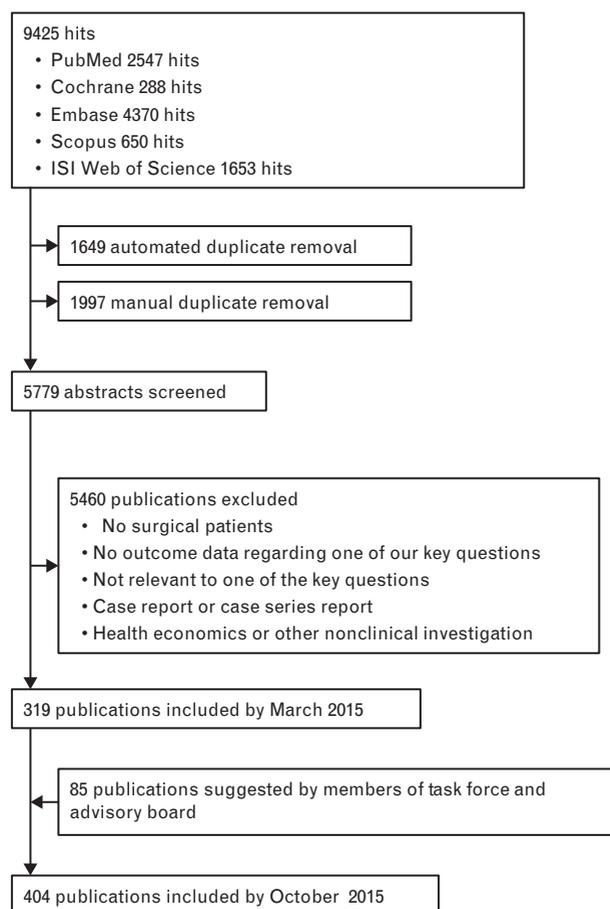
POD, postoperative delirium.

involvement from the healthcare industry. Sub-committees were established to address the questions of interest.

### Evidence-based and consensus-based methods

The guideline was designed following the 'Appraisal of Guidelines for Research and Evaluation (AGREE II)'.<sup>1-3</sup>

During its meetings, the Task Force agreed on several key questions (Table 1). To answer these questions and to develop evidence-based recommendations, search strategies included PubMed, Cochrane, Scopus, ISI Web of knowledge and Embase up to March 2015. Afterwards, only selected new published articles in respect of current clinical practice were considered. Search terms were (delirium OR confusion OR confusion\* OR disorientation OR bewilderment) AND (postoperative OR postoperative period OR postoperative period\* OR post surgical OR postsurgical OR anesthesia recovery period OR anesthesia recovery period\* OR postanesthesia). The searches were performed between January 2014 and March 2015. These searches led to 9425 hits. After automated and manual removal of duplicates, 5779 hits were screened for relevance. Relevant articles included existing systematic and narrative reviews, editorials, meta-analyses, randomised controlled trials (RCTs), cohort studies, case-control studies and cross-sectional studies. Case (series) reports were not included but screened for relevant references. We additionally used the 'Cited by xx PubMed Central articles' function in PubMed to identify potentially

**Fig. 1**

Flow chart of the study selection process.

overlooked but relevant articles. We also screened the reference lists of relevant articles for further publications and included references suggested by the members of the Task Force and the advisory board. Overall, 405 articles were included in the guideline (Fig. 1). Relevant articles were graded according to their level of evidence (LoE) using the Critical Appraisal Worksheets from the Centre for Evidence-Based Medicine of the University of Oxford.<sup>4</sup> The grade of recommendation (GoR) was obtained on the basis of the LoE of the literature (Table 2) and the consensus expert opinions by the majority ( $\geq 75\%$ ) of the Task Force and the advisory board. Experts had to disclose a conflict of interest before participating in the consensus-based voting on any recommendation. Experts were excluded from voting if a conflict of interest relating to any recommendation was possible. *For all statements, the strength of the recommendation is prefaced by the GRADE phrase 'we recommend' for strong recommendations (GoR A) or by the GRADE phrase 'we suggest' for conditional recommendations (GoR B).*

The final draft of the guideline was peer-reviewed by the relevant sub-committees of the ESA's Scientific Committee. The reviewed draft was made available between 8 October 2015 and 7 November 2015 on the ESA website for critical appraisal by ESA members. The final manuscript of the guideline was approved by the Guidelines Committee and Board of the ESA before publication. The guidelines expire after 5 years unless updated earlier.

## Background

Postoperative delirium (POD) is an adverse postoperative complication that can occur in patients of any age, from children to the elderly. Its incidence varies in the various age groups and is substantially influenced by patient-related risk factors that are variably distributed and differentially accumulate in the different age groups. Elderly patients are generally thought to be at higher risk because predisposing risk factors such as cognitive impairment, comorbidity, sensorial deficits, malnutrition, polymedication, impaired functional status and frailty (a condition that can only be observed among aged patients) accumulate and overlap with ageing.

Moreover, POD (refer to the specific definition in the 'Paediatric patients' section) is a common complication in children of pre-school age (5 to 7 years): whether this is due to age-related psychological issues or to additional inflammatory effects on the brain cannot currently be determined. There is a limited number of studies on cognitive outcomes in children.<sup>7</sup> For the USA, the Food and Drug Administration (FDA) recently recommended cautious indications for anaesthesia and surgery in children aged less than 3 years.<sup>8</sup> In Europe, the ESA launched an initiative, the EUROpean Safe Tots Anaesthesia Research (Eurostar) Initiative Task Force to promote translational research on anaesthesia neurotoxicity and long-term outcomes after paediatric anaesthesia and surgery.<sup>9</sup>

In addition, POD is more common in all age groups if precipitating risk factors such as major surgery<sup>10–13</sup> or emergency surgery<sup>14–19</sup> are present. The incidence increases with a high burden of comorbidities presenting as multiorgan dysfunction before surgery, for example low haemoglobin concentration,<sup>20–23</sup> low ejection fraction,<sup>16</sup> carotid artery stenosis,<sup>24</sup> or high serum creatinine concentration.<sup>25–28</sup> POD is associated with several negative clinical consequences, including major postoperative complications, cognitive decline, distress, longer hospitalisation with increased costs and higher mortality.<sup>17,20,29–36</sup> Therefore, prevention of POD should be the aim in all patients; if it cannot be prevented, it is essential to intervene immediately.<sup>29,37–39</sup>

## Definition

Delirium is defined by either the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)<sup>40</sup> or by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10, Table 3).<sup>41</sup> Delirium is an acute and fluctuating alteration of mental state of reduced awareness and disturbance of attention. POD often starts in the recovery room and occurs up to 5 days after surgery.<sup>42–44</sup> One investigation<sup>43</sup> found that many patients with POD on the peripheral ward already had POD in the recovery room.

**Table 2** From evidence to recommendations (modified from GRADE<sup>5</sup> and The European Council Recommendation<sup>6</sup>)

LoE	GoR	Wording of the statements
Level of Evidence (LoE) from the Centre for Evidence-Based Medicine of the University of Oxford	Considered judgement – group decision	
High	A – strong recommendation	We recommend
Data derived from multiple randomised clinical trials or meta-analyses	Evidence and/or general agreement that a given treatment or procedure is beneficial/useful/effective	
Moderate	B – recommendation	We suggest
Data derived from a single randomised clinical trial or large nonrandomised studies	Conflicting evidence and/or a divergence of opinion about the treatment or procedure, however evidence/opinion is in favour of usefulness/efficacy	
Weak	Not considered <sup>a</sup>	
Consensus of opinion of the experts and/or small studies, retrospective studies and registries		

<sup>a</sup> If evidence or general agreement that the given treatment or procedure is not useful/effective or in some cases may even be harmful, the information is included in the manuscript, but no statements are given.

**Table 3** Definition of delirium Gold standard according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,<sup>40</sup> or the 10th revision of the International Statistical Classification of Diseases and Related Health Problems<sup>41</sup>

ICD-10 criteria (F05.0) Delirium, not induced by alcohol and other psychoactive drugs and not superimposed on dementia	DSM-5 criteria
An aetiologically nonspecific organic cerebral syndrome characterised by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion and the sleep–wake schedule. The duration is variable and the degree of severity ranges from mild to very severe	A disturbance in attention (i.e. reduced ability to direct, focus, sustain and shift attention) and awareness (reduced orientation to the environment)
Diagnostic criteria:	The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day
A. Clouding of consciousness, that is reduced clarity of awareness of the environment, with reduced ability to focus, sustain or shift attention	An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability or perception)
B. Disturbance of cognition, manifest by both:	The disturbances in criteria a and c are not better explained by another preexisting, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma
(1) Impairment of immediate recall and recent memory, with relatively intact remote memory; and	There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies
(2) Disorientation in time, place or person	
C. At least one of the following psychomotor disturbances:	
(1) Rapid, unpredictable shifts from hypoactivity to hyperactivity	
(2) Increased reaction time;	
(3) Increased or decreased flow of speech	
(4) Enhanced startle reaction	
D. Disturbance of sleep or the sleep–wake cycle, manifest by at least one of the following:	
(1) Insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep–wake cycle	
(2) Nocturnal worsening of symptoms	
(3) Disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening	
E. Rapid onset and fluctuations of the symptoms over the course of the day	
F. Objective evidence from history, physical and neurological examination or laboratory tests of an underlying cerebral or systemic disease (other than psychoactive substance–related) that can be presumed to be responsible for the clinical manifestations in A to D	

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems.

Very early onset of POD in the immediate postanesthesia period before or on arrival at the recovery room is referred to as ‘emergence delirium’.<sup>45–49</sup> In children, paediatric emergence delirium (paedED) may present with purposeless agitation with kicking, absence of eye contact with caregivers or parents (with eyes staring or averting), inconsolability and absence of awareness of the surroundings.<sup>50</sup>

Delirium can present as hypoactive (decreased alertness, motor activity and anhedonia), as hyperactive (agitated and combative) or as mixed forms.<sup>51,52</sup> Increased age seems to be a predisposing factor for the hypoactive form.<sup>51,53</sup> The prognosis may be worse with hypoactive delirium, possibly due to relative under-detection by staff and consequently delayed treatment.<sup>51</sup>

## Relevance

More than 230 million surgical procedures are performed each year worldwide, of which more than 80 million are in Europe.<sup>54–56</sup> In Europe, the in-hospital mortality rate up

to a maximum of 60 days is 3% after elective surgery and nearly 10% after emergency surgery.<sup>55</sup> In addition to mortality, postoperative cognitive impairments such as POD and postoperative cognitive dysfunction (POCD) impose a huge burden on individuals and society.<sup>39</sup>

The incidence of POD is dependent on perioperative and intraoperative risk factors.<sup>57</sup> Therefore, the incidence of POD varies within a broad range.<sup>58,59</sup> For example, a meta-analysis of 26 studies of POD reported an incidence of 4.0 to 53.3% in hip fracture patients and 3.6 to 28.3% in elective patients.<sup>60</sup>

POD, and delirium in general, is often regarded as a temporary attenuation of brain function, usually followed by a full remission. However, strong evidence exists that POD is linked with longer term cognitive and noncognitive morbidity as well as reduced quality of life. It is also associated with increased mortality in the short term and long term. The impact of POD on mortality has been found across different surgical disciplines, in elective and emergency surgery.<sup>17,20,23,24,29,31–33,36,61–71</sup> Only a few

studies, some of them after adjustment for preoperative cognitive status, found no<sup>72–77</sup> or only borderline<sup>78</sup> association between POD and mortality.

There is evidence that POD is associated with deteriorating cognition in both the short term (months) and long term ( $\geq 1$  year) after its occurrence.<sup>39,79–81</sup> Often referred to as postoperative cognitive dysfunction (POCD), altered cognition has been found shortly after POD in the ICU setting.<sup>82–84</sup> Some investigators have found POD to be associated with POCD up to 12 months postsurgery<sup>30,78,85,86</sup> and even associated with dementia up to 5 years after POD.<sup>68</sup> In addition, POD has been associated with posttraumatic stress disorder 3 months after surgery.<sup>87</sup>

POD increases total hospital length of stay (LOS).<sup>13,15,20,23,31,34,84,88–96</sup> POD on day 1 after surgery is most predictive of hospital LOS.<sup>13</sup> In addition, even POD in the recovery room has been associated with increased total hospital LOS.<sup>13</sup> After discharge, patients with POD have an increased level of care dependency<sup>20,23,30,32,34–36,61,89,92</sup> or limitations in basic activities of daily living up to 12 months.<sup>31</sup>

Because patients can present with both delirium and cognitive impairment before surgery, preoperative evaluation of patients for the presence of delirium and cognitive impairment should be considered. Of note, studies that evaluated delirium on admission, that is before surgery, reported prevalence rates between 4.4 and 35.6%.<sup>92,97–104</sup> Cognitive impairment at any time during surgical stay, including preoperative delirium, was a risk factor in hip fracture patients for poor functional outcome 12 months later.<sup>104</sup> Any cognitive impairment before hospital admission was an independent risk factor for worse longer term cognitive impairment.<sup>104,105</sup>

### Risk factors

A widely accepted model of delirium differentiates predisposing factors (that are related to the patient) and precipitating factors (that trigger the onset of delirium).<sup>106</sup> The risk of developing delirium can be seen as the product of predisposing and precipitating factors. Risk assessment is considered as the responsibility of different disciplines and should be implemented in the perioperative clinical pathway.

The evidence-based and consensus statements and their GoR for preoperative, intraoperative and postoperative risk factors for POD are listed in Table 4. As many studies identified advanced age as a risk factor for POD both in univariate and in multivariate analysis, we show the evidence in two columns (all adults vs. elderly  $\geq 65$  years of age) according to the inclusion criteria of the cited studies. In the medical literature, elderly patients are often defined as aged at least 65 years.<sup>105</sup> However, chronological age may be an insufficient proxy to capture

the complex underlying pathological mechanism leading to increased vulnerability to POD.

In addition to the above statements, emergency surgery<sup>14–19,155</sup> and postoperative complications<sup>156</sup> increase the risk of higher rates and prolonged duration of POD as well as long-term cognitive impairment.<sup>157</sup> Protocols are required to identify these risk factors and to implement risk reduction strategies (e.g. fast track).<sup>105,158,159</sup>

Hypothermia on admission to the recovery room has also been reported to be a risk factor for hypoactive emergence.<sup>49</sup> In addition, preoperative fasting glucose concentrations are associated with more delirium after cardiac surgery.<sup>128,160</sup> Despite existing evidence on biomarkers for the detection and monitoring of POD from both the ICU setting<sup>93,161,162</sup> and the non-ICU setting,<sup>14,116,163–169</sup> their use in clinical routine cannot currently be recommended; further research is required.

### Monitoring of postoperative delirium

Early diagnosis of POD is critical to trigger focussed and effective treatment.<sup>29,37–39,79,80</sup> Patients should not leave the recovery room without being screened for POD. Current reference standards for diagnosing delirium, including POD, are the DSM-5<sup>40</sup> or the ICD 10<sup>41</sup> (Table 3). Extensive training is required to use these reference standards.<sup>105</sup> In addition, the new definition of DSM-5 compared with DSM IV-TR decreases the sensitivity to diagnose delirium because the disturbances do not occur in the context of a severely reduced level of arousal.<sup>170,171</sup> However, the DSM-5 guidance notes clarify this, stating that patients with a severely reduced level of arousal (of acute onset) above the level of coma should be considered as having ‘severe inattention’ and hence as having delirium.<sup>40,172</sup> As this is relevant in the postoperative and ICU setting, it is important that both a sedation/agitation tool such as the Richmond Agitation-Sedation Scale<sup>173</sup> (RASS; Table 5) and a delirium screening tool are used.

A delirium screening system suitable for use in the recovery room should be easily applicable and fast to perform.<sup>44</sup> A high sensitivity (to detect POD as early as possible) may be achieved with two scores – the Nursing Delirium Screening Scale<sup>174</sup> (Nu-DESC) and the Confusion Assessment Method (CAM).<sup>44,176</sup> However, in a recent study, the sensitivities of both of these tests were lower than expected,<sup>177</sup> and it is to be noted that the CAM has a low sensitivity when not used by staff specially trained in its use. In the latter study reporting lower sensitivities despite a high methodological standard, the measurements were performed in a prolonged time frame of 60 min, that is too slow to assess the sudden changes in the recovery room seen in this patient population.<sup>177</sup> The study reporting a higher sensitivity was embedded in an accreditation process in which all team members – nurses and physicians – were educated

Table 4 Evidence-based and consensus-based statements regarding risk factors

Statements	LoE	Age group (inclusion criteria)		GoR
		All adults	Elderly $\geq 65$ years	
We suggest evaluating the following preoperative risk factors for POD				
• Advanced age	[10], 1b; [14], 2b; [17], 4; [18], 2b; [20], 2b; [34], 2b; [35], 2b; [76], 2b; [105], 5	[10,14,17,20,34,107,108,112,113,116,118]	[18,35,76,105,111–113,114,117,119,119]	B
	[107], 2b; [108], 2b			
	[109], 2b; [110], 2b			
	[111], 2b; [112], 2b			
	[113], 2b; [114], 2b			
	[115], 2b; [116], 2b			
	[117], 2b; [118], 2b			
	[119], 2b			
• Comorbidities (e.g. cerebrovascular including stroke, cardiovascular, peripheral vascular diseases, diabetes, anaemia, Parkinson's disease, depression, chronic pain and anxiety disorders)	[17], 4; [20], 2b; [21], 2b; [71], 4; [103], 2b	[17,20,110,112,121,124,127,128]	[21,103,123,125,126,130,132]	B
	[108], 1b; [112], 2b			
	[121], 2b; [122], 1b			
	[123], 2b; [124], 3b			
	[125], 2b; [126], 4			
	[127], 2b; [128], 2b			
	[130], 1b; [131], 2b			
	[132], 2b			
• The results of comorbidity scores such as the American Society of Anesthesiologists' physical status classification system (ASA-PS) or the Charlson Comorbidity Index (CCI) or the Clinical Impairment Assessment Score (CIAS) before surgery	[28], 2b; [34], 2b; [89], 2b; [96], 4; [122], 4; [133], 2b; [134], 4; [135], 4	[28,34,135]	[89,94,122,133,134]	B
• Preoperative fluid fasting and dehydration	[13], 2b; [112], 2b	[13]	[112], Incl. $\geq 18$ years, obsvd. $66 \pm 11$ years, range 58 to 72 years	B
• Hyponatraemia or hypernatraemia	[34], 2b; [110], 1b	[34,135,136]	[110], Incl. $\geq 60$ years, obsvd. 75 years	B
	[135], 4; [136], 4			
• Drugs with anticholinergic effects (e.g. measured by an anticholinergic drug scale)	[92], 4; [109], 2b	[137,139,140]	[92,109,113], Incl. $\geq 50$ years, obsvd. $67 \pm 9$ years; [115,138], Incl. $\geq 18$ years, obsvd. $68 \pm 8$ years, range 46 to 88 years	B
	[113], 2b; [117], 2b			
	[137], 4; [138], 4			
	[139], 4; [140], 4			
We recommend evaluating alcohol-related disorders (ICD-10)/alcohol use disorders (DSM-5) as a further preoperative risk factor	[20], 2b; [23], 2b; [34], 2b; [71], 4; [105], 5; [116], 2b; [138], 2b; [141], 2b	[20,34,116], Incl. none, mean 63 years, range 24 to 90 years	[23], Incl. $\geq 50$ years, obsvd. $64 \pm 9$ years, POD+, $69 \pm 9$ years, POD-, $61 \pm 6$ years; [71,105,138,141], Incl. $\geq 18$ years, obsvd. $68 \pm 8$ years, range 46 to 88 years	A
	[142], no full text			
We suggest considering the following intraoperative risk factors for POD				
• Site of surgery (abdominal and cardiothoracic)	[13], 2b; [23], 2b; [34], 2b	[13,34]	[23], Incl. none, obsvd. POD+, 69 years, POD-, 61 years	B
• Intraoperative bleeding	[42], 2b; [128], 2b	[128,143–145]	[42], Incl. none, obsvd. POD+71 years, POD-, 61 years	B
	[143], 2b; [144], 2b			
	[145], 4			
We recommend considering duration of surgery as a further intraoperative risk factor	[16], 2b; [116], 2b	[16,116,136,149]	[147], Incl. $\geq 60$ years, obsvd. 72 years; [148], Incl. $>60$ years, obsvd. POD+, $76.1 \pm 6.1$ years, POD-, $69.8 \pm 6.0$ years; [144], Incl. $\geq 60$ years, obsvd. 72 years	A
	[136], 4; [146], 4			
	[147], 2b; [148], 2b			
	[149], 2b			
We recommend evaluating pain as a postoperative risk factor for POD	[13], 2b; [49], 2b; [93], 2b; [103], 2b; [129], 2b	[13,49]	[93], Incl. $\geq 60$ years, obsvd. 72 years; [103,129,150], Incl. $\geq 60$ years, obsvd. 75 years; [152], Incl. $\geq 50$ years, obsvd. 66 years; [153]; [154]	A
	[150], 4; [151], no full text; [152], 2b; [153], 1b; [154], 2b			

Data presented as reference number, GoR, grade of recommendation (strong = A, conditional = B); LoE, level of evidence; Incl., inclusion criterion; obsvd., observed; POD, postoperative delirium.

**Table 5** Richmond Agitation-Sedation Scale to assess sedation depths<sup>169</sup>

+4	Combative	Violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube (tubes) or catheter (catheters); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening and contact for more than or exactly 10 s)
-2	Light sedation	Briefly awakens to voice (eye opening and contact for <10 s)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice but movement or eye opening to physical stimulation
-5	Unroutable	No response to voice or physical stimulation

The usual target/aim of alertness is within the grey rectangle.

before implementing quality indicators for delirium, pain and postoperative nausea and vomiting assessment in the recovery room.<sup>44</sup> More research is needed regarding the optimal tools for detection of delirium in the recovery room.

If POD is detected, patients should not be discharged from the recovery room to the ward without having started aetiology-based and symptom-based treatment.<sup>179</sup> This is because the longer the duration of delirium and the later the treatment is started, the more cognitive decline may be expected.<sup>39,79</sup> On the postoperative ward, POD should be monitored at least once per shift due to the fluctuating course of POD.<sup>175</sup> The evidence-based and consensus-based statements regarding POD monitoring are listed in Table 6.

POD screening is recommended by using standardised rating scales validated for the postoperative setting. The scales usually take less than 1 min to complete. Only those scores that are validated for the recovery room or the peripheral ward with an adequate sensitivity are listed below. Scores validated only for the ICU or other settings are not listed.

For *emergence delirium* immediately after surgery, agitation scales such as the RASS<sup>173</sup> were used in all studies,<sup>47–49,180</sup>

whereas the Pediatric Anesthesia Emergence Delirium (PAED) scale (Table 7) was used in children.<sup>181</sup>

In the *recovery room* setting, the following delirium scores have undergone validation against the criteria according to the DSM:

- (1) Nu-DESC<sup>44,174,177</sup> reported sensitivity between 32 and 95% and reported specificity up to 87%.<sup>44</sup> If sensitivity in the different recovery room setting is in the lower range, it may be advisable to use a threshold of at least 1 point to increase sensitivity to 80%.<sup>177</sup>
- (2) CAM<sup>43,44,105,176</sup> or the CAM-ICU.<sup>178</sup> In a post-anesthesia care unit (PACU), sensitivity has been reported between 28 and 43%, with a specificity of 98%.<sup>45,177</sup>

In special patient populations, other scores have been used, and diagnostic validity has been assessed. Although, these scores might be applicable and have been validated regarding standards (not necessarily DSM), they have either been assessed in special patient populations or in settings different from the postoperative setting. Some of these scores, such as the Delirium Rating Scale-98<sup>182</sup> or the Memorial Delirium Assessment Scale,<sup>183</sup> might be useful to evaluate postoperative patients, but they might take longer to perform in a busy recovery room setting. Several scores can be used as alternatives: the Bedside Confusion Scale,<sup>184</sup> Clinical Assessment of Confusion,<sup>159</sup> Confusion Rating Scale,<sup>186</sup> the Delirium-O-Meter,<sup>187</sup> Delirium Observation Screening,<sup>188</sup> the delirium symptom interview (DSI),<sup>189</sup> the Neelon and Champagne Confusion Scale<sup>190</sup> or the 4 'A's Test.<sup>191</sup>

In general, the team (including nurses and physicians) should be involved in the choice of which score to use. For routine implementation, it is mandatory to train the team on the basic features of delirium as well as the features of any tools that will be used. This is not only because scores such as CAM require training, whereas the NuDesc does not, but also because the team needs to have a common understanding of delirium and to be able to communicate consistently on the results of tools used.<sup>105,192</sup>

**Table 6** Evidence-based and consensus-based statements regarding monitoring of postoperative delirium

Statements	LoE	Age group (inclusion criteria)		GoR
		All adults	≥65 years	
We recommend screening for POD in all patients starting in the recovery room and in each shift up to postoperative day 5	[42], 2b; [44], 2b; [178], 2b	[44,178]	[42]	A
We recommend using a validated delirium score for POD screening	[44], 2b; [172], 2b [175], 2b; [178], 2b	[44,172,178]	[175]	A

Data presented as reference number, GoR, grade of recommendation (strong = A, conditional = B); LoE, LoE, level of evidence; POD, postoperative delirium.

**Table 7** The Pediatric Anesthesia Emergence Delirium scale<sup>179</sup>

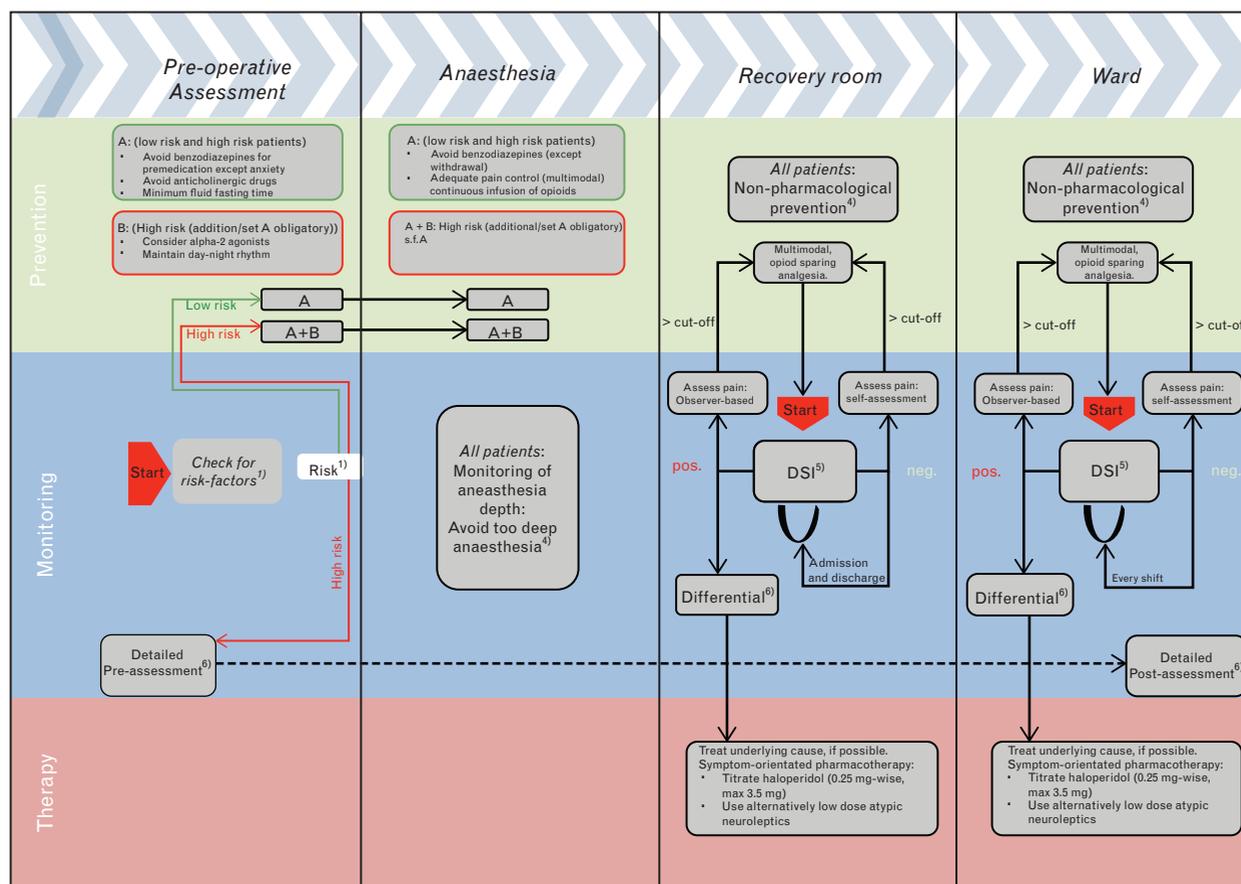
Item	
1	The child makes eye contact with the caregiver
2	The child's actions are purposeful
3	The child is aware of his/her surroundings
4	The child is restless
5	The child is inconsolable

Items 1, 2 and 3 are reverse 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 were summed to obtain a total Pediatric Anesthesia Emergence Delirium scale score. The degree of emergence delirium increased directly with the total score.

In addition, it is important to note that not all scores are available in different languages. Therefore, national societies might consider validating the scores in the language in which it is to be applied.

## Prevention and treatment

Prevention and treatment options are available to reduce the incidence and duration of POD. If POD occurs, immediate treatment of both causative factors and symptoms has a major impact in reducing its duration<sup>29,37–39</sup> (Fig. 2). The evidence-based and consensus-based statements regarding prevention and treatment are listed in Table 8.

**Fig. 2**

Algorithm for pre-operative, intra-operative and post-operative management of postoperative delirium in adult patients. The algorithm shows the different time stages of surgery (left to right) and, in a different axis, preventive (top), diagnostic (middle) and therapeutically (lower) actions that should be taken. The red 'start button' helps the user to start at the first step in the different time stages. (1) Risk estimation (clinical assessment taking into consideration predisposing and precipitating risk factors); risk factors can be found in detail in the guideline recommendation, determination of risk into a high and a low-risk group can be made as a clinical decision (2) Neuromonitoring (EEG/EMG-based) recommended if available; (3) DSI, Delirium Screening Instrument (should be validated in the applied language); (4) nonpharmacological measures to reduce postoperative delirium should include orientation (clock, communication, etc.); visual/hearing aids; noise reduction and facilitation of sleep; avoidance of useless indwelling catheters; early mobilisation; early nutrition; pharmacological treatment should be instituted to improve patient safety if nonpharmacological measures fail; (5) differential includes the assessment and possible modification of underlying causes for delirium: use, for example, the 'I WATCH DEATH'-acronym: Infectious (e.g. UTI and pneumonia); Withdrawal (e.g. alcohol, opioids and benzodiazepines); Acute metabolic disorder (electrolyte imbalance and renal dysfunction); trauma (operative trauma); CNS pathology (e.g. stroke and perfusion); hypoxia (e.g. anaemia, cardiac failure and pulmonary failure); deficiencies (e.g. vitamin B 12, folic acid and thiamine); endocrine pathologies (e.g. T3/T4 and glucose); acute vascular (e.g. hyper-/hypotension); toxins (e.g. anaesthetics, drugs with anticholinergic side-effects); heavy metals (rare cause); (6) detailed pre/post-surgical assessment of cognitive function with validated tools. EEG, Electroencephalograph; EMG, Electromyography; UTI, urinary tract infection; CNS, central nervous system.

**Table 8** Evidence-based and consensus-based statements regarding prevention and treatment

Statement	LoE	Age group (inclusion criteria)		GoR
		All adults	≥65 years	
We suggest implementing fast-track surgery to prevent POD	[158], 1b; [159], 2b; [193], 2b; [193], 2b	[159,193]	[158,194]	B
We suggest avoiding routine premedication with benzodiazepines except for patients with severe anxiety	[10], 2b; [105], 5; [195], 2b; [196], 3b; [197], NR; [198], 2b; [204], 2b		[10], Incl. none, POD+, 67.7 years, POD-, 50 years; [105,195,196], >60% were ≥65 years; [197]; [199] mean age 66.8 years and range 43–87 years	B
We recommend monitoring depth of anaesthesia	[105], 5; [199], 1b; [200], 1b; [201], 1b; [202], 1b	[199–201]	[105,202]	A
We recommend adequate pain assessment and treatment	[103], 2b; [153], 1b; [197], NR; [203], 4; [205], 2b; [206], (SR)	[202]	[103,153,197,199,205]	A
We suggest using a continuous intraoperative analgesia regimen (e.g. with remifentanyl)	[13], 2b; [207], 2b	[13,207]		B
We recommend promptly diagnosing POD, establishing a differential diagnosis, and instituting treatment	[37], 2b; [38], 2b; [179], 2b; [208], Consensus review	[37]	[38,179,208]	A
We suggest using low-dose haloperidol <sup>a</sup> or low-dose atypical neuroleptics to treat POD	[208], 5; [209], SR; [210], 2b; [211], 2b	[208,209]	[211,212]	B

Data presented as reference number, LoE. Incl. inclusion criteria; obsvd., observed; LoE, level of evidence; GoR, grade of recommendation (strong = A, conditional = B); POD, postoperative delirium. <sup>a</sup>Low-dose haloperidol means 0.25 mg stepwise titrated up to maximum of 3.5 mg.<sup>213</sup> An excessive dose of haloperidol of more than 6 mg a day should not be used.<sup>214</sup> Long-term use in dementia patients may increase harm.<sup>215</sup>

Pharmacological premedication (in particular benzodiazepines) is not always needed, and its routine use has been questioned.<sup>208</sup> However, for highly anxious patients or patients with alcohol or benzodiazepine use disorders, careful use of premedication for prevention and treatment can be considered.<sup>107,216,217</sup>

Prevention of POD in patients with alcohol use disorders (e.g. measured by the Alcohol Use Disorders Identification Test ≥8 points) may include long-acting benzodiazepines, neuroleptics,  $\alpha_2$ -agonists and alcohol.<sup>218</sup> In the subset of patients with alcohol withdrawal-induced delirium, benzodiazepines should be one of the first-line medications.<sup>105</sup> As second-line medication,  $\alpha_2$ -agonists or neuroleptics can be used. For emergence delirium, benzodiazepines might be a precipitating factor,<sup>48,107,219</sup> although this remains controversial.<sup>180</sup>

Data on melatonin for premedication on the evening before surgery are insufficient to draw final conclusions, and currently no clear recommendation can be given.<sup>220–223</sup> Perioperative  $\alpha_2$ -agonists, for example dexmedetomidine or clonidine, might be considered to decrease the incidence of POD after cardiac or vascular surgery.<sup>224–228</sup>

There are conflicting results regarding the incidence and severity of POD through prophylactic administration of haloperidol<sup>35,229–231</sup> or atypical neuroleptics.<sup>122,232–234</sup> Although there is some evidence that preventive low-dose haloperidol<sup>35,229–231</sup> or preventive low-dose atypical

neuroleptics<sup>122,233,234</sup> reduce the incidence of POD<sup>231</sup> or reduce its severity and duration,<sup>229</sup> these findings remain uncertain due to inconsistent results of aggregated evidence.<sup>232,235</sup> Therefore, their routine use is currently not advisable.

It remains unclear whether different regimens of anaesthesia influence the development of POD. Cohort studies, retrospective or secondary analyses<sup>185,236,237</sup> and RCTs<sup>88,126,238–242</sup> have shown mixed results and do not imply a role in adults. However, an important factor in managing POD is adequate stress reduction with sufficient analgesia, an appropriate choice of analgesia and the use of intraoperative opioids.<sup>13,180</sup> Currently, it remains unclear if intraoperative administration of short-acting analgesia impacts on POD. Some observational data are available suggesting that analgesia provided with continuous administration of remifentanyl might reduce the incidence of POD compared with a bolus-driven regimen with fentanyl,<sup>207</sup> but to draw convincing conclusions, evidence from RCTs is required.

To standardise the assessment and treatment of postoperative pain, we refer to the American Society of Anesthesiologists' guideline on acute pain management in the perioperative setting.<sup>243</sup> Although high preoperative<sup>129</sup> and postoperative pain<sup>244</sup> are risk factors for delirium, opioid analgesics may also be a risk factor in respect of side effects and organ dysfunction.<sup>115,180,197,245,246</sup> Patient-controlled analgesia (PCA)

could be one option if the patient is able to titrate the medication and find the right balance between analgesia and the minimum dose of opioids.<sup>247</sup> POD does not limit PCA use.<sup>247</sup> Regional anaesthesia and regional analgesia have not shown any benefit in respect of POD.<sup>248</sup>

A healing environment should be considered for the prevention of POD. Apart from the consensual statements on nonpharmacological treatment, this should be embedded in an environment for cognitive,<sup>249</sup> functional, social and emotional enhancement.<sup>250</sup> Further research is required to optimise the use of self-healing competencies of patients.

## Special patient groups

### Geriatric patients

A 'threshold theory of cognitive decline' was postulated to explain a situation of diminished brain reserve capacity occurring in older age, the genesis of which coincides with the degenerative phenomena occurring with ageing.<sup>251</sup> Due to this reduced brain capacity, older patients are on a 'functional cliff' for developing POD when undergoing a major physiological stress.

In Europe, the percentage of people aged at least 65 years currently ranges from 12% in 'young' countries such as Ireland to 21% in 'old' countries such as Germany and Italy.<sup>252</sup> With the passage of time, this will have a major impact on the demand for healthcare services, especially surgery. There are higher rates per population of both inpatient and outpatient surgical and nonsurgical procedures among the elderly compared with other age groups.<sup>253</sup> Patients older than 80 years are the most rapidly increasing group among surgical admissions.<sup>254</sup> In Italy, 38% of patients who undergo surgery are at least 65 years old.<sup>255</sup> In the USA, approximately half of operations are performed in patients aged at least 65 years.<sup>254,256</sup> Thus, the demand for surgery by older and sicker patients is increasing,<sup>257</sup> and POD is regarded as a major problem.

### Risk factors and preoperative evaluation

Ageing involves a continuum of changes in biological and functional parameters that increase vulnerability and reduce functional reserve.<sup>258</sup> Ageing is often accompanied by chronic multiple diseases, disability and frailty.

Although chronological age plays a role in predisposing to POD, it probably acts as a surrogate variable for the accumulation of age-related risk factors that are differentially expressed among individuals; it is almost certainly the sum of these risk factors that is most important in determining the probability of POD.

Dementia is a main predisposing factor for POD. This condition is very rare among patients under 60 years of age and becomes increasingly frequent as age

increases. Data provided by the WHO for Western Europe report a prevalence of 1.6% in patients aged 60 to 64 years and up to 43.1% in patients older than 90 years.<sup>259</sup> Previous dementia,<sup>23,67,146</sup> cognitive impairment<sup>11,12,15,18,34,71,90,93,108–110,113,115,116,125,169,260,261</sup> and depression<sup>20,22,71,91,110,112,123,143</sup> are associated with development of POD.

Other chronic diseases are often reported to be present in more than 50% of patients aged 65 to 70 years. In 30% of these patients, more than one single chronic disease is present. Cardiovascular<sup>14,16,17,24,28,77,95,103,125,127,148,260,262</sup> and metabolic<sup>15,34,131,135,136</sup> risk factors/diseases were found to be most frequently associated with POD.

Multimorbidity consists of a situation in which clinical patterns, evolution and treatment become more complicated than the simple sum of the different illnesses. Multimorbidity reduces the capability to cope with stress and increases global vulnerability – including the risk for POD.<sup>257,263</sup> Functional status, also called the sixth vital sign, is defined as the sum of behaviours that are needed to maintain daily activities, including social and cognitive functions.<sup>264</sup> Impaired functional status (i.e. reduced levels of independence, abilities and socialisation) is common among the elderly as a result of gait alteration, loss of coordination, reduced or abolished sphincter control, malnutrition, associated illnesses and/or cognitive deterioration. Impaired functional status is associated with surgical site infection, increased mortality and complication rate. In the preoperative setting, performance measures such as the timed 'Up & Go' Test<sup>265</sup> and other forms of Comprehensive Geriatric Assessment<sup>266</sup> have often been used. Impaired functional status has been reported as a predisposing factor for POD.<sup>23,34,89,169,267–271</sup>

The term 'frailty' indicates a situation of critically reduced functional reserves, involving multiple organ systems. It manifests with impaired capability to cope with intrinsic and environmental stressors and limited capability to maintain physiological and psychosocial homeostasis. Currently, 5.8 to 27.3% of the elderly ( $\geq 65$  years of age) in the general European population are reported to be frail.<sup>272</sup> However, studies examining older patients undergoing elective cardiac and noncardiac surgery quote prevalences of frailty between 41.8 and 50.3%<sup>273,274</sup>; this highlights the great vulnerability of this patient age group. Hypoalbuminaemia, hypocholesterolaemia and high levels of inflammation together with muscular atrophy are specific markers. Frailty has been found to be a predisposing factor for POD among elderly surgical patients.<sup>75,123,133,275</sup>

Hearing loss was found to be a predisposing factor for POD in three studies<sup>276–278</sup> and mentioned in three reviews<sup>58,270,279</sup>; the last two of these reviews and one additional study on internal medicine patients<sup>120</sup>

additionally mention visual impairment as a risk factor for POD.

Malnutrition affects 2 to 16% of community-dwelling elderly<sup>280</sup> and is frequently undiagnosed in those living at home. Between 20 and 65% of these patients suffer from nutritional deficits.<sup>281,282</sup> The main nutritional deficits concern proteins, minerals and vitamins. The most widely used test to diagnose malnutrition is the Mini-Nutritional Assessment<sup>283</sup> that can be performed at the bedside using a questionnaire. Malnutrition including low serum albumin concentration and/or homeostatic alterations and dehydration have been found to be associated with POD.<sup>112,117,122,132,148,267,284,285</sup>

Preoperative alcohol use disorders are seen in many elderly patients.<sup>286</sup> Many reports indicate that the number of older persons abusing alcohol is increasing in Europe.<sup>287–289</sup> Due to age-related changes, they present increased sensitivity and reduced tolerance to alcohol. POD has been reported as increased in elderly patients with a history of alcohol use disorders.<sup>20,34,71,116,138,141,142</sup>

Other preoperative variables that can influence the level of stress include the admission setting (emergency vs. nonemergency and inpatient vs. outpatient) and the adoption of dedicated perioperative strategies (prehabilitation,<sup>290</sup> fast-track vs. traditional strategy, admission to surgical wards vs. dedicated units). The consensus-based statements regarding risk factors of POD in elderly surgical patients are listed in Table 9.

### Intraoperative and postoperative management

Intraoperative neuromonitoring is important to avoid unnecessarily deep anaesthesia,<sup>203–206</sup> often reaching burst suppression in elderly patients.<sup>294</sup> In addition, inflammatory responses due to surgical trauma might be much more relevant for systemic organ dysfunction, including the brain, after surgery. Recently, it was shown that increased blood pressure fluctuation, not absolute or relative hypotension, was predictive of POD in elderly patients after noncardiac surgery.<sup>295</sup> If acute fluid replacement is required, cardiac function,<sup>296</sup> in particular atrial fibrillation,<sup>297–299</sup> should be the focus in respect of perfusion of the brain and all other organs.

Postoperatively, geriatric patients require immediate treatment of POD in the recovery room and on the peripheral ward because of their more vulnerable brain. Additional complications such as respiratory depression and hypoxia (e.g. due to analgesic requirements) should be avoided, and treated if necessary, despite the fact that it remains unclear whether postoperative hypoxia is an independent predictor of POD.<sup>22,267</sup>

POD and cognitive decline are seen more often after surgery and lead to a higher level of care dependency.<sup>36,260</sup> Therefore, monitoring with validated scales (see above) is recommended to detect POD as early as

possible. Besides, previous studies evaluating spontaneous eye movements, particularly blinks that appear to be affected in delirious patients, hold promise for delirium detection.<sup>300</sup> In addition, EEG (electroencephalography) monitoring, using the relative  $\delta$ -power from an eyes-closed EEG recording with two electrodes in a frontal–parietal lead, can distinguish between postoperative cardiac surgery patients who developed POD (mean age 77 years) and those who did not (mean age 74 years).<sup>301</sup>

In patients with dementia, a variety of instruments is available for the measurement of pain, including the Faces Pain Scale and other instruments such as the Pain Assessment in Advanced Dementia Scale<sup>302</sup> or the Non-Communicative Patient's Pain Assessment Instrument.<sup>303</sup> An overview of validated instruments is given by Hadjistavropoulos *et al.*<sup>304</sup> Apart from pain, opioids are also associated with an increased risk of POD<sup>89,245,305,306</sup> and require close monitoring of POD.<sup>180,197,246</sup>

In the elderly, nonpharmacological measures are reported to reduce the incidences of POD and falls.<sup>307–309</sup> Further research should evaluate different multi-component programmes to select the most useful interventions. The consensus-based statement regarding prevention and treatment of POD in elderly surgical patients is listed in Table 10.

### Organisational issues

POD is an expensive complication and multi-component interventions can reduce acute and long-term nursing home costs.<sup>312–314</sup> Sufficient evidence supports the idea that organisational measures such as dedicated pathways are preventive.<sup>312</sup> However, dedicated geriatric units aimed to promote co-management and a team-based approach are only (and rarely) present in academic hospitals. In many other small or intermediate hospitals, they are not at hand. In these hospitals, anaesthesiologists and surgeons share the responsibility to establish adequate organisational solutions. Increasing evidence exists that outcomes in geriatric surgery are highly dependent on the level of care that elderly patients receive perioperatively.<sup>315</sup> Both the American Geriatric Association Guidelines on POD<sup>316</sup> and the American College of Surgeons/National Surgical Quality Improvement Program Guidelines<sup>317</sup> emphasise the importance of dedicated pathways as a means to improve quality of care in geriatric surgery. The most important dedicated models of care are Geriatric Consultation Services,<sup>318–321</sup> Acute Care for the Elderly Units<sup>322,323</sup> and co-management based models (Orthogeriatric Units and/or Geriatric Consultation Services).<sup>324,325</sup> These structures were conceived with the aim of reducing complication rates and mortality in geriatric surgery, especially after hip fracture. Team-based approaches, quality of care and, in some cases, hospital design are basic elements. The introduction of proactive multidisciplinary geriatric interventions in

**Table 9** Evidence-based and consensus-based statements regarding risk factors in elderly surgical patients

Statements	LoE	All adults	Age group (inclusion criteria)		GoR
				Elderly $\geq 65$ years	
We recommend evaluating the following preoperative risk factors for POD					
• Cognitive impairment	[11], 2b; [12], 2b; <sup>15</sup> [15], 2b; [18], 2b; [34], 4; [59], SR			[11,12,15,18,34,71,90,93,105,108], Incl. $\geq 60$ years, obsvd. 74 years; [109,110], Incl. $\geq 60$ years, obsvd. 67 $\pm$ 9 years; [115,125], Incl. $\geq 60$ years, obsvd. 72 years; [134,147], Incl. $\geq 60$ years, obsvd. 72 years; [150], Incl. $\geq 60$ years, obsvd. 75 years; [169,260], Incl. $\geq 60$ years, obsvd. 72 (IQR 66 to 77) years; [132,261,291,293]	A
	[71], SR; [90], 4				
	[93], 2b; [105], 5; [108], 4; [109], 2b; [110], 2b; [113], 2b; [115], 2b; [125], 2b; [134], 4; [147], 4; [150], 4; [170], 4; [260], 2b; [261], 2b; [279], SR; [291], 2b; [292], SR; [293], 4				
• Reduced functional status and/or frailty	[23], 2b; [34], 4			[23,34,89,105,113,123,133,169,267,268,271,275]	A
	[89], 4; [105], 5; [113], 2b; [123], 2b; [133], 2b; [169], 4; [267], 2b; [268], 2b; [269], SR; [270], SR; [271], 2b; [275], 2b				
• Malnutrition (low serum albumin)	[112], 2b; [117], 2b; [122], 2b; [132], 2b; [267], 2b; [284], 2b			[112], No incl. criterion, obsvd. median age 66 (range 58 to 72) years; [117,122,267,284], No incl. criterion, obsvd. POD+, 69.9 years, POD-, 67.4 years; [132], Incl. $\geq 60$ years, obsvd. 74 years	A
• Sensory impairment	[270], SR; [276], 4; [277] SR; [278], 4; [279], NR			[276], No incl. criterion, obsvd. POD+, 67.4 years, POD-, 66.0 years; [278], Incl. $\geq 60$ years, obsvd. 69.8 (range 53 to 84) years	A

Data presented as reference number, LoE. GoR, grade of recommendation (strong = A, conditional = B); Incl., inclusion criterion; IQR, interquartile range; LoE, level of evidence; NR, narrative review; obsvd., observed; POD, postoperative delirium; SR, systematic review.

elderly patients with acute hip surgery has been followed by a significant reduction in the incidence of POD.<sup>242,326–332</sup>

### Paediatric patients

Delirium after anaesthesia in children is reported often. The majority of reported paediatric cases focus on emergence delirium (paedED) in the recovery room with a wide range of incidence from 2 to 80%.<sup>50,181,333</sup> PaedED is based on the theoretical framework of delirium defined by DSM.<sup>40</sup> PaedED was defined as a disturbance in a child's awareness of and attention to his or her environment with disorientation and perceptual alterations including hypersensitivity to stimuli and hyperactive motor behaviour in the immediate postanaesthesia period.<sup>181,334</sup> The term 'emergence agitation' should not be used interchangeably with paedED because agitation is excessive motor activity, is more common than paedED in the postoperative period and is associated with discomfort, pain or anxiety.<sup>335</sup> The majority of children who develop paedED do so in the recovery room/PACU.<sup>50,181,334,335</sup> Research on paedED in peripheral wards is warranted.

For paediatric patients, risk factors for development of paedED should be considered, monitoring for paedED should be established and preventive and treatment measures should be taken to decrease the incidence of paedED. The evidence-based and consensus-based statements are listed in Table 11.

In addition to the Task Force's recommendations, there are several relevant topics of interest with regard to paedED. These topics need to be discussed and several of them warrant further studies.

### Predisposing factors

Children with low adaptability to new situations seem more prone to develop paedED.<sup>343</sup> Other influences on emotional stress such as the temperament of the child or the anxiety of parents/guardians might have an influence on paedED.<sup>352,383–385</sup> The risk of recurrence of paedED after repetitive procedures is unclear. Research should be undertaken to identify preoperative (psychological, social and medical) risk factors for paedED to help the anaesthesiologist adapt preoperative preparation, whether psychological or pharmacological, to the child's needs.

**Table 10** Evidence-based and consensus-based statements regarding prevention and treatment in elderly patients

Statement	LoE	Age group (inclusion criteria)		GoR
		All adults	≥65 years	
We suggest implementing nonpharmacological measures to reduce POD: orientation (clock, communication, etc.), visual/hearing aids, noise reduction and maintenance of a day/night rhythm avoidance of unnecessary indwelling catheters, early mobilisation and early nutrition <sup>a</sup>	[105], 5; [248], SR; [309], SR; [310], 4; [311], 4		[105,310,311]	B

Data presented as reference number, LoE. GoR, grade of recommendation (conditional = B); LoE, level of evidence; POD, postoperative delirium. <sup>a</sup>For example, implementation recommended in geriatric and/or fast-track surgical protocols.<sup>105,159,208</sup>

### Premedication

Premedication with midazolam reduces paedED after sevoflurane anaesthesia.<sup>361,362,364–366</sup> However, different durations of procedures and different methods used to assess paedED make it difficult to provide a conclusion regarding the influence of midazolam on paedED.<sup>363,367</sup> Melatonin might be superior to midazolam to decrease the risk of paedED but it does not reduce anxiety.<sup>386,387</sup> Availability of melatonin differs widely among European

countries. It is either an ‘over the counter’ drug or has to be prescribed.

Premedication with or intraoperative use of  $\alpha_2$ -agonists (dexmedetomidine<sup>372–374</sup> or clonidine<sup>50</sup>) decreases the incidence of paedED.<sup>50,359,375–378</sup> In a recent double-blind RCT, preoperative intranasal dexmedetomidine was more effective than clonidine in decreasing the incidence and severity of emergence agitation and also

**Table 11** Evidence-based and consensus-based statements regarding paediatric patients

Statements	LoE	GoR
Risk factors		
We recommend considering pre-school age as a risk factor for paediatric emergence delirium (paedED)	[336], 4; [337], 1b; [338], 1b; [339], 2b; [340], SR; [341], 1b; [342], 1b; [343], 2b	A
We suggest not considering sex as a risk factor for paedED	[344], 1b; [345], 2b; [346], 1b; [347], 2b; [348], 2b	B
We suggest considering ENT surgery as a risk factor for paedED	[336], 4; [343], 2b	B
We recommend evaluating pain as a risk factor for paedED	[333], SR & MA [348], 1b; [349], 2b; [350], 2b	A
Monitoring		
We suggest assessing anxiety by a validated score	[337], 2b; [342], 1b; [343], 2b; [344], 2b; [351], 2b; [352], 1b; [353], 2b; [354], 1b	B
We recommend treating pain according to a validated age-adapted scale	[181], 1b; [355], 2b; [356], 2b	A
We recommend assessing paedED using an age-adapted validated tool	[340], SR; [357], 2b; [358], 2b	A
We recommend assessing pain at the same time as paedED	[181], 1b; [355], 2b	A
Prevention and treatment		
We suggest implementing the ADVANCE <sup>a</sup> strategy of cognitive preparation for surgery, this is considered superior to premedication with midazolam for the reduction of paedED incidence	[352], 1b; [359], MA; [360], 2b	B
We suggest using midazolam to reduce preoperative anxiety in children	[339], 2b; [361], 1b; [362], 1b; [363], 1b; [364], 1b; [365], 1b; [366], NR; [367], 1b	B
We suggest implementing nonpharmacological strategies included in the treatment of paedED to calm the patient and limit harm	[352], 1b; [359], MA; [360], 2b	B
We suggest balancing the use of short acting volatile anaesthetics (Sevoflurane/Desflurane > Isoflurane) against their risk for paedED.	[345], 1b; [349], 2b; [368], 1b; [369], MA; [370], 1b; [371], 1b	B
We suggest using $\alpha_2$ -agonists (clonidine and dexmedetomidine) intravenously, intranasally or epidurally to reduce the risk of paedED	[382], 1b; [373], MA; [374], MA; [375], 1b; [376], 1b; [377], 1b; [378], SR & MA [379], 1b	B
We suggest using propofol as a bolus on emergence to decrease paedED	[380], 1b	B
We suggest using preventive analgesia, e.g. caudal, fascia iliaca block, to reduce paedED	[354], 1b; [381], 2b; [382], 1b	B

Data presented as reference number, LoE. GoR, grade of recommendation (strong = A; conditional = B); LoE, level of evidence; MA, meta-analysis; NR, narrative review; paedED, paediatric anaesthesia emergence delirium; SR, systematic review. <sup>a</sup>The ADVANCE strategy describes a family-centred preparation programme for children. The acronym stands for Anxiety-reduction, Distraction, Video-modelling and education, Adding parents, No excessive reassurance, Coaching and Exposure/shaping.<sup>352</sup>

decreased fentanyl consumption after surgery.<sup>379</sup> More recently, in small series, premedication with gabapentin,<sup>388</sup> premedication with ketamine,<sup>389</sup> intraoperative dexamethasone<sup>390</sup> or magnesium<sup>391</sup> were also found to decrease paedED.

### Neuromonitoring

Continuous EEG monitoring might help to distinguish between patients who will or will not develop paedED. Increased frontal lobe cortical functional connectivity observed in paedED, immediately after the termination of sevoflurane anaesthesia, might have important implications for the development of methods to predict paedED.<sup>392</sup>

### Anaesthesia

For short-term procedures, propofol is considered to be well tolerated in children. The best model to provide total intravenous anaesthesia in small children seems to be the model designed by Short for adults.<sup>393</sup> One should always bear in mind the small risk of developing a propofol infusion syndrome (PRIS), the pathophysiology of which is complex and may involve mitochondria.<sup>394</sup> The risk of PRIS seems to be reduced if propofol can be titrated to  $4 \text{ mg kg}^{-1} \text{ h}^{-1}$  and is used for a short duration ( $<48 \text{ h}$ )<sup>395</sup> and if IV glucose is provided ( $6 \text{ mg kg}^{-1} \text{ min}^{-1}$ ) to avoid lipid catabolism.<sup>396</sup>

Common side effects of using a continuous infusion of propofol for 60 min in small children are reversible increases in plasma lipid, triglyceride and pancreatic enzymes concentrations.<sup>397</sup> Propofol infusions appear to be well tolerated when limiting doses to  $4 \text{ mg kg}^{-1} \text{ h}^{-1}$  – 1 for less than 24 h.<sup>398</sup>

### Postoperative pain

Acute perioperative pain in infants and children is still often undertreated.<sup>399,400</sup> Three of the most commonly performed surgical procedures in children (tonsillectomy, appendectomy and orchidopexy) are more painful than usually expected. Up to 44% of children still suffer from severe pain until day 3, and up to 30% until day 7 after surgery.<sup>401</sup> Several analgesic techniques, such as regional anaesthesia (caudal block<sup>354,381</sup> and fascia iliaca compartment block<sup>349,402</sup>) or pharmacological interventions (fentanyl<sup>350,382</sup> or nalbuphine<sup>351,403,404</sup>) are available and seem to reduce the incidence of paedED.

### Implementation

Strategies to reduce the risk of paedED require a protocol to facilitate implementation. Figure 3 presents a condensed version of the statements. This figure can be used to integrate evidence-based recommendations into local standards to fulfil the requirements of the best practice care of the hospital.

### Conclusion

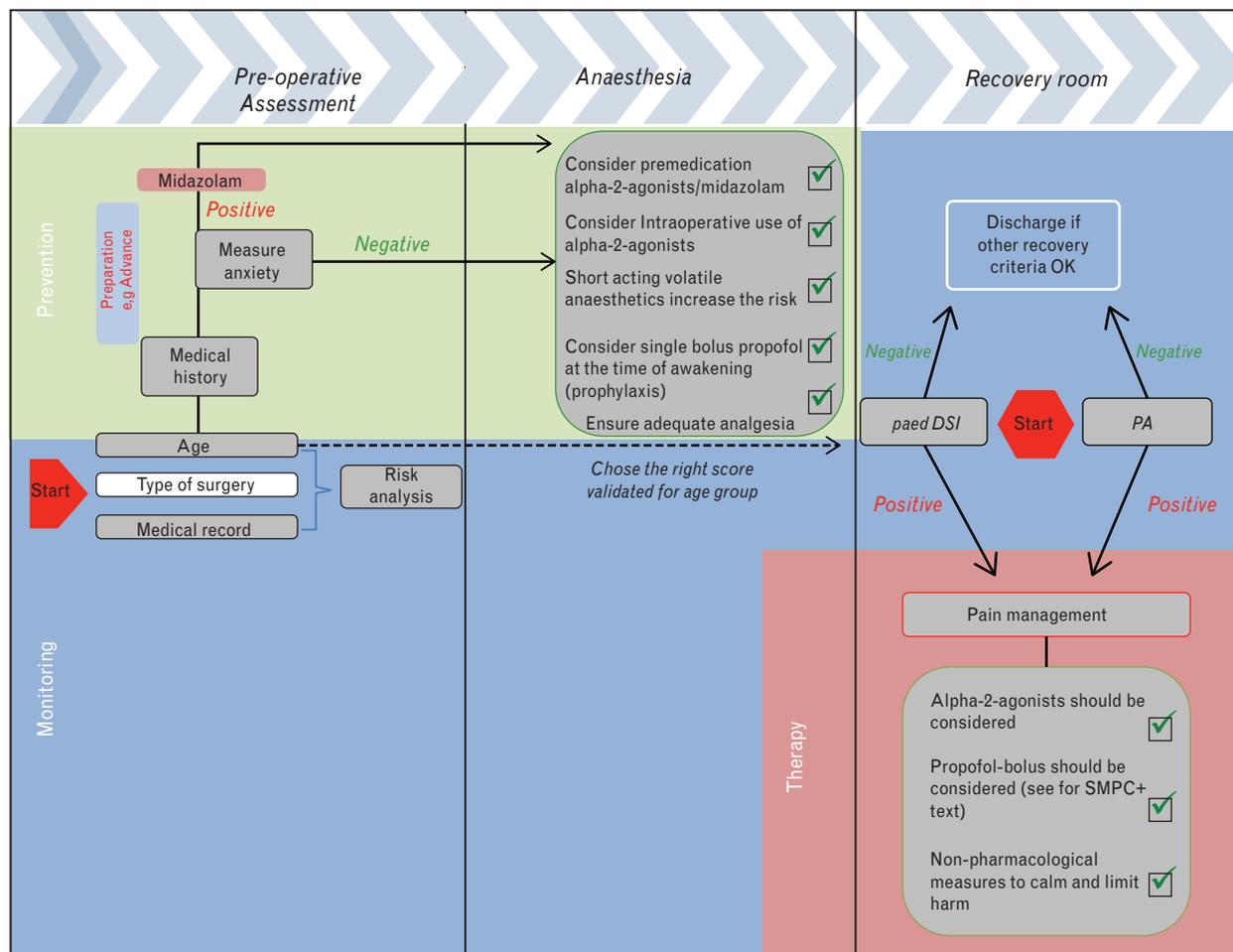
POD is a frequent complication and requires preventive measures as well as immediate and adequate treatment. Although numerous studies have documented the clinical and economic consequences of POD, systematic interventions aimed to reduce its incidence and duration are rarely implemented. Currently, care is not sufficiently focussed on the patient's safety with the aim of reducing long-term harms such as cognitive dysfunction and post-traumatic stress disorder, which can impair quality of life. Despite the huge costs of POD and its preventability, it receives little attention in terms of resource allocation from hospital administrators and healthcare institutional governance representatives. To date, no nation-based strategies have been applied in Europe to minimise POD or monitor its incidence. However, process control has become a key issue for success in many healthcare organisations.

Given the enormous burden exerted by POD on patients, their families, healthcare organisations and public resources, anaesthesiologists operating in Europe should engage to make efforts in designing integrated actions aimed to reduce the incidence and duration of POD. These efforts will become effective when conceived through a team-based multi-component approach. Single items reported may not gain sufficient power alone to ensure effective results. A collaborative path with all the suggested measures to improve the 'quality chain' is highly warranted. The main steps include

- (1) preoperative evaluation of POD risk and identification of patients at risk
- (2) communication about this risk to patients, their family and care team members
- (3) best possible preoperative conditions to be achieved
- (4) perioperative avoidance of use of anticholinergic agents and benzodiazepines except when needed. Benzodiazepines can be considered in cases of alcohol withdrawal
- (5) attempts to reduce surgical stress, together with organ-protective intraoperative management, including neuromonitoring to avoid excessively deep anaesthesia
  - (a) effective multimodal opioid-sparing analgesia
  - (b) implementation of enhanced recovery programmes
- (6) cognitive monitoring to be aimed at recognition of preoperative cognitive decline and to detect POD as early as possible, including in the recovery room
- (7) effective treatment of POD by protocols
- (8) follow-up of POD patients all along their hospital stay
- (9) patient information on adequate medical support, to ensure continuity of care after discharge.

Patient organisations, politicians and decision-makers for resource allocation and quality assurance, as well as

Fig. 3



- 1) paedDSI paediatric delirium screening tool, validated for certain age group
- 2) PA pain assessments tool
- 3) ADVANCE strategy for cognitive preparation for surgery

Algorithm for pre-operative, intra-operative and post-operative management of postoperative delirium in children. The algorithm shows the different time stages of surgery (left to right) and, in a different axis, preventive (top), diagnostic (middle) and therapeutically (lower) actions that should be taken. The red 'start button' helps the user to start at the first step in the different time stages.

healthcare institutional representatives, should consider reduction of POD as a main goal of their activity for the benefit of the community.

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### References

- 1 AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Healthcare* 2003; **12**:18–23.
- 2 Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, Part 1: Performance, usefulness and areas for improvement. *CMAJ* 2010; **182**:1045–1052.
- 3 Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, Part 2: Assessment of validity of items and tools to support application. *CMAJ* 2010; **182**:E472–E478.
- 4 CEBM Centre for Evidence-Based Medicine. *Critical appraisal tools*. University of Oxford; 2015; <http://www.cebm.net/critical-appraisal/> [Accessed 24 July 2015].

- 5 Atkins D, Best D, Briss PA, *et al.* Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328**:1490.
- 6 Council of Europe CoM. *Recommendation Rec(2001)13 of the Committee of Ministers to member states on developing a methodology for drawing up guidelines on best medical practices*. Council of Europe Publishing; 2001; <https://wcd.coe.int/ViewDoc.jsp?id=228755&Site=COE>. [Accessed 27 July 2015].
- 7 Flick RP, Katusic SK, Colligan RC, *et al.* Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. *Pediatrics* 2011; **128**:e1053–e1061.
- 8 Rappaport BA, Suresh S, Hertz S, *et al.* Anesthetic neurotoxicity – clinical implications of animal models. *N Engl J Med* 2015; **372**:796–797.
- 9 European Society of Anaesthesiology. *EUROpean safe tots anaesthesia research initiative task force*. 2015; <https://www.esahq.org/research/research-groups/eurostar/>. [Accessed 10 December 2015].
- 10 Do T-D, Lemogne C, Journois D, *et al.* Low social support is associated with an increased risk of postoperative delirium. *J Clin Anesth* 2012; **24**:126–132.
- 11 Hempenius L, Slaets JPJ, van Asselt DZB, *et al.* Interventions to prevent postoperative delirium in elderly cancer patients should be targeted at those undergoing nonsuperficial surgery with special attention to the cognitive impaired patients. *Eur J Surg Oncol* 2015; **41**:28–33.
- 12 Leung JM, Sands LP, Lim E, *et al.* Does preoperative risk for delirium moderate the effects of postoperative pain and opiate use on postoperative delirium? *Am J Geriatr Psychiatry* 2013; **21**:946–956.
- 13 Radtke FM, Franck M, MacGuill M, *et al.* Duration of fluid fasting and choice of analgesic are modifiable factors for early postoperative delirium. *Eur J Anaesthesiol* 2010; **27**:411–416.
- 14 Abelho FJ, Fernandes V, Botelho M, *et al.* Apolipoprotein E e4 allele does not increase the risk of early postoperative delirium after major surgery. *J Anesth* 2012; [Epub ahead of print].
- 15 Ansaloni L, Catena F, Chattat R, *et al.* Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. *Br J Surg* 2010; **97**:273–280.
- 16 Bucerius J, Gummert JF, Borger MA, *et al.* Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. *J Thorac Cardiovasc Surg* 2004; **127**:57–64.
- 17 Gottesman RF, Grega MA, Bailey MM, *et al.* Delirium after coronary artery bypass graft surgery and late mortality. *Ann Neurol* 2010; **67**:338–344.
- 18 Kalisvaart KJ, Vreeswijk R, de Jonghe JFM, *et al.* Risk factors and prediction of postoperative delirium in elderly hip-surgery patients: implementation and validation of a medical risk factor model. *J Am Geriatr Soc* 2006; **54**:817–822.
- 19 Koebrugge B, van Wensen RJ, Bosscha K, *et al.* Delirium after emergency/elective open and endovascular aortoiliac surgery at a surgical ward with a high-standard delirium care protocol. *Vascular* 2010; **18**:279–287.
- 20 Fineberg SJ, Nandyala SV, Marquez-Lara A, *et al.* Incidence and risk factors for postoperative delirium after lumbar spine surgery. *Spine (Phila Pa 1976)* 2013; **38**:1790–1796.
- 21 Joosten E, Lemiengre J, Nelis T, *et al.* Is anaemia a risk factor for delirium in an acute geriatric population? *Gerontology* 2006; **52**:382–385.
- 22 Kazmierski J, Kowman M, Banach M, *et al.* Incidence and predictors of delirium after cardiac surgery: results from The IPDACS Study. *J Psychosom Res* 2010; **69**:179–185.
- 23 Robinson TN, Raeburn CD, Tran ZV, *et al.* Postoperative delirium in the elderly: risk factors and outcomes. *Ann Surg* 2009; **249**:173–178.
- 24 Norkiene I, Ringaitiene D, Misiuriene I, *et al.* Incidence and precipitating factors of delirium after coronary artery bypass grafting. *Scand Cardiovasc J* 2007; **41**:180–185.
- 25 Bakker RC, Osse RJ, Tulen JHM, *et al.* Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. *Eur J Cardiothorac Surg* 2012; **41**:544–549.
- 26 Hatano Y, Narumoto J, Shibata K, *et al.* White-matter hyperintensities predict delirium after cardiac surgery. *Am J Geriatr Psychiatry* 2013; **21**:938–945.
- 27 Miyazaki S, Yoshitani K, Miura N, *et al.* Risk factors of stroke and delirium after off-pump coronary artery bypass surgery. *Interact Cardiovasc Thorac Surg* 2011; **12**:379–383.
- 28 Tan MC, Felde A, Kuskowski M, *et al.* Incidence and predictors of postcardiotomy delirium. *Am J Geriatr Psychiatry* 2008; **16**:575–583.
- 29 Bellelli G, Mazzola P, Morandi A, *et al.* Duration of postoperative delirium is an independent predictor of 6-month mortality in older adults after hip fracture. *J Am Geriatr Soc* 2014; **62**:1335–1340.
- 30 Bickel H, Grading R, Kochs E, *et al.* High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. *Dement Geriatr Cogn Disord* 2008; **26**:26–31.
- 31 Edelstein DM, Aharonoff GB, Karp A, *et al.* Effect of postoperative delirium on outcome after hip fracture. *Clin Orthop Relat Res* 2004; **422**:195–200.
- 32 Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *JAMA* 1990; **263**:1097–1101.
- 33 Krzych LJ, Wybraniec MT, Krupka-Matuszczyk I, *et al.* Detailed insight into the impact of postoperative neuropsychiatric complications on mortality in a cohort of cardiac surgery subjects: a 23,000-patient-year analysis. *J Cardiothorac Vasc Anesth* 2014; **28**:448–457.
- 34 Marcantonio ER, Goldman L, Mangione CM, *et al.* A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA* 1994; **271**:134–139.
- 35 Vochteloo AJ, Moerman S, van der Burg BL, *et al.* Delirium risk screening and haloperidol prophylaxis program in hip fracture patients is a helpful tool in identifying high-risk patients, but does not reduce the incidence of delirium. *BMC Geriatr* 2011; **11**:39.
- 36 Witlox J, Eurelings LSM, de Jonghe JFM, *et al.* Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010; **304**:443–451.
- 37 Heymann A, Radtke F, Schiemann A, *et al.* Delayed treatment of delirium increases mortality rate in intensive care unit patients. *J Int Med Res* 2010; **38**:1584–1595.
- 38 Pisani MA, Kong SY, Kasl SV, *et al.* Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med* 2009; **180**:1092–1097.
- 39 Saczynski JS, Marcantonio ER, Quach L, *et al.* Cognitive trajectories after postoperative delirium. *N Engl J Med* 2012; **367**:30–39.
- 40 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (Dsm-5®)*, 5th ed. Washington, DC: Amer Psychiatric Pub Inc; 2013.
- 41 World Health Organization. *International Statistical Classification of Diseases and Related Health Problems 10th Revision*. <http://apps.who.int/classifications/icd10/browse/2016/en>, 2015. [Accessed 9 December 2015].
- 42 Olin K, Eriksdotter-Jonhagen M, Jansson A, *et al.* Postoperative delirium in elderly patients after major abdominal surgery. *Br J Surg* 2005; **92**:1559–1564.
- 43 Sharma PT, Sieber FE, Zakriya KJ, *et al.* Recovery room delirium predicts postoperative delirium after hip-fracture repair. *Anesth Analg* 2005; **101**:1215–1220.
- 44 Radtke FM, Franck M, Schneider M, *et al.* Comparison of three scores to screen for delirium in the recovery room. *Br J Anaesth* 2008; **101**:338–343.
- 45 Bastron RD, Moyers J. Emergence delirium. *JAMA* 1967; **200**:883.
- 46 Hudek K. Emergence delirium: a nursing perspective. *AORN J* 2009; **89**:509–516.
- 47 Lepouse C, Lautner CA, Liu L, *et al.* Emergence delirium in adults in the postanesthesia care unit. *Br J Anaesth* 2006; **96**:747–753.
- 48 Radtke FM, Franck M, Hagemann L, *et al.* Risk factors for inadequate emergence after anesthesia: emergence delirium and hypoactive emergence. *Minerva Anesthesiol* 2010; **76**:394–403.
- 49 Xara D, Silva A, Mendonca J, *et al.* Inadequate emergence after anesthesia: emergence delirium and hypoactive emergence in the Postanesthesia Care Unit. *J Clin Anesth* 2013; **25**:439–446.
- 50 Dahmani S, Delivet H, Hilly J. Emergence delirium in children: an update. *Curr Opin Anaesthesiol* 2014; **27**:309–315.
- 51 Robinson TN, Raeburn CD, Tran ZV, *et al.* Motor subtypes of postoperative delirium in older adults. *Arch Surg* 2011; **146**:295–300.
- 52 Meagher DJ, O'Hanlon D, O'Mahony E, *et al.* Relationship between symptoms and motoric subtype of delirium. *J Neuropsychiatry Clin Neurosci* 2000; **12**:51–56.
- 53 Meagher D, Moran M, Raju B, *et al.* A new data-based motor subtype schema for delirium. *J Neuropsychiatry Clin Neurosci* 2008; **20**:185–193.
- 54 Eurostat. *Your key to European statistics*. European Union; 2015; <http://ec.europa.eu/eurostat/data/database> [Accessed 15 March 2015].
- 55 Pearce RM, Moreno RP, Bauer P, *et al.* Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; **380**:1059–1065.
- 56 Weiser TG, Regenbogen SE, Thompson KD, *et al.* An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; **372**:139–144.
- 57 Smulter N, Lingehall HC, Gustafson Y, *et al.* Delirium after cardiac surgery: incidence and risk factors. *Interact Cardiovasc Thorac Surg* 2013; **17**:790–796.
- 58 Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. *J Am Geriatr Soc* 2006; **54**:1578–1589.
- 59 Dyer CB, Ashton CM, Teasdale TA. Postoperative delirium. A review of 80 primary data-collection studies. *Arch Intern Med* 1995; **155**:461–465.

- 60 Bruce AJ, Ritchie CW, Blizard R, et al. The incidence of delirium associated with orthopedic surgery: a meta-analytic review. *Int Psychogeriatr* 2007; **19**:197–214.
- 61 Abelha FJ, Luis C, Veiga D, et al. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. *Crit Care* 2013; **17**:R257.
- 62 Borhani Haghighi A, Malekghoseini SA, Bahramali E, et al. Neurological complications of first 100 orthotopic liver transplantation patients in southern Iran. *Transplant Proc* 2005; **37**:3197–3199.
- 63 Bussièrre M, Hopman W, Day A, et al. Indicators of functional status for primary malignant brain tumour patients. *Can J Neurol Sci* 2005; **32**:50–56.
- 64 Dubljanin-Raspopovic E, Markovic Denic L, Marinkovic J, et al. Use of early indicators in rehabilitation process to predict one-year mortality in elderly hip fracture patients. *Hip Int* 2012; **22**:661–667.
- 65 Heijmeriks JA, Dassen W, Prenger K, et al. The incidence and consequences of mental disturbances in elderly patients post cardiac surgery – a comparison with younger patients. *Clin Cardiol* 2000; **23**:540–546.
- 66 Koster S, Hensens AG, Schuurmans MJ, et al. Consequences of delirium after cardiac operations. *Ann Thorac Surg* 2012; **93**:705–711.
- 67 Lee KH, Ha YC, Lee YK, et al. Frequency, risk factors, and prognosis of prolonged delirium in elderly patients after hip fracture surgery. *Clin Orthop Relat Res* 2011; **469**:2612–2620.
- 68 Lundström M, Edlund A, Bucht G, et al. Dementia after delirium in patients with femoral neck fractures. *J Am Geriatr Soc* 2003; **51**:1002–1006.
- 69 Mangoni AA, van Munster BC, Woodman RJ, et al. Measures of anticholinergic drug exposure, serum anticholinergic activity, and all-cause postdischarge mortality in older hospitalized patients with hip fractures. *Am J Geriatr Psychiatry* 2013; **21**:785–793.
- 70 Mazzola P, Bellelli G, Brogini V, et al. Postoperative delirium and prefracture disability predict 6-month mortality among the oldest old hip fracture patients. *Aging Clin Exp Res* 2015; **27**:53–60.
- 71 Pompei P, Foreman M, Rudberg MA, et al. Delirium in hospitalized older persons: outcomes and predictors. *J Am Geriatr Soc* 1994; **42**:809–815.
- 72 Berry SD, Samelson EJ, Bordes M, et al. Survival of aged nursing home residents with hip fracture. *J Gerontol A Biol Sci Med Sci* 2009; **64**:771–777.
- 73 Juliebo V, Krogseth M, Skovlund E, et al. Delirium is not associated with mortality in elderly hip fracture patients. *Dement Geriatr Cogn Disord* 2010; **30**:112–120.
- 74 Kat MG, de Jonghe JF, Vreeswijk R, et al. Mortality associated with delirium after hip-surgery: a 2-year follow-up study. *Age Ageing* 2011; **40**:312–318.
- 75 Kim S, Han H-S, Jung H, et al. Multidimensional frailty score for the prediction of postoperative mortality risk. *JAMA Surg* 2014; **149**:633–640.
- 76 Large MC, Reichard C, Williams JTB, et al. Incidence, risk factors, and complications of postoperative delirium in elderly patients undergoing radical cystectomy. *Urology* 2013; **81**:123–128.
- 77 Sasajima Y, Sasajima T, Azuma N, et al. Factors related to postoperative delirium in patients with lower limb ischaemia: a prospective cohort study. *Eur J Vasc Endovasc Surg* 2012; **44**:411–415.
- 78 Kat MG, Vreeswijk R, de Jonghe JFM, et al. Long-term cognitive outcome of delirium in elderly hip surgery patients. A prospective matched controlled study over two and a half years. *Dement Geriatr Cogn Disord* 2008; **26**:1–8.
- 79 Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013; **369**:1306–1316.
- 80 Neufeld KJ, Leoutsakos JM, Oh E, et al. Long-term outcomes of older adults with and without delirium immediately after recovery from general anesthesia for surgery. *Am J Geriatr Psychiatry* 2015; **23**:1067–1074.
- 81 Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008; **108**:18–30.
- 82 Bryson GL, Wyand A, Wozny D, et al. A prospective cohort study evaluating associations among delirium, postoperative cognitive dysfunction, and apolipoprotein E genotype following open aortic repair. *Can J Anaesth* 2011; **58**:246–255.
- 83 Hudetz JA, Patterson KM, Byrne AJ, et al. Postoperative delirium is associated with postoperative cognitive dysfunction at one week after cardiac surgery with cardiopulmonary bypass. *Psychol Rep* 2009; **105**:921–932.
- 84 Norkiene I, Samalavicius R, Misiuriene I, et al. Incidence and risk factors for early postoperative cognitive decline after coronary artery bypass grafting. *Medicina (Kaunas)* 2010; **46**:460–464.
- 85 Brown LJ, Ferner HS, Robertson J, et al. Differential effects of delirium on fluid and crystallized cognitive abilities. *Arch Gerontol Geriatr* 2011; **52**:153–158.
- 86 Wacker P, Nunes PV, Cabrita H, et al. Postoperative delirium is associated with poor cognitive outcome and dementia. *Dement Geriatr Cogn Disord* 2006; **21**:221–227.
- 87 Drews T, Franck M, Radtke FM, et al. Postoperative delirium is an independent risk factor for posttraumatic stress disorder in the elderly patient: a prospective observational study. *Eur J Anaesthesiol* 2015; **32**:147–151.
- 88 Berggren D, Gustafson Y, Eriksson B, et al. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. *Anesth Analg* 1987; **66**:497–504.
- 89 Brouquet A, Cudennec T, Benoist S, et al. Impaired mobility, ASA status and administration of tramadol are risk factors for postoperative delirium in patients aged 75 years or more after major abdominal surgery. *Ann Surg* 2010; **251**:759–765.
- 90 Furlaneto ME, Garcez-Leme LE. Delirium in elderly individuals with hip fracture: causes, incidence, prevalence, and risk factors. *Clinics (Sao Paulo)* 2006; **61**:35–40.
- 91 Greene NH, Attix DK, Weldon BC, et al. Measures of executive function and depression identify patients at risk for postoperative delirium. *Anesthesiology* 2009; **110**:788–795.
- 92 Gustafson Y, Berggren D, Brannstrom B, et al. Acute confusional states in elderly patients treated for femoral neck fracture. *J Am Geriatr Soc* 1988; **36**:525–530.
- 93 Liu P, Li Y, Wang X, et al. High serum interleukin-6 level is associated with increased risk of delirium in elderly patients after noncardiac surgery: a prospective cohort study. *Chin Med J* 2013; **126**:3621–3627.
- 94 Markar SR, Smith IA, Karthikesalingam A, et al. The clinical and economic costs of delirium after surgical resection for esophageal malignancy. *Ann Surg* 2013; **258**:77–81.
- 95 Santos FS, Velasco IT, Fráguas R. Risk factors for delirium in the elderly after coronary artery bypass graft surgery. *Int Psychogeriatr* 2004; **16**:175–193.
- 96 Street JT, Noonan VK, Cheung A, et al. Incidence of acute care adverse events and long-term health-related quality of life in patients with TSCI. *Spine J* 2015; **15**:923–932.
- 97 Brauer C, Morrison RS, Silberzweig SB, et al. The cause of delirium in patients with hip fracture. *Arch Intern Med* 2000; **160**:1856–1860.
- 98 Edlund A, Lundstrom M, Lundstrom G, et al. Clinical profile of delirium in patients treated for femoral neck fractures. *Dement Geriatr Cogn Disord* 1999; **10**:325–329.
- 99 Edlund A, Lundstrom M, Brannstrom B, et al. Delirium before and after operation for femoral neck fracture. *J Am Geriatr Soc* 2001; **49**:1335–1340.
- 100 Formiga F, Lopez-Soto A, Sacanella E, et al. Mortality and morbidity in nonagenarian patients following hip fracture surgery. *Gerontology* 2003; **49**:41–45.
- 101 Johansson IS, Hamrin EK, Larsson G. Psychometric testing of the NEECHAM Confusion Scale among patients with hip fracture. *Res Nurs Health* 2002; **25**:203–211.
- 102 Kagansky N, Rimon E, Naor S, et al. Low incidence of delirium in very old patients after surgery for hip fractures. *Am J Geriatr Psychiatry* 2004; **12**:306–314.
- 103 Morrison RS, Magaziner J, Gilbert M, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci* 2003; **58**:76–81.
- 104 Gruber-Baldini AL, Zimmerman S, Morrison RS, et al. Cognitive impairment in hip fracture patients: timing of detection and longitudinal follow-up. *J Am Geriatr Soc* 2003; **51**:1227–1236.
- 105 American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. *J Am Coll Surg* 2015; **220**:136–148.
- 106 Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996; **275**:852–857.
- 107 Kim SD, Park SJ, Lee DH, et al. Risk factors of morbidity and mortality following hip fracture surgery. *Korean J Anesthesiol* 2013; **64**:505–510.
- 108 Bickel H, Grading R, Kochs E, et al. Incidence and risk factors of delirium after hip surgery. *Psychiatr Praxis* 2004; **31**:360–365.
- 109 Dai YT, Lou MF, Yip PK, et al. Risk factors and incidence of postoperative delirium in elderly Chinese patients. *Gerontology* 2000; **46**:28–35.
- 110 Galanakis P, Bickel H, Grading R, et al. Acute confusional state in the elderly following hip surgery: incidence, risk factors and complications. *Int J Geriatr Psychiatry* 2001; **16**:349–355.

- 111 Gani H, Domi R, Kodra N, *et al.* The incidence of postoperative delirium in elderly patients after urologic surgery. *Med Arch* 2013; **67**:45–47.
- 112 Harasawa N, Mizuno T. A novel scale predicting postoperative delirium (POD) in patients undergoing cerebrovascular surgery. *Arch Gerontol Geriatr* 2014; **59**:264–271.
- 113 Litaker D, Locala J, Franco K, *et al.* Preoperative risk factors for postoperative delirium. *Gen Hosp Psychiatry* 2001; **23**:84–89.
- 114 McAlpine JN, Hodgson EJ, Abramowitz S, *et al.* The incidence and risk factors associated with postoperative delirium in geriatric patients undergoing surgery for suspected gynecologic malignancies. *Gynecol Oncol* 2008; **109**:296–302.
- 115 Schor JD, Levkoff SE, Lipsitz LA, *et al.* Risk factors for delirium in hospitalized elderly. *JAMA* 1992; **267**:827–831.
- 116 Shah S, Weed HG, He X, *et al.* Alcohol-related predictors of delirium after major head and neck cancer surgery. *Arch Otolaryngol Head Neck Surg* 2012; **138**:266–271.
- 117 Tei M, Ikeda M, Haraguchi N, *et al.* Risk factors for postoperative delirium in elderly patients with colorectal cancer. *Surg Endosc* 2010; **24**:2135–2139.
- 118 Yoshimura Y, Kubo S, Shirata K, *et al.* Risk factors for postoperative delirium after liver resection for hepatocellular carcinoma. *World J Surg* 2004; **28**:982–986.
- 119 Chen YL, Lin HC, Lin KH, *et al.* Low hemoglobin level is associated with the development of delirium after hepatectomy for hepatocellular carcinoma patients. *PLoS One* 2015; **10**:e0119199.
- 120 Edlund A, Lundström M, Karlsson S, *et al.* Delirium in older patients admitted to general internal medicine. *J Geriatr Psychiatry Neurol* 2006; **19**:83–90.
- 121 Bucarius J, Gummert JF, Walther T, *et al.* Diabetes in patients undergoing coronary artery bypass grafting. Impact on perioperative outcome. *Z Kardiol* 2005; **94**:575–582.
- 122 Larsen KA, Kelly SE, Stern TA, *et al.* Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. *Psychosomatics* 2010; **51**:409–418.
- 123 Leung JM, Tsai TL, Sands LP. Brief report: preoperative frailty in older surgical patients is associated with early postoperative delirium. *Anesth Analg* 2011; **112**:1199–1201.
- 124 Nötzold A, Michel K, Khattab AA, *et al.* Diabetes mellitus increases adverse neurocognitive outcome after coronary artery bypass grafting surgery. *Thorac Cardiovasc Surg* 2006; **54**:307–312.
- 125 Otomo S, Maekawa K, Goto T, *et al.* Preexisting cerebral infarcts as a risk factor for delirium after coronary artery bypass graft surgery. *Interact Cardiovasc Thorac Surg* 2013; **17**:799–804.
- 126 Papaioannou A, Fraidakis O, Michaloudis D, *et al.* The impact of the type of anaesthesia on cognitive status and delirium during the first postoperative days in elderly patients. *Eur J Anaesthesiol* 2005; **22**:492–499.
- 127 Rudolph JL, Jones RN, Rasmussen LS, *et al.* Independent vascular and cognitive risk factors for postoperative delirium. *Am J Med* 2007; **120**:807–813.
- 128 Krzych LJ, Wybraniec MT, Krupka-Matuszczyk I, *et al.* Complex assessment of the incidence and risk factors of delirium in a large cohort of cardiac surgery patients: a single-center 6-year experience. *Biomed Res Int* 2013; **2013**:835850.
- 129 Vaurio LE, Sands LP, Wang Y, *et al.* Postoperative delirium: the importance of pain and pain management. *Anesth Analg* 2006; **102**:1267–1273.
- 130 Kosar CM, Tabloski PA, Trivison TG, *et al.* Effect of preoperative pain and depressive symptoms on the development of postoperative delirium. *Lancet Psychiatry* 2014; **1**:431–436.
- 131 Bucarius J, Gummert JF, Walther T, *et al.* Impact of diabetes mellitus on cardiac surgery outcome. *Thorac Cardiovasc Surg* 2003; **51**:11–16.
- 132 Rudolph JL, Jones RN, Levkoff SE, *et al.* Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation* 2009; **119**:229–236.
- 133 Kelly AM, Batke JNN, Dea N, *et al.* Prospective analysis of adverse events in surgical treatment of degenerative spondylolisthesis. *Spine J* 2014; **14**:2905–2910.
- 134 Koebrugge B, Koek HL, van Wensen RJA, *et al.* Delirium after abdominal surgery at a surgical ward with a high standard of delirium care: incidence, risk factors and outcomes. *Dig Surg* 2009; **26**:63–68.
- 135 Weed HG, Lutman CV, Young DC, *et al.* Preoperative identification of patients at risk for delirium after major head and neck cancer surgery. *Laryngoscope* 1995; **105**:1066–1068.
- 136 Yildizeli B, Ozyurtkan MO, Batirel HF, *et al.* Factors associated with postoperative delirium after thoracic surgery. *Ann Thorac Surg* 2005; **79**:1004–1009.
- 137 Tune LE, Damlouji NF, Holland A, *et al.* Association of postoperative delirium with raised serum levels of anticholinergic drugs. *Lancet* 1981; **2**:651–653.
- 138 Minden SL, Carbone LA, Barsky A, *et al.* Predictors and outcomes of delirium. *Gen Hosp Psychiatry* 2005; **27**:209–214.
- 139 Vermeersch PEH. The clinical assessment of confusion-A. *Appl Nurs Res* 1990; **3**:128–133.
- 140 Tune L, Carr S, Cooper T, *et al.* Association of anticholinergic activity of prescribed medications with postoperative delirium. *J Neuropsychiatry Clin Neurosci* 1993; **5**:208–210.
- 141 Kudoh A, Takase H, Matsuno S, *et al.* A history of aggression is a risk factor for postoperative confusion in elderly male drinkers. *J Anesth* 2007; **21**:13–18.
- 142 Williams-Russo P, Urquhart BL, Sharrock NE, *et al.* Postoperative delirium: predictors and prognosis in elderly orthopedic patients. *J Am Geriatr Soc* 1992; **40**:759–767.
- 143 Katznelson R, Djaiani GN, Borger MA, *et al.* Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery. *Anesthesiology* 2009; **110**:67–73.
- 144 Marcantonio ER, Goldman L, Orav EJ, *et al.* The association of intraoperative factors with the development of postoperative delirium. *Am J Med* 1998; **105**:380–384.
- 145 Gao R, Yang ZZ, Li M, *et al.* Probable risk factors for postoperative delirium in patients undergoing spinal surgery. *Eur Spine J* 2008; **17**:1531–1537.
- 146 Chrispal A, Mathews KP, Surekha V. The clinical profile and association of delirium in geriatric patients with hip fractures in a tertiary care hospital in India. *J Assoc Physicians India* 2010; **58**:15–19.
- 147 Hamann J, Bickel H, Schwaibold H, *et al.* Postoperative acute confusional state in typical urologic population: incidence, risk factors, and strategies for prevention. *Urology* 2005; **65**:449–453.
- 148 Sasajima Y, Sasajima T, Uchida H, *et al.* Postoperative delirium in patients with chronic lower limb ischaemia: what are the specific markers? *Eur J Vasc Endovasc Surg* 2000; **20**:132–137.
- 149 Afonso A, Scurlock C, Reich D, *et al.* Predictive model for postoperative delirium in cardiac surgical patients. *Semin Cardiothorac Vasc Anesth* 2010; **14**:212–217.
- 150 Nie H, Zhao B, Zhang Y-Q, *et al.* Pain and cognitive dysfunction are the risk factors of delirium in elderly hip fracture Chinese patients. *Arch Gerontol Geriatr* 2012; **54**:e172–e174.
- 151 DeCrane SK, Stark LD, Johnston B, *et al.* Pain, opioids, and confusion after arthroplasty in older adults. *Orthop Nurs* 2014; **33**:226–232.
- 152 Lynch EP, Lazor MA, Gellis JE, *et al.* The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg* 1998; **86**:781–785.
- 153 Mouzopoulos G, Vasiliadis G, Lasanianos N, *et al.* Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study. *J Orthop Traumatol* 2009; **10**:127–133.
- 154 Kinjo S, Lim E, Sands LP, Bozic KJ, Leung JM. Does using a femoral nerve block for total knee replacement decrease postoperative delirium? *BMC Anesthesiol* 2012; **12**:4.
- 155 Krahenbuhl ES, Immer FF, Stalder M, *et al.* Temporary neurological dysfunction after surgery of the thoracic aorta: a predictor of poor outcome and impaired quality of life. *Eur J Cardiothorac Surg* 2008; **33**:1025–1029.
- 156 Martin BJ, Buth KJ, Arora RC, Baskett RJ. Delirium as a predictor of sepsis in postcoronary artery bypass grafting patients: a retrospective cohort study. *Crit Care* 2010; **14**:R171.
- 157 Nadelson MR, Sanders RD, Avidan MS. Perioperative cognitive trajectory in adults. *Br J Anaesth* 2014; **112**:440–451.
- 158 Jia Y, Jin G, Guo S, *et al.* Fast-track surgery decreases the incidence of postoperative delirium and other complications in elderly patients with colorectal carcinoma. *Langenbecks Arch Surg* 2014; **399**:77–84.
- 159 Krenk L, Rasmussen LS, Hansen TB, *et al.* Delirium after fast-track hip and knee arthroplasty. *Br J Anaesth* 2012; **108**:607–611.
- 160 Krzych LJ, Wybraniec MT, Krupka-Matuszczyk I, *et al.* Delirium Screening in Cardiac Surgery (DESCARD): a useful tool for nonpsychiatrists. *Can J Cardiol* 2014; **30**:932–939.
- 161 Burkhart CS, Dell-Kuster S, Gamberini M, *et al.* Modifiable and nonmodifiable risk factors for postoperative delirium after cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2010; **24**:555–559.
- 162 Robinson TN, Raeburn CD, Angles EM, *et al.* Low tryptophan levels are associated with postoperative delirium in the elderly. *Am J Surg* 2008; **196**:670–674.

- 163 Cerejeira J, Batista P, Nogueira V, et al. The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 axis. *J Geriatr Psychiatry Neurol* 2013; **26**:185–194.
- 164 Chen XW, Shi JW, Yang PS, et al. Preoperative plasma leptin levels predict delirium in elderly patients after hip fracture surgery. *Peptides* 2014; **57**:31–35.
- 165 Root JC, Pryor KO, Downey R, et al. Association of preoperative brain pathology with postoperative delirium in a cohort of nonsmall cell lung cancer patients undergoing surgical resection. *Psychooncology* 2013; **22**:2087–2094.
- 166 van Munster BC, Korevaar JC, Zwinderman AH, et al. Time-course of cytokines during delirium in elderly patients with hip fractures. *J Am Geriatr Soc* 2008; **56**:1704–1709.
- 167 Watne LO, Hall RJ, Molden E, et al. Anticholinergic activity in cerebrospinal fluid and serum in individuals with hip fracture with and without delirium. *J Am Geriatr Soc* 2014; **62**:94–102.
- 168 Westhoff D, Witlox J, Koenderman L, et al. Preoperative cerebrospinal fluid cytokine levels and the risk of postoperative delirium in elderly hip fracture patients. *J Neuroinflammation* 2013; **10**:122.
- 169 Witlox J, Kalisvaart KJ, de Jonghe JFM, et al. Cerebrospinal fluid  $\beta$ -amyloid and tau are not associated with risk of delirium: a prospective cohort study in older adults with hip fracture. *J Am Geriatr Soc* 2011; **59**:1260–1267.
- 170 Blazer DG, van Nieuwenhuizen AO. Evidence for the diagnostic criteria of delirium: an update. *Curr Opin Psychiatry* 2012; **25**:239–243.
- 171 Neufeld KJ. Delirium classification by the diagnostic and statistical manual – a moving target. *Int Psychogeriatr* 2015; **27**:881–882.
- 172 European Delirium Association, American Delirium Society. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. *BMC Med* 2014; **12**:141.
- 173 Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; **166**:1338–1344.
- 174 Gaudreau JD, Gagnon P, Harel F, et al. Fast, systematic, and continuous delirium assessment in hospitalized patients: the Nursing Delirium Screening Scale. *J Pain Symptom Manage* 2005; **29**:368–375.
- 175 Radtke FM, Franck M, Schust S, et al. A comparison of three scores to screen for delirium on the surgical ward. *World J Surg* 2010; **34**:487–494.
- 176 Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the Confusion Assessment Method. A new method for detection of delirium. *Ann Intern Med* 1990; **113**:941e948.
- 177 Neufeld KJ, Leoutsakos JS, Sieber FE, et al. Evaluation of two delirium screening tools for detecting postoperative delirium in the elderly. *Br J Anaesth* 2013; **111**:612–618.
- 178 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.
- 179 Neufeld KJ, Leoutsakos JM, Sieber FE, et al. Outcomes of early delirium diagnosis after general anesthesia in the elderly. *Anesth Analg* 2013; **117**:471–478.
- 180 Card E, Pandharipande P, Tomes C, et al. Emergence from general anaesthesia and evolution of delirium signs in the postanesthesia care unit. *Br J Anaesth* 2015; **115**:411–417.
- 181 Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology* 2004; **100**:1138–1145.
- 182 Trzepacz PT, Mittal D, Torres R, et al. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci* 2001; **13**:229–242.
- 183 Breitbart W, Rosenfeld B, Roth A, et al. The memorial delirium assessment scale. *J Pain Symptom Manage* 1997; **13**:128–137.
- 184 Stillman MS, Rybicki LA. The Bedside Confusion Scale: development of a portable bedside test for confusion and its application to the palliative medicine population. *J Palliat Med* 2000; **3**:449–456.
- 185 Slor CJ, de Jonghe JF, Vreeswijk R, et al. Anesthesia and postoperative delirium in older adults undergoing hip surgery. *J Am Geriatr Soc* 2011; **59**:1313–1319.
- 186 Williams MA. Delirium/acute confusional states: evaluation devices in nursing. *Int Psychogeriatr* 1991; **3**:301–308.
- 187 de Jonghe JF, Kalisvaart KJ, Timmers JF, et al. Delirium-O-Meter: a nurses' rating scale for monitoring delirium severity in geriatric patients. *Int J Geriatr Psychiatry* 2005; **20**:1158–1166.
- 188 Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. *Res Theory Nurs Pract* 2003; **17**:31–50.
- 189 Albert MS, Levkoff SE, Reilly C, et al. The delirium symptom interview: an interview for the detection of delirium symptoms in hospitalized patients. *J Geriatr Psychiatry Neurol* 1992; **5**:14–21.
- 190 Neelon VJ, Champagne MT, Carlson JR, et al. The NEECHAM Confusion Scale: construction, validation, and clinical testing. *Nurs Res* 1996; **45**:324–330.
- 191 Bellelli G, Morandi A, Davis DH, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age Ageing* 2014; **43**:496–502.
- 192 Trogrlic Z, van der Jagt M, Bakker J, et al. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. *Crit Care* 2015; **19**:157.
- 193 Pedersen SJ, Borgbjerg FM, Schousboe B, et al. A comprehensive hip fracture program reduces complication rates and mortality. *J Am Geriatr Soc* 2008; **56**:1831–1838.
- 194 Larsson G, Holgers K-M. Fast-track care for patients with suspected hip fracture. *Injury* 2011; **42**:1257–1261.
- 195 Milstein A, Pollack A, Kleinman G, et al. Confusion/delirium following cataract surgery: an incidence study of 1-year duration. *Int Psychogeriatr* 2002; **14**:301–306.
- 196 Nandi S, Harvey WF, Saillant J, et al. Pharmacologic risk factors for postoperative delirium in total joint arthroplasty patients: a case–control study. *J Arthroplasty* 2014; **29**:268–271.
- 197 Davies EA, O'Mahony MS. Adverse drug reactions in special populations – the elderly. *Br J Clin Pharmacol* 2015; **80**:796–807.
- 198 Panitchote A, Tangvoraphonkchai K, Suebsoh N, et al. Under-recognition of delirium in older adults by nurses in the intensive care unit setting. *Ageing Clin Exp Res* 2015; **27**:735–740.
- 199 Radtke FM, Franck M, Lendner J, et al. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth* 2013; **110** (Suppl. 1): i98–i105.
- 200 Chan MTV, Cheng BCP, Lee TMC, et al., CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* 2013; **25**:33–42.
- 201 Whitlock EL, Torres BA, Lin N, et al. Postoperative delirium in a substudy of cardiothoracic surgical patients in the BAG-RECALL clinical trial. *Anesth Analg* 2014; **118**:809–817.
- 202 Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clin Proc* 2010; **85**:18–26.
- 203 Heo DY, Hwang BM. Intravenous patient-controlled analgesia has a positive effect on the prognosis of delirium in patients undergoing orthopedic surgery. *Korean J Pain* 2014; **27**:271–277.
- 204 Taipale PG, Ratner PA, Galdas PM, et al. The association between nurse-administered midazolam following cardiac surgery and incident delirium: an observational study. *Int J Nurs Stud* 2012; **49**:1064–1073.
- 205 Kurbegovic S, Andersen J, Krenk L, et al. Delirium in fast-track colonic surgery. *Langenbecks Arch Surg* 2015; **400**:513–516.
- 206 Zywił MG, Prabhu A, Perruccio AV, et al. The influence of anesthesia and pain management on cognitive dysfunction after joint arthroplasty: a systematic review. *Clin Orthop Relat Res* 2014; **472**:1453–1466.
- 207 Radtke FM, Franck M, Lorenz M, et al. Remifentanyl reduces the incidence of postoperative delirium. *J Int Med Res* 2010; **38**:1225–1232.
- 208 Lassen K, Soop M, Nygren J, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg* 2009; **144**: 961–969.
- 209 Montes DM. Postoperative delirium in head and neck cancer patients: a survey of oncologic oral and maxillofacial surgeon practices. *J Oral Maxillofac Surg* 2014; **72**:2591–2600.
- 210 Khan BA, Zawahiri M, Campbell NL, et al. Delirium in hospitalized patients: implications of current evidence on clinical practice and future avenues for research – a systematic evidence review. *J Hosp Med* 2012; **7**:580–589.
- 211 Yoon HJ, Park KM, Choi WJ, et al. Efficacy and safety of haloperidol versus atypical antipsychotic medications in the treatment of delirium. *BMC Psychiatry* 2013; **13**:240.
- 212 Hatta K, Kishi Y, Wada K, et al. Antipsychotics for delirium in the general hospital setting in consecutive 2453 inpatients: a prospective observational study. *Int J Geriatr Psychiatry* 2014; **29**:253–262.
- 213 Loneragan E, Britton AM, Luxenberg J, et al. Antipsychotics for delirium. *Cochrane Database Syst Rev* (2):2007;CD005594.
- 214 Pisani MA, Araujo KL, Murphy TE. Association of cumulative dose of haloperidol with next-day delirium in older medical ICU patients. *Crit Care Med* 2015; **43**:996–1002.
- 215 Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry* 2015; **72**:438–445.

- 216 Spies CD, Dubisz N, Neumann T, *et al.* Therapy of alcohol withdrawal syndrome in intensive care unit patients following trauma: results of a prospective, randomized trial. *Crit Care Med* 1996; **24**:414–422.
- 217 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.
- 218 Spies CD, Dubisz N, Funk W, *et al.* Prophylaxis of alcohol withdrawal syndrome in alcohol-dependent patients admitted to the intensive care unit after tumour resection. *Br J Anaesth* 1995; **75**:734–739.
- 219 Rasmussen LS, Steentoft A, Rasmussen H, *et al.* Benzodiazepines and postoperative cognitive dysfunction in the elderly. ISPOCD Group. International Study of Postoperative Cognitive Dysfunction. *Br J Anaesth* 1999; **83**:585–589.
- 220 Bourne RS, Mills GH. Melatonin: possible implications for the postoperative and critically ill patient. *Intensive Care Med* 2006; **32**:371–379.
- 221 Cavaliere F, D'Ambrosio F, Volpe C, *et al.* Postoperative delirium. *Curr Drug Targets* 2005; **6**:807–814.
- 222 Gosch M, Nicholas JA. Pharmacologic prevention of postoperative delirium. *Z Gerontol Geriatr* 2014; **47**:105–109.
- 223 Hanania M, Kitain E. Melatonin for treatment and prevention of postoperative delirium. *Anesth Analg* 2002; **94**:338–339.
- 224 Barr J, Fraser GL, Puntillo K, *et al.* Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41**:263–306.
- 225 Ji F, Li Z, Young N, *et al.* Perioperative dexmedetomidine improves mortality in patients undergoing coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2014; **28**:267–273.
- 226 Park JB, Bang SH, Chee HK, *et al.* Efficacy and safety of dexmedetomidine for postoperative delirium in adult cardiac surgery on cardiopulmonary bypass. *Korean J Thorac Cardiovasc Surg* 2014; **47**:249–254.
- 227 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.
- 228 Young J, Murthy L, Westby M, *et al.* Diagnosis, prevention, and management of delirium: summary of NICE guidance. *BMJ* 2010; **341**:c3704.
- 229 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**:1658–1666.
- 230 Kaneko T, Cai J, Ishikura T, *et al.* Prophylactic consecutive administration of haloperidol can reduce the occurrence of postoperative delirium in gastrointestinal surgery. *Yonago Acta Medica* 1999; **42**:179–184.
- 231 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.
- 232 Teslyar P, Stock VM, Wilk CM, *et al.* Prophylaxis with antipsychotic medication reduces the risk of postoperative delirium in elderly patients: a meta-analysis. *Psychosomatics* 2013; **54**:124–131.
- 233 Hakim SM, Othman AI, Naoum DO. Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial. *Anesthesiology* 2012; **116**:987–997.
- 234 Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesth Intensive Care* 2007; **35**:714–719.
- 235 Hirota T, Kishi T. Prophylactic antipsychotic use for postoperative delirium: a systematic review and meta-analysis. *J Clin Psychiatry* 2013; **74**:e1136–e1144.
- 236 Ellard L, Katznelson R, Wasowicz M, *et al.* Type of anesthesia and postoperative delirium after vascular surgery. *J Cardiothorac Vasc Anesth* 2014; **28**:458–461.
- 237 Liu JL, Wang XL, Gong MW, *et al.* Comparative outcomes of peripheral nerve blocks versus general anesthesia for hip fractures in geriatric Chinese patients. *Patient Prefer Adherence* 2014; **8**:651–659.
- 238 Bryson GL, Wyand A. Evidence-based clinical update: general anesthesia and the risk of delirium and postoperative cognitive dysfunction. *Can J Anaesth* 2006; **53**:669–677.
- 239 Luger TJ, Kammerlander C, Gosch M, *et al.* Neuroaxial versus general anaesthesia in geriatric patients for hip fracture surgery: does it matter? *Osteoporos Int* 2010; **21**:S555–S572.
- 240 Luger TJ, Kammerlander C, Luger MF, *et al.* Mode of anesthesia, mortality and outcome in geriatric patients. *Z Gerontol Geriatr* 2014; **47**:110–124.
- 241 Mason SE, Noel-Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of postoperative cognitive dysfunction and postoperative delirium: a systematic review with meta-analysis. *J Alzheimers Dis* 2010; **22**:67–79.
- 242 Moyce Z, Rodseth RN, Biccard BM. The efficacy of peri-operative interventions to decrease postoperative delirium in noncardiac surgery: a systematic review and meta-analysis. *Anaesthesia* 2014; **69**:259–269.
- 243 American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2012; **116**:248–273.
- 244 Leung JM, Sands LP, Paul S, *et al.* Does postoperative delirium limit the use of patient-controlled analgesia in older surgical patients? *Anesthesiology* 2009; **111**:625–631.
- 245 Laurila JV, Laakkonen ML, Tilvis RS, *et al.* Predisposing and precipitating factors for delirium in a frail geriatric population. *J Psychosom Res* 2008; **65**:249–254.
- 246 Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. *Age Ageing* 2011; **40**:23–29.
- 247 Mercadante S. Intravenous patient-controlled analgesia and management of pain in postsurgical elderly with cancer. *Surg Oncol* 2010; **19**:173–177.
- 248 Zhang H, Lu Y, Liu M, *et al.* Strategies for prevention of postoperative delirium: a systematic review and meta-analysis of randomized trials. *Crit Care* 2013; **17**:R47.
- 249 Zucchella C, Capone A, Codella V, *et al.* Cognitive rehabilitation for early postsurgery inpatients affected by primary brain tumor: a randomized, controlled trial. *J Neurooncol* 2013; **114**:93–100.
- 250 Hiltunen EF, Winder PA, Rait MA, *et al.* Implementation of efficacy enhancement nursing interventions with cardiac elders. *Rehabil Nurs* 2005; **30**:221–229.
- 251 Robinson TN, Wallace JI, Wu DS, *et al.* Accumulated frailty characteristics predict postoperative discharge institutionalization in the geriatric patient. *J Am Coll Surg* 2011; **213**:37–42.
- 252 European Commission Directorate-General for Economic and Financial Affairs, Unit Communication and Interinstitutional Relations. *The 2015 ageing report. Underlying assumptions and projection methodologies. European Economy Series*. 2014; [http://ec.europa.eu/economy\\_finance/publications/european\\_economy/2014/pdf/ee8\\_en.pdf](http://ec.europa.eu/economy_finance/publications/european_economy/2014/pdf/ee8_en.pdf). [Accessed 22 June 2016], 21, Table I.1.13.
- 253 Chow WB, Rosenthal RA, Merkow RP, *et al.* Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. *J Am Coll Surg* 2012; **215**:453–466.
- 254 Reiss R, Deutsch A, Nudelman I. Surgical problems in octogenarians: epidemiological analysis of 1,083 consecutive admissions. *World J Surg* 1992; **16**:1017–1020.
- 255 Ministero della Salute. Direzione Generale della Comunicazione e dei rapporti europei e internazionali. *Rapporto annual sull'attività di ricovero ospedaliero*. 2011; [www.salute.gov.it/imgs/C\\_17\\_pubblicazioni\\_1690\\_allegato.pdf](http://www.salute.gov.it/imgs/C_17_pubblicazioni_1690_allegato.pdf). [Accessed 20 July 2015].
- 256 Etzioni DA, Liu JH, Maggard MA, *et al.* The aging population and its impact on the surgery workforce. *Ann Surg* 2003; **238**:170–177.
- 257 Bettelli G. Preoperative evaluation in geriatric surgery: comorbidity, functional status and pharmacological history. *Minerva Anestesiol* 2011; **77**:637–646.
- 258 Nobili A, Garattini MPM. Multiple disease and polypharmacy in the elderly. *J Comorbid* 2011; **1**:28–44.
- 259 World Health Department (WHO) Department of Mental Health and Substance Abuse. *Dementia: a public health priority*. Geneva: WHO; 2012.
- 260 Visser L, Prent A, van der Laan MJ, *et al.* Predicting postoperative delirium after vascular surgical procedures. *J Vasc Surg* 2015; **62**:183–189.
- 261 Freter SH, Dunbar MJ, MacLeod H, *et al.* Predicting postoperative delirium in elective orthopaedic patients: the Delirium Elderly At-Risk (DEAR) instrument. *Age Ageing* 2005; **34**:169–171.
- 262 Kazmierski J, Banys A, Latek J, *et al.* Mild cognitive impairment with associated inflammatory and cortisol alterations as independent risk factor for postoperative delirium. *Dement Geriatr Cogn Disord* 2014; **38**:65–78.
- 263 Gallardo-Prieto LM, Nellen-Hummel H, Hamui-Sutton A, *et al.* Perioperative evaluation in elderly patients. *Cir Cir* 2006; **74**:59–68.
- 264 Inouye SK, Peduzzi PN, Robison JT, *et al.* Importance of functional measures in predicting mortality among older hospitalized patients. *JAMA* 1998; **279**:1187–1193.
- 265 Podsiadlo D, Richardson S. The timed 'Up & Go': a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; **39**:142–148.
- 266 Rubenstein LZ, Wieland D. Comprehensive geriatric assessment. *Annu Rev Gerontol Geriatr* 1989; **9**:145–192.

- 267 Ganai S, Lee KF, Merrill A, et al. Adverse outcomes of geriatric patients undergoing abdominal surgery who are at high risk for delirium. *Arch Surg* 2007; **142**:1072–1078.
- 268 Jankowski CJ, Trenerry MR, Cook DJ, et al. Cognitive and functional predictors and sequelae of postoperative delirium in elderly patients undergoing elective joint arthroplasty. *Anesth Analg* 2011; **112**:1186–1193.
- 269 Shim JJ, Leung JM. An update on delirium in the postoperative setting: prevention, diagnosis and management. *Best Pract Res Clin Anaesthesiol* 2012; **26**:327–343.
- 270 Steiner LA. Postoperative delirium. Part 1: Pathophysiology and risk factors. *Eur J Anaesthesiol* 2011; **28**:628–636.
- 271 Tognoni P, Simonato A, Robutti N, et al. Preoperative risk factors for postoperative delirium (POD) after urological surgery in the elderly. *Arch Gerontol Geriatr* 2011; **52**:e166–e169.
- 272 Santos-Eggimann B, Cuenoud P, Spagnoli J, et al. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. *J Gerontol A Biol Sci Med Sci* 2009; **64**:675–681.
- 273 Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010; **210**:901–908.
- 274 Sundermann S, Dademasch A, Praetorius J, et al. Comprehensive assessment of frailty for elderly high-risk patients undergoing cardiac surgery. *Eur J Cardiothorac Surg* 2011; **39**:33–37.
- 275 Pol RA, van Leeuwen BL, Visser L, et al. Standardised frailty indicator as predictor for postoperative delirium after vascular surgery: a prospective cohort study. *Eur J Vasc Endovasc Surg* 2011; **42**:824–830.
- 276 Böhner H, Schneider F, Stierstorfer A, et al. Delirium after vascular surgery interventions. Intermediate-term results of a prospective study. *Chirurg* 2000; **71**:215–221.
- 277 Dupplis GS, Wikblad K. Acute confusional states in patients undergoing hip surgery. A prospective observation study. *Gerontology* 2000; **46**:36–43.
- 278 Ushida T, Yokoyama T, Kishida Y, et al. Incidence and risk factors of postoperative delirium in cervical spine surgery. *Spine (Phila Pa 1976)* 2009; **34**:2500–2504.
- 279 Dovjak P, Iglseeder B, Mikosch P, et al. Treatment and prevention of postoperative complications in hip fracture patients: infections and delirium. *Wien Med Wochenschr* 2013; **163**:448–454.
- 280 Whitehead C, Finucane P. Malnutrition in elderly people. *Aust N Z J Med* 1997; **27**:68–74.
- 281 Elmstahl S, Persson M, Andren M, et al. Malnutrition in geriatric patients: a neglected problem? *J Adv Nurs* 1997; **26**:851–855.
- 282 Sullivan D, Lipschitz D. Evaluating and treating nutritional problems in older patients. *Clin Geriatr Med* 1997; **13**:753–768.
- 283 Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. *Nutr Rev* 1996; **54**:S59–S65.
- 284 Ringaitienė D, Gineitytė D, Vicka V, et al. Impact of malnutrition on postoperative delirium development after on pump coronary artery bypass grafting. *J Cardiothorac Surg* 2015; **10**:74.
- 285 Chu CS, Liang CK, Chou MY, et al. Short-Form Mini Nutritional Assessment as a useful method of predicting the development of postoperative delirium in elderly patients undergoing orthopedic surgery. *Gen Hosp Psychiatry* 2016; **38**:15–20.
- 286 Kip MJ, Neumann T, Jugel C, et al. New strategies to detect alcohol use disorders in the preoperative assessment clinic of a German university hospital. *Anesthesiology* 2008; **109**:171–179.
- 287 Groerer J, Penne M, Pemberton M, et al. Substance abuse treatment need among older adults in 2020: the impact of the aging baby-boom cohort. *Drug Alcohol Depend* 2003; **69**:127–135.
- 288 O'Connell H, Chin AV, Cunningham C, et al. Alcohol use disorders in elderly people – redefining an age old problem in old age. *BMJ* 2003; **327**:664–667.
- 289 Wang YP, Andrade LH. Epidemiology of alcohol and drug use in the elderly. *Curr Opin Psychiatry* 2013; **26**:343–348.
- 290 Jack S, West M, Grocott MP. Perioperative exercise training in elderly subjects. *Best Pract Res Clin Anaesthesiol* 2011; **25**:461–472.
- 291 Juliebø V, Bjørø K, Krogseth M, et al. Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. *J Am Geriatr Soc* 2009; **57**:1354–1361.
- 292 Oresanya LB, Lyons WL, Finlayson E. Preoperative assessment of the older patient: a narrative review. *JAMA* 2014; **311**:2110–2120.
- 293 Robinson TN, Wu DS, Pointer LF, et al. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. *J Am Coll Surg* 2012; **215**:12–17.
- 294 Soehle M, Dittmann A, Ellerkmann RK, et al. Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. *BMC Anesthesiol* 2015; **15**:61.
- 295 Hirsch J, DePalma G, Tsai TT, et al. Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after noncardiac surgery. *Br J Anaesth* 2015; **115**:418–426.
- 296 Schoen J, Meyerrose J, Paarmann H, et al. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. *Crit Care* 2011; **15**:R218.
- 297 Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. *J Card Surg* 2012; **27**:481–492.
- 298 van Diepen S, Bakal JA, McAlister FA, et al. Mortality and readmission of patients with heart failure, atrial fibrillation, or coronary artery disease undergoing noncardiac surgery: an analysis of 38 047 patients. *Circulation* 2011; **124**:289–296.
- 299 Zhang WY, Wu WL, Gu JJ, et al. Risk factors for postoperative delirium in patients after coronary artery bypass grafting: a prospective cohort study. *J Crit Care* 2015; **30**:606–612.
- 300 van der Kooi AW, Rots ML, Huiskamp G, et al. Delirium detection based on monitoring of blinks and eye movements. *Am J Geriatr Psychiatry* 2014; **22**:1575–1582.
- 301 van der Kooi AW, Zaai IJ, Klijn FA, et al. Delirium detection using EEG: what and how to measure. *Chest* 2015; **147**:94–101.
- 302 Warden V, Hurley AC, Volicer L. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. *J Am Med Dir Assoc* 2003; **4**:9–15.
- 303 Horgas AL, Nichols AL, Schapson CA, et al. Assessing pain in persons with dementia: relationships among the Noncommunicative Patient's Pain Assessment Instrument, self-report, and behavioral observations. *Pain Manag Nurs* 2007; **8**:77–85.
- 304 Hadjistavropoulos T, Herr K, Prkachin KM, et al. Pain assessment in elderly adults with dementia. *Lancet Neurol* 2014; **13**:1216–1227.
- 305 Adunsky A, Levy R, Heim M, et al. Meperidine analgesia and delirium in aged hip fracture patients. *Arch Gerontol Geriatr* 2002; **35**:253–259.
- 306 Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994; **272**:1518–1522.
- 307 Abraha I, Trotta F, Rimland JM, et al. Efficacy of nonpharmacological interventions to prevent and treat delirium in older patients: a systematic overview. The SENATOR project ONTOP series. *PLoS One* 2015; **10**:e0123090.
- 308 Hshieh TT, Yue J, Oh E, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Intern Med* 2015; **175**:512–520.
- 309 Martinez F, Tobar C, Hill N. Preventing delirium: should nonpharmacological, multicomponent interventions be used? A systematic review and meta-analysis of the literature. *Age Ageing* 2015; **44**:196–204.
- 310 Björkelund KB, Hommel A, Thorngren K-G, et al. Reducing delirium in elderly patients with hip fracture: a multifactorial intervention study. *Acta Anaesthesiol Scand* 2010; **54**:678–688.
- 311 Harari D, Hopper A, Dhisi J, et al. Proactive care of older people undergoing surgery ('POPS'): designing, embedding, evaluating and funding a comprehensive geriatric assessment service for older elective surgical patients. *Age Ageing* 2007; **36**:190–196.
- 312 Leslie DL, Zhang Y, Bogardus ST, et al. Consequences of preventing delirium in hospitalized older adults on nursing home costs. *J Am Geriatr Soc* 2005; **53**:405–409.
- 313 Rizzo JA, Bogardus ST Jr, Leo-Summers L, et al. Multicomponent targeted intervention to prevent delirium in hospitalized older patients: what is the economic value? *Med Care* 2001; **39**:740–752.
- 314 Rubin FH, Williams JT, Lescisin DA, et al. Replicating the Hospital Elder Life Program in a community hospital and demonstrating effectiveness using quality improvement methodology. *J Am Geriatr Soc* 2006; **54**:969–974.
- 315 Dodds C, Foo I, Jones K, et al. Peri-operative care of elderly patients – an urgent need for change: a consensus statement to provide guidance for specialist and nonspecialist anaesthetists. *Perioper Med (Lond)* 2013; **2**:6.
- 316 American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. American geriatrics society abstracted clinical practice guideline for postoperative delirium in older adults. *J Am Geriatr Soc* 2015; **63**:142–150.
- 317 Anaya DA, Johanning J, Spector SA, et al. Summary of the panel session at the 38th Annual Surgical Symposium of the Association of VA Surgeons: what is the big deal about frailty? *JAMA Surg* 2014; **149**:1191–1197.
- 318 Cameron ID, Kurlle S. Geriatric consultation services-are wards more effective than teams? *BMC Med* 2013; **11**:49.
- 319 Grigoryan KV, Javedan H, Rudolph JL. Orthogeriatric care models and outcomes in hip fracture patients: a systematic review and meta-analysis. *J Orthop Trauma* 2014; **28**:e49–e55.

- 320 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.
- 321 Zenilman ME. Geriatric consultation services for surgical patients. *JAMA Surg* 2014; **149**:90.
- 322 Ahmed NN, Pearce SE. Acute care for the elderly: a literature review. *Popul Health Manag* 2010; **13**:219–225.
- 323 Palmer RM, Landefeld CS, Kresevic D, *et al.* A medical unit for the acute care of the elderly. *J Am Geriatr Soc* 1994; **42**:545–552.
- 324 Friedman SM, Mendelson DA, Kates SL, *et al.* Geriatric co-management of proximal femur fractures: total quality management and protocol-driven care result in better outcomes for a frail patient population. *J Am Geriatr Soc* 2008; **56**:1349–1356.
- 325 Liem IS, Kammerlander C, Suhm N, *et al.* Identifying a standard set of outcome parameters for the evaluation of orthogeriatric co-management for hip fractures. *Injury* 2013; **44**:1403–1412.
- 326 Deschodt M, Braes T, Flamaing J, *et al.* Preventing delirium in older adults with recent hip fracture through multidisciplinary geriatric consultation. *J Am Geriatr Soc* 2012; **60**:733–739.
- 327 Friedman SM, Mendelson DA, Bingham KW, *et al.* Impact of a comanaged Geriatric Fracture Center on short-term hip fracture outcomes. *Arch Intern Med* 2009; **169**:1712–1717.
- 328 Gustafson Y, Brannstrom B, Berggren D, *et al.* A geriatric-anesthesiologic program to reduce acute confusional states in elderly patients treated for femoral neck fractures. *J Am Geriatr Soc* 1991; **39**:655–662.
- 329 Lundstrom M, Olofsson B, Stenvall M, *et al.* Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. *Aging Clin Exp Res* 2007; **19**:178–186.
- 330 Marcantonio ER, Flacker JM, Wright RJ, *et al.* Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc* 2001; **49**:516–522.
- 331 Stenvall M, Berggren M, Lundstrom M, *et al.* A multidisciplinary intervention program improved the outcome after hip fracture for people with dementia – subgroup analyses of a randomized controlled trial. *Arch Gerontol Geriatr* 2012; **54**:e284–e289.
- 332 Chaput AJ, Bryson GL. Postoperative delirium: risk factors and management: continuing professional development. *Can J Anaesth* 2012; **59**:304–320.
- 333 Dahmani S, Stany I, Brasher C, *et al.* Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. *Br J Anaesth* 2010; **104**:216–223.
- 334 Costi D, Cyna AM, Ahmed S, *et al.* Effects of sevoflurane versus other general anaesthesia on emergence agitation in children. *Cochrane Database Syst Rev* (9):2014;CD007084.
- 335 Wong DD, Bailey CR. Emergence delirium in children. *Anaesthesia* 2015; **70**:383–387.
- 336 Eckenhoff JE, Kneale DH, Dripps RD. The incidence and etiology of postanesthetic excitement. A clinical survey. *Anesthesiology* 1961; **22**:667–673.
- 337 Aono J, Ueda W, Mamiya K, *et al.* Greater incidence of delirium during recovery from sevoflurane anesthesia in preschool boys. *Anesthesiology* 1997; **87**:1298–1300.
- 338 Breschan C, Platzner M, Jost R, *et al.* Midazolam does not reduce emergence delirium after sevoflurane anesthesia in children. *Paediatr Anaesth* 2007; **17**:347–352.
- 339 Cole JW, Murray DJ, McAllister JD, *et al.* Emergence behaviour in children: defining the incidence of excitement and agitation following anaesthesia. *Paediatr Anaesth* 2002; **12**:442–447.
- 340 Daoud A, Duff JP, Joffe AR. Diagnostic accuracy of delirium diagnosis in pediatric intensive care: a systematic review. *Crit Care* 2014; **18**:489.
- 341 Nakayama S, Furukawa H, Yanai H. Propofol reduces the incidence of emergence agitation in preschool-aged children as well as in school-aged children: a comparison with sevoflurane. *J Anesth* 2007; **21**:19–23.
- 342 Przybylo HJ, Martini DR, Mazurek AJ, *et al.* Assessing behaviour in children emerging from anaesthesia: can we apply psychiatric diagnostic techniques? *Paediatr Anaesth* 2003; **13**:609–616.
- 343 Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. *Anesth Analg* 2003; **96**:1625–1630.
- 344 Beringer RM, Segar P, Pearson A, *et al.* Observational study of perioperative behavior changes in children having teeth extracted under general anesthesia. *Paediatr Anaesth* 2014; **24**:499–504.
- 345 Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. *Paediatr Anaesth* 2000; **10**:419–424.
- 346 Faulk DJ, Twite MD, Zuk J, *et al.* Hypnotic depth and the incidence of emergence agitation and negative postoperative behavioral changes. *Paediatr Anaesth* 2010; **20**:72–81.
- 347 Smessaert A, Schehr CA, Artusio JF Jr. Observations in the immediate postanaesthesia period. II. Mode of recovery. *Br J Anaesth* 1960; **32**:181–185.
- 348 Araki H, Fujiwara Y, Shimada Y. Effect of flumazenil on recovery from sevoflurane anesthesia in children premedicated with oral midazolam before undergoing herniorrhaphy with or without caudal analgesia. *J Anesth* 2005; **19**:204–207.
- 349 Davis PJ, Greenberg JA, Gendelman M, *et al.* Recovery characteristics of sevoflurane and halothane in preschool-aged children undergoing bilateral myringotomy and pressure equalization tube insertion. *Anesth Analg* 1999; **88**:34–38.
- 350 Galinkin JL, Fazi LM, Cuy RM, *et al.* Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia. *Anesthesiology* 2000; **93**:1378–1383.
- 351 Bringuier S, Dadure C, Raux O, *et al.* The perioperative validity of the visual analog anxiety scale in children: a discriminant and useful instrument in routine clinical practice to optimize postoperative pain management. *Anesth Analg* 2009; **109**:737–744.
- 352 Kain ZN, Caldwell-Andrews AA, Mayes LC, *et al.* Family-centered preparation for surgery improves perioperative outcomes in children: a randomized controlled trial. *Anesthesiology* 2007; **106**:65–74.
- 353 Kain ZN, Caldwell-Andrews AA, Maranets I, *et al.* Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. *Anesth Analg* 2004; **99**:1648–1654.
- 354 Weldon BC, Bell M, Craddock T. The effect of caudal analgesia on emergence agitation in children after sevoflurane versus halothane anesthesia. *Anesth Analg* 2004; **98**:321–326.
- 355 Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. *Paediatr Anaesth* 2010; **20**:704–711.
- 356 Johansson M, Kokinsky E. The COMFORT behavioural scale and the modified FLACC scale in paediatric intensive care. *Nurs Crit Care* 2009; **14**:122–130.
- 357 Janssen NJ, Tan EY, Staal M, *et al.* On the utility of diagnostic instruments for pediatric delirium in critical illness: an evaluation of the Pediatric Anesthesia Emergence Delirium Scale, the Delirium Rating Scale 88, and the Delirium Rating Scale-Revised R-98. *Intensive Care Med* 2011; **37**:1331–1337.
- 358 Somaini M, Sahillioglu E, Marzorati C, *et al.* Emergence delirium, pain or both? A challenge for clinicians. *Paediatr Anaesth* 2015; **25**:524–529.
- 359 Dahmani S, Brasher C, Stany I, *et al.* Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies. *Acta Anaesthesiol Scand* 2010; **54**:397–402.
- 360 Martin SR, Chorney JM, Tan ET, *et al.* Changing healthcare providers' behavior during pediatric inductions with an empirically based intervention. *Anesthesiology* 2011; **115**:18–27.
- 361 Arai YC, Fukunaga K, Hirota S. Comparison of a combination of midazolam and diazepam and midazolam alone as oral premedication on preanesthetic and emergence condition in children. *Acta Anaesthesiol Scand* 2005; **49**:698–701.
- 362 Chen J, Li W, Hu X, *et al.* Emergence agitation after cataract surgery in children: a comparison of midazolam, propofol and ketamine. *Paediatr Anaesth* 2010; **20**:873–879.
- 363 Cohen IT, Drewsen S, Hannallah RS. Propofol or midazolam do not reduce the incidence of emergence agitation associated with desflurane anaesthesia in children undergoing adenotonsillectomy. *Paediatr Anaesth* 2002; **12**:604–609.
- 364 Ko YP, Huang CJ, Hung YC, *et al.* Premedication with low-dose oral midazolam reduces the incidence and severity of emergence agitation in pediatric patients following sevoflurane anesthesia. *Acta Anaesthesiol Sin* 2001; **39**:169–177.
- 365 Lapin SL, Auden SM, Goldsmith LJ, *et al.* Effects of sevoflurane anaesthesia on recovery in children: a comparison with halothane. *Paediatr Anaesth* 1999; **9**:299–304.
- 366 Veyckemans F. Excitation phenomena during sevoflurane anaesthesia in children. *Curr Opin Anaesthesiol* 2001; **14**:339–343.
- 367 Viitanen H, Annala P, Viitanen M, *et al.* Premedication with midazolam delays recovery after ambulatory sevoflurane anesthesia in children. *Anesth Analg* 1999; **89**:75–79.
- 368 Chandler JR, Myers D, Mehta D, *et al.* Emergence delirium in children: a randomized trial to compare total intravenous anesthesia with propofol and remifentanyl to inhalational sevoflurane anesthesia. *Paediatr Anaesth* 2013; **23**:309–315.
- 369 Kuratani N, Oi Y. Greater incidence of emergence agitation in children after sevoflurane anesthesia as compared with halothane: a meta-analysis of randomized controlled trials. *Anesthesiology* 2008; **109**:225–232.

- 370 Singh R, Kharbanda M, Sood N, et al. Comparative evaluation of incidence of emergence agitation and postoperative recovery profile in paediatric patients after isoflurane, sevoflurane and desflurane anaesthesia. *Indian J Anaesth* 2012; **56**:156–161.
- 371 Welborn LG, Hannallah RS, Norden JM, et al. Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. *Anesth Analg* 1996; **83**:917–920.
- 372 Ali MA, Abdellatif AA. Prevention of sevoflurane related emergence agitation in children undergoing adenotonsillectomy: a comparison of dexmedetomidine and propofol. *Saudi J Anaesth* 2013; **7**:296–300.
- 373 Pasin L, Febres D, Testa V, et al. Dexmedetomidine vs midazolam as preanesthetic medication in children: a meta-analysis of randomized controlled trials. *Paediatr Anaesth* 2015; **25**:468–476.
- 374 Sun L, Guo R, Sun L. Dexmedetomidine for preventing sevoflurane-related emergence agitation in children: a meta-analysis of randomized controlled trials. *Acta Anaesthesiol Scand* 2014; **58**:642–650.
- 375 Almenrader N, Passariello M, Cocchetti B, et al. Premedication in children: a comparison of oral midazolam and oral clonidine. *Paediatr Anaesth* 2007; **17**:1143–1149.
- 376 Bock M, Kunz P, Schreckenberger R, et al. Comparison of caudal and intravenous clonidine in the prevention of agitation after sevoflurane in children. *Br J Anaesth* 2002; **88**:790–796.
- 377 Kulka PJ, Bressemer M, Tryba M. Clonidine prevents sevoflurane-induced agitation in children. *Anesth Analg* 2001; **93**:335–338.
- 378 Pickard A, Davies P, Birnie K, et al. Systematic review and meta-analysis of the effect of intraoperative  $\alpha_2$ -adrenergic agonists on postoperative behaviour in children. *Br J Anaesth* 2014; **112**:982–990.
- 379 Mukherjee A, Das A, Basunia SR, et al. Emergence agitation prevention in paediatric ambulatory surgery: a comparison between intranasal dexmedetomidine and clonidine. *J Res Pharm Pract* 2015; **4**: 24–30.
- 380 Aouad MT, Yazbeck-Karam VG, Nasr VG, et al. A single dose of propofol at the end of surgery for the prevention of emergence agitation in children undergoing strabismus surgery during sevoflurane anaesthesia. *Anesthesiology* 2007; **107**:733–738.
- 381 Aouad MT, Kanazi GE, Siddik-Sayyid SM, et al. Preoperative caudal block prevents emergence agitation in children following sevoflurane anaesthesia. *Acta Anaesthesiol Scand* 2005; **49**:300–304.
- 382 Kim MS, Moon BE, Kim H, et al. Comparison of propofol and fentanyl administered at the end of anaesthesia for prevention of emergence agitation after sevoflurane anaesthesia in children. *Br J Anaesth* 2013; **110**:274–280.
- 383 Kain ZN. Premedication and parental presence revisited. *Curr Opin Anaesthesiol* 2001; **14**:331–337.
- 384 Kain ZN, MacLaren J, McClain BC, et al. Effects of age and emotionality on the effectiveness of midazolam administered preoperatively to children. *Anesthesiology* 2007; **107**:545–552.
- 385 Yip P, Middleton P, Cyna AM, et al. Nonpharmacological interventions for assisting the induction of anaesthesia in children. *Cochrane Database Syst Rev* (3):2009;CD006447.
- 386 Kain ZN, MacLaren JE, Herrmann L, et al. Preoperative melatonin and its effects on induction and emergence in children undergoing anaesthesia and surgery. *Anesthesiology* 2009; **111**:44–49.
- 387 Ozcengiz D, Gunes Y, Ozmete O. Oral melatonin, dexmedetomidine, and midazolam for prevention of postoperative agitation in children. *J Anesth* 2011; **25**:184–188.
- 388 Salman AE, Camkiran A, Oguz S, et al. Gabapentin premedication for postoperative analgesia and emergence agitation after sevoflurane anaesthesia in pediatric patients. *Agri* 2013; **25**:163–168.
- 389 Karamaz A, Kaya S, Turhanoglu S, et al. Oral ketamine premedication can prevent emergence agitation in children after desflurane anaesthesia. *Paediatr Anaesth* 2004; **14**:477–482.
- 390 Sajedi P, Bagheri K, Hagibabie E, et al. Prophylactic use of oral acetaminophen or iv dexamethasone and combination of them on prevention emergence agitation in pediatric after adenotonsillectomy. *Int J Prev Med* 2014; **5**:721–727.
- 391 Abdulatif M, Ahmed A, Mukhtar A, et al. The effect of magnesium sulphate infusion on the incidence and severity of emergence agitation in children undergoing adenotonsillectomy using sevoflurane anaesthesia. *Anaesthesia* 2013; **68**:1045–1052.
- 392 Martin JC, Liley DT, Harvey AS, et al. Alterations in the functional connectivity of frontal lobe networks preceding emergence delirium in children. *Anesthesiology* 2014; **121**:740–752.
- 393 Sepulveda P, Cortinez LI, Saez C, et al. Performance evaluation of paediatric propofol pharmacokinetic models in healthy young children. *Br J Anaesth* 2011; **107**:593–600.
- 394 Vanlander AV, Okun JG, de Jaeger A, et al. Possible pathogenic mechanism of propofol infusion syndrome involves coenzyme q. *Anesthesiology* 2015; **122**:343–352.
- 395 Bray RJ. Propofol infusion syndrome in children. *Paediatr Anaesth* 1998; **8**:491–499.
- 396 Kam PC, Cardone D. Propofol infusion syndrome. *Anaesthesia* 2007; **62**:690–701.
- 397 Chauhan M, Garg A, Bharadwaj A. Effect of short-term propofol administration on pancreatic enzymes and lipid biochemistry in children between 1 month and 36 months. *Paediatr Anaesth* 2013; **23**:355–359.
- 398 Koriyama H, Duff JP, Guerra GG, et al. Is propofol a friend or a foe of the pediatric intensivist? Description of propofol use in a PICU. *Pediatr Crit Care Med* 2014; **15**:e66–e71.
- 399 Gerbershagen HJ, Aduckathil S, van Wijck AJ, et al. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013; **118**:934–944.
- 400 Schultz-Machata AM, Weiss M, Becke K. What's new in pediatric acute pain therapy? *Curr Opin Anaesthesiol* 2014; **27**:316–322.
- 401 Stanko D, Bergesio R, Davies K, et al. Postoperative pain, nausea and vomiting following adeno-tonsillectomy – a long-term follow-up. *Paediatr Anaesth* 2013; **23**:690–696.
- 402 Kim HS, Kim CS, Kim SD, et al. Fascia iliaca compartment block reduces emergence agitation by providing effective analgesic properties in children. *J Clin Anesth* 2011; **23**:119–123.
- 403 Dalens BJ, Pinard AM, Letourneau DR, et al. Prevention of emergence agitation after sevoflurane anaesthesia for pediatric cerebral magnetic resonance imaging by small doses of ketamine or nalbuphine administered just before discontinuing anaesthesia. *Anesth Analg* 2006; **102**:1056–1061.
- 404 Schnabel A, Reichl SU, Zahn PK, et al. Nalbuphine for postoperative pain treatment in children. *Cochrane Database Syst Rev* (7):2014;CD009583.