











RESEARCH ARTICLE

Assessment and management of iatrogenic withdrawal syndrome and delirium in pediatric intensive care units across Europe: An ESPNIC survey

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The Analgosedation CONSORTIUM on behalf of the Pharmacology Section and the Nurse Science Section of the European Society for Paediatric and Neonatal Intensive Care

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Abstract

Introduction: Analgesia and sedation are essential for the care of children in the pediatric intensive care unit (PICU); however, when prolonged, they may be associated with iatrogenic withdrawal syndrome (IWS) and delirium. We sought to evaluate current practices on IWS and delirium assessment and management (including non-pharmacologic strategies as early mobilization) and to investigate associations between the presence of an analgosedation protocol and IWS and delirium monitoring, analgosedation weaning, and early mobilization.

Methods: We conducted a multicenter cross-sectional survey-based study collecting data from one experienced physician or nurse per PICU in Europe from January to April 2021. We then investigated differences among PICUs that did or did not follow an analgosedation protocol.

the Analgosedation CONSORTIUM on behalf of the Pharmacology Section and the Nurse Science Section of the European Society for Paediatric and Neonatal Intensive Care present in Appendix A.

Francesca Sperotto and Anne-Sylvie Ramelet contributed equally as first authors. Paula Pokorna and Angela Amigoni contributed equally as the last senior authors.

Results: Among 357 PICUs, 215 (60%) responded across 27 countries. IWS was systematically monitored with a validated scale in 62% of PICUs, mostly using the Withdrawal Assessment Tool-1 (53%). The main first-line treatment for IWS was a rescue bolus with interruption of weaning (41%). Delirium was systematically monitored in 58% of PICUs, mostly with the Cornell Assessment of Pediatric Delirium scale (48%) and the Sophia Observation Scale for Pediatric Delirium (34%). The main reported first-line treatment for delirium was dexmedetomidine (45%) or antipsychotic drugs (40%). Seventy-one percent of PICUs reported to follow an analgosedation protocol. Multivariate analyses adjusted for PICU characteristics showed that PICUs using a protocol were significantly more likely to systematically monitor IWS (odds ratio [OR] 1.92, 95% confidence interval [CI] 1.01–3.67) and delirium (OR 2.00, 95% CI 1.07–3.72), use a protocol for analgosedation weaning (OR 6.38, 95% CI 3.20–12.71) and promote mobilization (OR 3.38, 95% CI 1.63–7.03).

Conclusions: Monitoring and management of IWS and delirium are highly variable among European PICUs. The use of an analgosedation protocol was associated with an increased likelihood of monitoring IWS and delirium, performing a structured analgosedation weaning and promoting mobilization. Education on this topic and interprofessional collaborations are highly needed to help reduce the burden of analgosedation-associated adverse outcomes.

KEYWORDS

delirium, iatrogenic withdrawal syndrome, mobilization, pediatric intensive care unit, protocol, sedation

1 | INTRODUCTION

Despite being essential for the care of critically ill patients, sedation remains an important source of adverse outcomes, including iatrogenic withdrawal syndrome (IWS) and pediatric delirium. IWS manifests in the context of rapid weaning or abrupt cessation of analgosedation therapy in dependent patients, particularly with opioids and benzodiazepines.¹ Recent studies described that up to 57% of critically ill children in the pediatric intensive care unit (PICU) may be affected by IWS,^{2,3} with incidence increasing up to 65–80% after receiving more than 5 days of analgosedation therapy.^{4,5} This wide range may be due to variation in study design, population characteristics, as well as IWS criteria. Similarly, delirium – an acute cerebral dysfunction caused by systemic illness – may manifest, in its hyperactive or hypoactive form, in up to 66% of the patients depending on the PICU subgroup studied, with a pooled incidence of 34%.^{6–9} Overall, patients with IWS and delirium are at higher risk of prolonged mechanical ventilation, prolonged PICU and hospital stay, and receiving additional drugs including antipsychotics.^{1,7,9,10}

Optimization of pain and sedation management, as well as prevention of IWS and delirium, are integral to the care of critically ill infants and children. Along with early mobilization, they are often listed and promoted within the *ICU liberation bundle*.¹¹ Early mobilization and delirium are also very interconnected, with early mobility being proven to be associated with reduced delirium incidence.^{9,11,12} To date, several

studies showed that monitoring and management of IWS and delirium are not commonly performed in PICUs.^{11,13,14} Additionally, a recent survey showed that only one-quarter of PICUs had a guideline, protocol, or policy for early mobilization in place.¹¹ Overall, observational multicenter data on the monitoring and management of IWS and delirium are relatively limited, often surveyed multiple respondents for each PICU, and included limited European data.^{11,13,14} Additionally, studies addressing associations among different practices, such as the association between the presence of an analgosedation protocol and IWS, delirium, or early mobilization practices, are currently lacking.

We aimed to evaluate current practices on monitoring and management of IWS, delirium and early mobilization across European PICUs. We also aimed to investigate associations between the use of a structured analgosedation protocol and the implementation of protocols for IWS and delirium monitoring, analgosedation weaning and early mobilization.

2 | METHODS

2.1 | Study design, survey development and testing

We performed a multicenter international cross-sectional survey-based study. The survey was developed in English by members of the Pharmacology section of the European Society of Paediatric and

Neonatal Intensive Care (ESPNIC) (A.A., D.T., M.C.M., M.D., F.S., P.P.) and adapted for a survey-dedicated website format (<https://www.google.com/forms/about>). The survey was designed by the authors based on an extensive review of the literature, expert discussion, delineation of the most important question domains, and was subsequently reviewed by two members of the Nursing Science Section (A.S.R., E.I.) to endorse the multidisciplinary nature of the topic. The survey included single- and multiple-choice closed-ended questions to facilitate analyses and comparisons, as well as free-text questions to allow the extrapolation of more detailed information. The first part of the survey was dedicated to define the analgesia and sedation practices in Europe and was previously published.¹⁵ The second part of the survey is presented here and consisted of 11 overlapping questions with the first survey on PICU characteristics, and another 32 questions organized within the following sections: *Section 1*: practices related to the analgosedation weaning and IWS prevention; *Section 2*: diagnosis and management of IWS and delirium; and *Section 3*: practices related to early mobilization (Appendix S1). The study adheres to the American Association for Public Opinion Research (AAPOR) guidelines and the Declaration of Helsinki. Since no patient data were collected in this survey, no Institutional Review Board (IRB) review was necessary (and thus no number was assigned) because it did not fall under the board's guidelines as human subjects' research. Informed consent from participants was implied from their completion of the survey.

2.2 | Recruitment of European PICUs and data collection

The process of data collection has been previously described in detail.¹⁵ The target audience of the survey was experienced intensivists and nurses working in PICUs in Europe. Throughout the ESPNIC and personal networks, we identified one representative for each European country (*country-lead*, January 2021). The country-lead disseminated the survey by contacting one PICU referent per PICU in their own country. The PICU referent was asked to respond by representing at best the PICU practice. To maximize the response rate, reminders were sent by email to all country leads and, subsequently, were targeted to leads of countries with a low response rate. No identifiable patient data were collected, and consent was implied by completing the survey. All valid responses received before April 16, 2021, were included in the analysis.

2.3 | Statistical analysis

Data are described as frequencies and percentages for categorical variables, median and interquartile range (IQR) for continuous variables based on distribution. PICU and responders' characteristics, analgosedation weaning modalities, IWS and delirium management details, and mobilization practices were compared between two groups based on the use of an analgosedation protocol. The Pearson

chi-squared test was used to test categorical data; the Fisher exact test was used when expected counts in >20% of cells were <5. The Mann-Whitney *U*-test was used to compare continuous variables. Univariate and multivariable logistic regression were used to investigate associations between use of an analgosedation protocol and the use of structured IWS and delirium monitoring tools, the use of sedation weaning, and mobilization practices. The models were adjusted by PICU baseline characteristics found to have a *p*-value <0.1 at univariate analysis. Collinearity and logistic regression assumptions were tested before modeling. Results were reported as odds ratios (ORs) and 95% confidence intervals (CIs). All the statistical analyses were performed using R Statistics (version 3.6.2; R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a two-sided *p*-value <0.05.

3 | RESULTS

3.1 | Survey responders, PICU characteristics and presence of an analgosedation protocol

Responders' and PICUs' characteristics are outlined in Table 1. A total of 357 PICU representatives were contacted among 35 countries and a total of 224 surveys were returned. After excluding eight duplicates and one PICU admitting exclusively neonates, the total number of responders was 215 (60% response rate, range 20–100%, Figure 1), from 27 countries. The majority of PICUs were exclusively pediatric (74%), 22% were mixed neonatal and pediatric and 4% were mixed adult and pediatric. Ninety-one percent of PICUs were part of an academic/teaching institution. About one third of the PICUs (32%) admitted early post-cardiac surgery patients and 85% provided palliative care and/or terminal sedation. The median number of bed capacity among the participating PICUs was nine beds (IQR 7–16), with a median number of 450 admissions/year (IQR 260–700). Seventy-one percent of the PICUs (*n*=152) used an internal protocol for analgosedation management. PICUs using an analgosedation protocol were more frequently part of an academic/teaching institution (*p*<0.001), more frequently admit post-cardiac surgery patients (*p*=0.046), and more frequently provide palliative care (*p*=0.027, Table 1).

3.2 | IWS monitoring and management

Fifty-seven percent of the PICUs (*n*=122) had a structured protocol for the analgosedation weaning; this was more frequent among PICUs that had an analgosedation protocol in place (*p*<0.001, Table 2). Sedation was discontinued without weaning at maximum 3 days after starting sedation (IQR 2–5); PICUs with no analgosedation protocol considered suspending the analgosedation without weaning later compared to PICUs that used a protocol (*p*=0.032). After >5 days of sedation, opioids and benzodiazepines were mostly weaned by 10–20% daily, while propofol and ketamine were mostly suspended with no wean, or weaned >20% daily. There were no

TABLE 1 PICU and responders' characteristics according to presence of an analgosedation protocol.

Characteristics	Total PICUs n = 215	PICUs with analgosedation protocol n = 152	PICUs with no analgosedation protocol n = 63	p-value
Type of PICU				
Pediatric ICU	158 (74)	113 (74)	45 (71)	0.724
Mixed neonatal and pediatric ICU	48 (22)	32 (21)	16 (25)	
Mixed adult and pediatric ICU	9 (4)	7 (5)	2 (3)	
PICU in an academic/teaching hospital	196 (91)	145 (95)	51 (81)	<0.001
PICU admitting post-cardiac surgery	69 (32)	55 (36)	14 (22)	0.046
PICU providing palliative care/terminal sedation	182 (85)	134 (88)	48 (76)	0.027
PICUs dimensions, median (IQR), min-max				
Maximum bed capacity	9 (7–16), 2–35	9 (7–16), 2–35	9 (7–15), 2–32	0.907
Number of admissions per year	450 (260–700), 30–2050	400 (265–637), 30–2050	500 (250–700), 50–1800	0.33
Responders' role, n^a				
Physician specialized in Pediatrics	139 (65)	101 (66)	38 (60)	
Physician specialized in Anesthesiology	62 (29)	43 (28)	19 (30)	
Physician specialized in General and Cardiac Critical ICU	44 (21)	31 (20)	13 (21)	0.075
Nurse	20 (9)	9 (6)	11 (17)	
Physician specialized in Surgery	4 (2)	2 (1)	2 (3)	

Note: Data are reported as frequency and (percentage) for categorical variables, median and (interquartile ranges) for continuous variables.

Bold is used to indicate statistically significant *p* values.

Abbreviations: ICU, Intensive Care Unit; IQR, interquartile range; PICU, Pediatric ICU.

^aThe sum of percentages is more than 100% because responders could indicate more than one option.

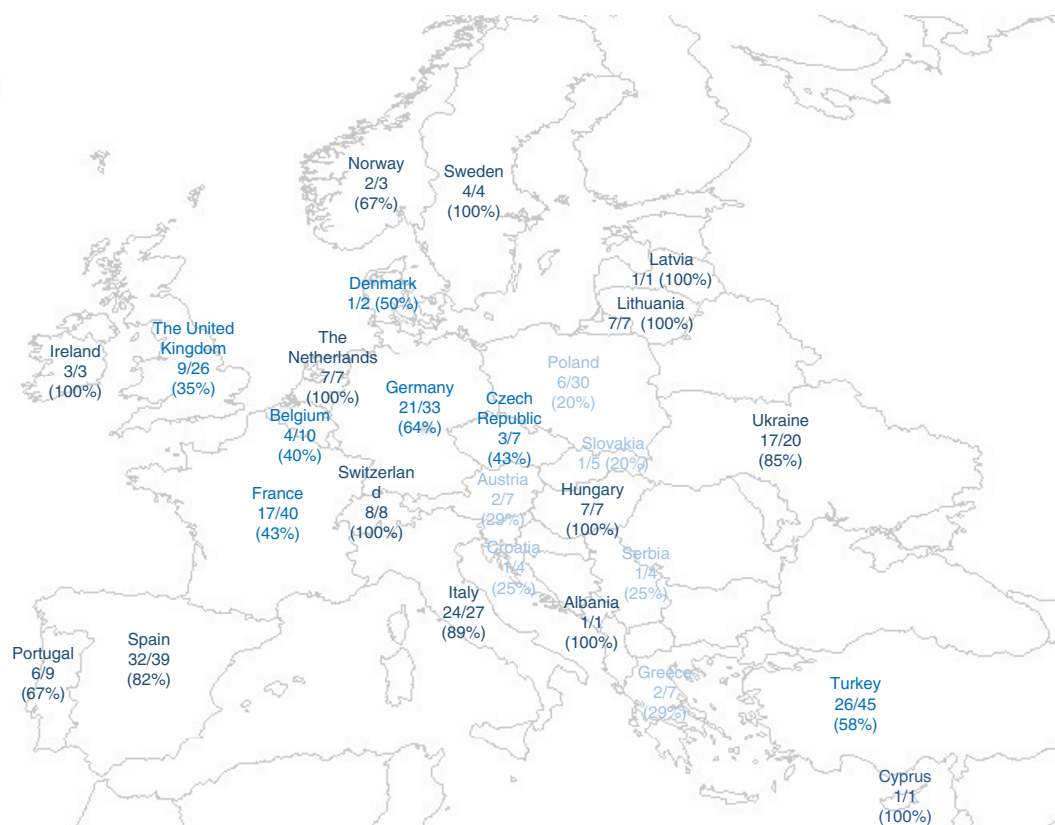


FIGURE 1 Distribution of survey responders across European countries. The number of PICUs who replied to the survey is shown as a numerator, the number of PICUs in each country as a denominator. Percentages represent the response rates for each country. Countries with a response rate <33% are shown in light blue, those with a response rate 33–66% in blue, and countries with a response rate >66% in dark blue.

significant differences in weaning practices among PICUs with or without an analgesedation protocol (Table 2).

IWS was monitored with a validated scale in 62% of the PICUs ($n = 136$), more frequently in those that used an analgesedation protocol ($p = 0.002$, Table 3). The Withdrawal Assessment Tool 1 was the most frequently used tool (83/156, 53% of the PICUs that used a structured tool, 83/215 [39%] among all the PICUs), and was more frequently used in PICUs that used an analgesedation protocol compared to PICUs with no analgesedation protocol ($p = 0.010$). Signs of IWS were assessed more than once daily in 64% of PICUs, more frequently when an analgesedation protocol was present ($p = 0.002$), and mainly by nurses (83%). The first-line strategy for treatment of IWS was mostly a rescue bolus with interruption of weaning (41%). The switch to a longer half-life molecule was mostly used in PICUs

with an analgesedation protocol ($p = 0.045$). The second-line strategy for the management of IWS was mostly the start of a dexmedetomidine infusion (35%); stopping the drug weaning was mostly used in PICUs that did not use an analgesedation protocol ($p = 0.020$).

3.3 | Delirium monitoring and management

Delirium was systematically monitored with a validated scale in 58% of the PICUs, more frequently in PICUs using an analgesedation protocol ($p = 0.013$, Table 4). The most frequently used tools were the Cornell Assessment of Pediatric Delirium scale (CAPD, 53/111, 48% of the PICUs that used a structured tool, 53/191 [28%] among all the PICUs) and the Sophia Observation Scale for Pediatric

TABLE 2 Analgesia and sedation weaning modalities according to presence of an analgesedation protocol.

Characteristics	Total PICUs $n = 215$	PICUs with analgesedation protocol $n = 152$	PICUs with no analgesedation protocol $n = 63$	<i>p</i> value
Use of protocol for sedation weaning ^a	122 (57)	107 (70)	15 (24)	<0.001
Within how many days of sedation do you consider to be possible to stop the sedation without any weaning?				
Days, median (IQR)	3 (2–5)	3 (2–5)	4 (3–5)	0.032
Opioids, type of weaning after >5 days of sedation				
<10% daily reduction	18 (8)	12 (8)	6 (9)	
10–20% daily reduction	143 (67)	106 (70)	37 (59)	0.469
>20% daily reduction	51 (24)	32 (21)	19 (30)	
Suspension without weaning	3 (1)	2 (1)	1 (2)	
Benzodiazepines, type of weaning after >5 days of sedation				
<10% daily reduction	17 (8)	14 (9)	3 (5)	
10–20% daily reduction	131 (61)	93 (61)	38 (60)	0.482
>20% daily reduction	61 (28)	42 (28)	19 (30)	
Suspension without weaning	6 (3)	3 (2)	3 (5)	
Propofol, type of weaning after >5 days of sedation				
<10% daily reduction	9 (4)	7 (5)	2 (3)	
10–20% daily reduction	38 (18)	25 (16)	13 (21)	0.87
>20% daily reduction	71 (33)	51 (34)	20 (32)	
Suspension without weaning	97 (45)	69 (45)	28 (44)	
Ketamine, type of weaning after >5 days of sedation				
<10% daily reduction	15 (7)	8 (5)	7 (11)	
10–20% daily reduction	72 (33)	53 (35)	19 (30)	0.421
>20% daily reduction	81 (38)	59 (39)	22 (35)	
Suspension without weaning	47 (22)	32 (21)	15 (24)	
Dexmedetomidine, type of weaning after >5 days of sedation				
<10% daily reduction	18 (8)	14 (9)	4 (6)	
10–20% daily reduction	88 (41)	65 (43)	23 (36)	0.22
>20% daily reduction	72 (33)	52 (34)	20 (32)	
Suspension without weaning	37 (17)	21 (14)	16 (25)	

Note: Data are reported as frequency and (percentage) for categorical variables, median and (interquartile ranges) for continuous variables.

Bold is used to indicate statistically significant *p* values.

Abbreviations: IQR, interquartile range; PICU, Pediatric Intensive Care Unit.

^a11 (5%) replied "not sure" (7 in PICU with an analgesedation protocol, 4 in PICUs with no analgesedation protocol).

Delirium (SOS-PD) (38/111, 34%), mainly by nurses (81%). Delirium was screened routinely (more than once daily) more frequently in PICUs with an analgesedation protocol ($p=0.004$). Light control and noise reduction were the most used bundles for delirium prevention (73% and 71%, respectively). Sleep promotion was implemented in 52% of the PICUs, mostly in those with an analgesedation protocol ($p=0.002$). The first-line treatment for delirium was mostly the use of a dexmedetomidine infusion (45%), followed by an antipsychotic drug (40%), the latter of which was used most often in PICUs without an analgesedation protocol ($p=0.030$).

3.4 | Mobilization and rehabilitation practice

Seventy-seven (36%) of the PICUs had a mobilization protocol, more frequently in those with an analgesedation protocol ($p=0.001$, Table 5). Mobilization is more often planned during morning rounds (57%). The majority of the PICUs (57%) did not have dedicated staff for mobilization and rehabilitation, whereas 39% had physical therapy personnel, and only 5% had occupational therapy staff. No other differences in mobilization and rehabilitation practices were found between PICUs with or without an analgesedation protocol.

TABLE 3 Iatrogenic Withdrawal syndrome diagnostic tools, management, and treatment according to presence of an analgesedation protocol.

Characteristics	Survey responders <i>n</i> = 215	PICU with analgesedation protocol <i>n</i> = 152	PICU with no analgesedation protocol <i>n</i> = 63	<i>p</i> value	<i>p</i> value [‡]
Scales/tools used for monitoring IWS ^a					
Withdrawal Assessment Tool 1 scale (WAT-1)	83 (39)	67 (44)	16 (25)		0.01
Sophia Observation Withdrawal Symptoms Scale (SOS-WS)	59 (28)	47 (31)	12 (19)		0.076
Finnegan scale	8 (4)	8 (5)	0 (0)	0.085	0.108
Others	6 (3)	6 (4)	0 (0)		0.115
No scales used	79 (38)	44 (29)	32 (51)		0.002
IWS monitoring interval (<i>n</i> = 209)					
Regularly, one time per day	22 (10)	11 (7)	11 (17)		0.024
Routinely, more than one time per day	137 (64)	107 (70)	30 (48)	0.012	0.002
Only on special indications	50 (23)	30 (20)	20 (32)		0.058
Never	6 (3)	4 (3)	2 (3)		1
Figure responsible for IWS monitoring and documentation ^a (<i>n</i> = 209)					
Nurse	179 (83)	129 (85)	50 (79)		0.325
Physician	102 (49)	68 (45)	34 (54)	0.36	0.217
Trainee	13 (7)	12 (8)	1 (2)		0.114
IWS first-line treatment strategy ^a (<i>n</i> = 209)					
Stop drug weaning	52 (25)	37 (24)	15 (24)		0.934
Stop weaning and drug bolus	86 (41)	58 (38)	28 (44)		0.392
Switch to longer half-life molecule	42 (20)	35 (23)	7 (11)	0.444	0.045
Start dexmedetomidine infusion	39 (19)	29 (19)	10 (16)		0.579
Start clonidine infusion	5 (2)	4 (3)	1 (2)		1
IWS second-line treatment strategy ^a (<i>n</i> = 209)					
Stop drug weaning	35 (17)	19 (12)	16 (25)		0.02
Drug bolus and stop weaning	8 (4)	33 (22)	11 (18)		0.482
Switch to longer half-life molecule	57 (27)	41 (27)	16 (25)	0.059	0.812
Start dexmedetomidine infusion	73 (35)	56 (37)	17 (27)		0.165
Start clonidine infusion	44 (21)	5 (3)	3 (5)		0.695

Note: Data are reported as frequency and (percentage) for categorical variables.

Bold is used to indicate statistically significant *p* values.

Abbreviations: IWS, Iatrogenic Withdrawal Syndrome; PICU, Pediatric Intensive Care Unit.

^aThe sum of percentages is more than 100% because responders could indicate more than one option.

[‡]*p*-values comparing each category as a dichotomic variable.

TABLE 4 Pediatric delirium diagnostic tools, management, and treatment according to presence of an analgesedation protocol.

Characteristics	Survey responders n = 215	PICU with analgesedation protocol n = 152	PICU with no analgesedation protocol n = 63	p-value	p-value [‡]
Scales/tools used for monitoring delirium (n = 191)					
Cornell Assessment of Pediatric Delirium (CAPD)	53 (28)	41 (27)	12 (19)		0.22
Sophia Observation Scale for Pediatric Delirium (SOS-PD)	38 (20)	31 (20)	7 (11)	0.141	0.104
Pediatric Confusion Assessment Method (PCAM)	20 (11)	16 (10)	4 (6)		0.337
None	80 (42)	73 (48)	42 (67)		0.013
Delirium Monitoring interval					
Regularly, one time per day	25 (12)	17 (11)	8 (13)		0.753
Routinely, more than one time per day	72 (34)	60 (39)	12 (19)	0.031	0.004
Only on special indications	93 (43)	59 (39)	34 (54)		0.041
Never	24 (11)	16 (10)	8 (13)		0.645
Figure responsible for delirium monitoring and documentation ^a (n = 191)					
Nurse	155 (81)	110 (72)	45 (71)		0.889
Physician	115 (60)	80 (53)	35 (56)	0.573	0.696
Trainee	12 (6)	11 (7)	1 (2)		0.188
Use of protocol/bundles for delirium prevention ^a					
Light control	156 (73)	108 (71)	48 (76)		0.442
Noise reduction	153 (71)	108 (71)	45 (71)		0.956
Use of dexmedetomidine	123 (57)	91 (60)	32 (51)	0.11	0.221
Sleep promotion / use of melatonin	111 (52)	89 (59)	22 (35)		0.002
Reduction of benzodiazepine administration	109 (51)	76 (50)	33 (52)		0.751
Activities/procedures	95 (44)	72 (47)	23 (36)		0.144
Delirium first line treatment strategy					
Dexmedetomidine infusion	97 (45)	74 (49)	23 (36)		0.102
Antipsychotic drugs	85 (40)	53 (35)	32 (51)	0.176	0.03
Non-pharmacological strategies	18 (8)	16 (10)	2 (3)		0.076
Clonidine infusion	5 (2)	4 (3)	1 (2)		1
Delirium second line treatment strategy					
Antipsychotic drugs	129 (60)	89 (59)	40 (63)		0.501
Dexmedetomidine infusion	57 (27)	40 (26)	17 (27)		0.92
Psychiatric evaluation	7 (3)	5 (3)	2 (3)	0.541	1
Non-pharmacological strategies	4 (2)	3 (2)	1 (2)		1
Clonidine infusion	2 (1)	1 (1)	1 (2)		0.501
Delirium antipsychotic drug of choice					
Haloperidol	137 (64)	97 (64)	40 (64)		0.964
Risperidone	65 (30)	49 (32)	16 (25)		0.32
Phenothiazine	24 (11)	18 (12)	6 (9)	0.354	0.623
Quetiapine	26 (12)	17 (11)	9 (14)		0.526
Olanzapine	20 (9)	19 (12)	1 (2)		0.012

Note: Data are reported as frequency and (percentage) for categorical variables.

Bold is used to indicate statistically significant *p* values.

Abbreviation: PICU, Pediatric Intensive Care Unit.

^aThe sum of percentages is more than 100% because responders could indicate more than one option.

[‡]*p*-values comparing each category as dichotomic variable.

TABLE 5 Mobilization and rehabilitation characteristics according to presence of an analgesedation protocol.

Characteristics	Survey responders n = 215	PICUs with analgesedation protocol n = 152	PICUs with no analgesedation protocol n = 63	p-value
Use of an early mobilization protocol	77 (36)	66 (43)	11 (17)	0.001
Early mobilization protocol type ^{a,b} (n = 77)				
Order set	40 (52)	31 (72)	9 (53)	0.12
Guideline	20 (26)	19 (44)	1 (6)	
Published hospital's policy	15 (20)	12 (28)	3 (18)	
Other	6 (8)	5 (12)	1 (6)	
Presence of dedicated therapy staff for early mobilization/rehabilitation in the PICU ^a				
No	122 (57)	79 (52)	43 (68)	0.064
Yes, PT	84 (39)	66 (43)	18 (28)	
Yes, OT	10 (5)	9 (6)	1 (2)	
Yes, other	4 (2)	4 (3)	0 (0)	
The order for PT and OT consults regarding mobilization can be ordered by ^a				
Physician	172 (80)	122 (80)	50 (79)	0.155
Nurse	59 (27)	45 (30)	14 (22)	
Directly from PT	46 (21)	32 (21)	14 (22)	
Directly from OT	8 (4)	4 (3)	4 (6)	
No prescription is required	8 (4)	8 (5)	0 (0)	
When mobilization is planned ^a				
During morning rounds	122 (57)	86 (57)	36 (57)	0.57
Anytime during the day	89 (41)	63 (41)	26 (41)	
During mobilization rounds	22 (10)	14 (9)	8 (13)	
Spontaneously shortly before rounds	12 (6)	6 (4)	6 (9)	
No plan at all	12 (6)	8 (5)	4 (6)	

Note: Data are reported as frequency and (percentage) for categorical variables.

Bold is used to indicate statistically significant *p* values.

Abbreviations: OT, occupational therapy; PICU, Pediatric Intensive Care Unit; PT, Physical therapy.

^aThe sum of percentages is more than 100% because responders could indicate more than one option.

^b66 in PICUs with an analgesedation protocol, 11 in PICUs with no analgesedation protocol.

TABLE 6 Multivariable logistic regression analysis assessing the association between presence of an analgesedation protocol and outcomes.

Primary predictor	Outcome			
	Systematic monitoring of IWS	Systematic monitoring of delirium	Presence of an analgesedation weaning protocol	Presence of an early mobilization protocol
Presence of analgesedation protocol				
Odd ratios (95% CI), unadjusted, <i>p</i> -value	2.53 (1.38–4.64) <i>p</i> = 0.003	2.16 (1.17–3.99) <i>p</i> = 0.014	7.25 (3.68–14.28) <i>p</i> < 0.001	3.63 (1.76–7.49) <i>p</i> < 0.001
Odd ratios (95% CI), adjusted ^a , <i>p</i> -value	1.92 (1.01–3.67) <i>p</i> = 0.048	2.00 (1.07–3.72) <i>p</i> = 0.021	6.38 (3.20–12.71) <i>p</i> < 0.001	3.38 (1.63–7.03) <i>p</i> = 0.001

Note: Bold is used to indicate statistically significant *p* values.

Abbreviations: CI, confidence interval; WS, withdrawal syndrome.

^aModels were adjusted for baseline PICU characteristics including academic/teaching hospital vs. non-academic, admission of post-cardiac surgery vs. not, provision of palliative care vs. not.

3.5 | Association between use of an analgesedation protocol and systematic monitoring of IWS, delirium, presence of protocols for sedation weaning and mobilization

When adjusting for baseline PICU characteristics (academic/teaching hospital vs. non-academic, admission of post-cardiac surgery vs. not, provision of palliative care vs. not), PICUs with an analgesedation protocol were significantly more likely to systematically monitor IWS and delirium (adjusted OR 1.92, 95% CI 1.01–3.67, $p=0.048$; and adjusted OR 2.00, 95% CI 1.07–3.72, $p=0.021$, respectively), to follow a sedation weaning protocol (adjusted OR 6.38, 95% CI 3.20–12.71, $p<0.001$), and to promote mobilization (adjusted OR 3.38, 95% CI 1.63–7.03, $p=0.001$, Table 6).

4 | DISCUSSION

In this multicenter survey-based study, we have shown that practices related to the monitoring and management of IWS and delirium are highly variable among PICUs, and that a relatively high proportion of PICUs do not systematically screen for these complications. In fact, only 62% of the queried PICUs systematically monitor IWS with validated scales and only 58% monitor delirium. Additionally, only 36% of the PICUs had a mobilization protocol in place. Notably, on multivariate analysis adjusted for PICU characteristics, we found that PICUs that follow an analgesedation protocol are twice as likely to systematically monitor IWS and delirium with validated tools, six times more likely to follow a weaning protocol for the analgesedation, and three times more likely to promote mobilization.

Given emerging evidence on the significant impact of IWS and delirium in patients' outcomes,^{1,7,10} in the last decades an intense effort has been made to develop new strategies to prevent and detect early signs of IWS or delirium,^{16–18} implement delirium bundle initiatives within quality improvements projects^{19,20} and develop generalizable recommendations.^{7,21} In 2016, ESPNIC issued detailed recommendations for the monitoring and management of pain, sedation, IWS, and delirium²¹ and similar indications were included subsequently in dedicated pediatric sedation guidelines.^{7,22} Despite this effort, our study showed that still a relatively high percentage of European PICUs do not systematically screen for IWS (38%) or delirium (42%). These percentages are similar or slightly lower compared to those previously reported. In 2014, an international survey investigating sedation practices among 341 PICU health professionals (70% of which were in the United States) reported that 71% of respondents did not perform routine delirium screening.¹³ Smaller country-based surveys showed even more extreme results, with delirium screening not routinely performed in up to 75–100% of the centers^{23,24}; these smaller country-based surveys have however intrinsically limited generability. A more recent international survey of 161 PICUs in 18 countries evaluating the implementation of the *ICU liberation bundle* showed that 56% had not yet incorporated delirium

screening practices.¹¹ As for IWS, studies have shown that only 21–40% of the PICUs regularly assessed signs of IWS with validated tools.^{23,24} Reasons for this diversion from the current recommendations may include decreased awareness of the problem, limited educational opportunities, limited resources and personnel, limited interprofessional collaborations, as well as limited level of evidence of most of the recommendations in the current guidelines.^{22,25} The assessment of IWS and delirium is challenging for health care professionals, even when validated tools are used. Adequate training and implementation of protocols or guidelines is necessary, but this requires carefully prepared and orchestrated strategies for a successful uptake in its local context.²⁶ A recent meta-analysis showed significantly improved patient outcomes where implementation programs included six or more strategies, and when a framework integrating evidence-based pain, agitation and delirium management was used.²⁷ Additionally, our survey showed how nurses play a fundamental role in the implementation of the structured protocols. In adult ICUs, context that showed a robust interprofessional collaboration had facilitated implementation of *ICU liberation bundle*.²⁸ Implementation sciences and interprofessional collaboration are key to ensure that pediatric critical care research translate into practice.^{28,29} Finally, interprofessional research collaboration should help with filling the knowledge and evidence gaps underlined in the recent guidelines.^{22,25}

One of the interventions proven to be effective in decreasing the incidence of delirium in the PICU is the promotion of early mobilization.^{9,12} Along with analgesia and pain management, early mobilization is often listed and promoted as part of the *ICU liberation bundle*, conceived with the aim of improving PICU care and decreasing the length of hospital stay.^{11,12} Although a recent survey assessing PICU providers' beliefs and concerns with regard to early mobilization in the PICU showed that all of the providers ($n=71$) believed early mobilization to be beneficial, and 93% of them expressed a desire to implement it,³⁰ our study showed that only 36% of the PICUs currently had an early mobilization protocol in place. This percentage is comparable to what was reported in a previous survey that involved 161 PICUs in 18 countries and found that only 26% of the respondents had a mobility protocol or guideline in place.¹¹ Our study confirmed that research to facilitate an understanding of the existing barriers and educational efforts are highly needed to help early mobility become a routine in the PICU, while considering any cultural and regional differences.

Our survey also showed significant variability regarding IWS and delirium management. Interestingly, in the presence of IWS, less than half of the centers (41%) reported preferring to administer a rescue bolus and modifying the weaning process, which have been considered the *gold standard* of IWS treatment so far.^{1,22,25} Twenty-five percent of PICUs reported suspending the weaning only, 20% reported switching to a longer half-life molecule, and – interestingly – another 19% reported starting an infusion of dexmedetomidine. Although the switch to a longer half-life molecule has been proven to be effective and is currently recommended,^{22,25,31} efficacy of dexmedetomidine in the treatment or prevention of IWS

is still to be determined, with some observational data in favor³² but also a randomized controlled trial against its effectiveness.³³ Dexmedetomidine was also used for delirium treatment, with up to 45% of centers adopting it as a first-line strategy. This is very interesting since evidence on the use of dexmedetomidine for the treatment or prevention of delirium in the PICU is scarce, with current recommendations mainly derived from observational data and from the adult population.^{32,34,35} The use of antipsychotic drugs as a first-line therapy for delirium was also very common (40%), although the more recent pediatric guidelines are not suggesting their routine use.²⁵ Interestingly, more than 70% of the PICUs used at least one non-pharmacologic strategy for delirium prevention, mainly light control and noise reduction, but also sleep promotion and reduction of benzodiazepine administration, which is in line with current recommendations and guidelines.^{22,25}

Whether protocolized sedation in the PICU may help in improving patients' outcome is still discussed. A multicenter randomized clinical trial of protocolized sedation versus usual care in mechanically ventilated patients published in 2015 showed that the use of a sedation protocol compared with usual care did not reduce the duration of mechanical ventilation; however, patients following a protocol had significantly fewer days of opioid administration, were exposed to less sedative classes, and were more often calm while intubated.³⁶ In parallel, multiple observational and quality improvement studies have suggested that sedation protocolization may still have a significant value in determining patients outcome. Particularly, studies have shown that a pediatric sedation protocol may significantly decrease days of benzodiazepine administration,^{37,38} opioid administration³⁷ and withdrawal symptoms.^{39,40} Although our study did not evaluate specific patient-level outcomes per se, it was able to demonstrate an association between the use of an analgosedation protocol and the implementation of systematic IWS and delirium monitoring, structured analgosedation weaning and early mobilization. Since multiple studies have shown either an association between IWS, delirium, immobilization and adverse outcomes^{1,7,10} or the efficacy of protocol-based intervention and improved outcomes,^{19,20,41} we could speculate that the presence of an analgosedation protocol may serve as a trigger for protocolization and structurization of other clinically meaningful protocols able to reduce patients' morbidity, and ultimately improve patients' outcomes.

Our study has limitations. First, this is a survey-based study, thus data, especially those related to IWS and delirium management, may be biased by the respondent experience and may not reflect the overall center practice. Second, although we had a relatively good response rate, it was difficult to collect data from the Eastern part of Europe despite strong efforts to overcome language barriers, missing responses, and lack of knowledge of nation-based health organizations. Additionally, the presence of a protocol in the center does not ensure a full compliance to the protocol; however, we did not aim to use survey-based data to predict patient's level outcomes; instead, we limited our inference to assess associations between different practices.

5 | CONCLUSIONS

These multicenter data show that monitoring and management of IWS and delirium are highly variable among PICUs. A relatively high percentage of PICUs do not systematically screen for IWS (38%) or delirium (42%). Current practices often divert from international guidelines and recommendations. The presence of an analgosedation protocol is associated with increased likelihood of monitoring IWS and delirium, performing a controlled analgosedation weaning and promoting mobilization. We believe these results represent informative data to guide future educational and intervention measures, as well as international interprofessional research collaborations aimed to fill the knowledge and evidence gaps underlined by the recent guidelines. Education on this topic is highly needed and should reach all ICUs to help provide equal and high-level care around the world.

AUTHOR CONTRIBUTIONS

All the authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by MD and FS. The first draft of the manuscript was written by FS, AA, MD, A-SR, EI, PP and all authors reviewed and commented on this version. All the authors approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

the Analgo-sedation CONSORTIUM on behalf of the Pharmacology Section and the Nurse Science Section of the European Society for Paediatric and Neonatal Intensive Care

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