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Review

Consensus protocol for EEG and amplitude-integrated EEG assessment and monitoring in neonates

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HIGHLIGHTS

- This paper is a consensus statement on neonatal EEG and aEEG written by an Italian interdisciplinary working group.
- A systematic review of literature and discussions among experts took place to elaborate shared recommendations.
- We provide a flexible frame of recommendations applicable by neonatal units according to local resources and patient features.

ABSTRACT

The aim of this work is to establish inclusive guidelines on electroencephalography (EEG) applicable to all neonatal intensive care units (NICUs). Guidelines on ideal EEG monitoring for neonates are available, but there are significant barriers to their implementation in many centres around the world. These include

Abbreviations: **EEG**, Electroencephalography; **vEEG**, video-Electroencephalography; **aEEG**, amplitude-integrated EEG; **CFM**, Cerebral Function Monitor; **NICU**, Neonatal intensive care unit; **TH**, Therapeutic hypothermia; **HIE**, Hypoxic-ischemic encephalopathy; **NS**, Neonatal seizures; **IBI**, Inter-Burst Interval; **SWC**, Sleep-Wake Cycle; **SE**, Status Epilepticus; **INNESCO**, Italian Neonatal Seizure Collaborative Network; **ACNS**, American Clinical Neurophysiology Society.

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barriers due to limited resources regarding the availability of equipment and technical and interpretive round-the-clock personnel. On the other hand, despite its limitations, amplitude-integrated EEG (aEEG) (previously called Cerebral Function Monitor [CFM]) is a common alternative used in NICUs.

The Italian Neonatal Seizure Collaborative Network (INNESCO), working with all national scientific societies interested in the field of neonatal clinical neurophysiology, performed a systematic literature review and promoted interdisciplinary discussions among experts (neonatologists, paediatric neurologists, neurophysiologists, technicians) between 2017 and 2020 with the aim of elaborating shared recommendations.

A consensus statement on videoEEG (vEEG) and aEEG for the principal neonatal indications was established. The authors propose a flexible frame of recommendations based on the complementary use of vEEG and aEEG applicable to the various neonatal units with different levels of complexity according to local resources and specific patient features. Suggestions for promoting cooperation between neonatologists, paediatric neurologists, and neurophysiologists, organisational restructuring, and teleneurophysiology implementation are provided.

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Contents

1. Introduction . . . 888
2. Materials and methods . . . 888
2.1. Review of the surveys on neonatal EEG and aEEG practices around the world . . . 888
2.2. Review of the evidence regarding the contribution of EEG and aEEG to the management of neonatal diseases . . . 888
2.3. Review of guidelines on neonatal EEG and aEEG . . . 888
2.4. Discussions among the INNESCO members and consensus statement development . . . 890
3. Results: Literature review . . . 892
3.1. Review of the surveys on neonatal EEG and aEEG practices . . . 892
3.1.1. Surveys on EEG/aEEG use for neonates with HIE . . . 892
3.1.2. Surveys on EEG/aEEG in neonatal seizures (NS) . . . 892
3.1.3. Surveys on availability/use of EEG/aEEG for all indications in neonatal units . . . 892
3.2. Evidence regarding the contribution of EEG and aEEG in neonatal diseases . . . 893
3.2.1. Hypoxic-ischemic encephalopathy (HIE) . . . 893
3.2.2. Neonatal seizures (NS) . . . 893
3.2.3. aEEG/EEG in neonates at high neurological risk . . . 894
3.2.4. Postnatal transition/resuscitation . . . 894
3.3. Review of guideline articles on neonatal EEG and aEEG . . . 894
4. Results: Consensus statement on EEG and aEEG assessment and monitoring . . . 894
4.1. Hypoxic-ischemic encephalopathy . . . 894
4.1.1. Neurophysiological assessment protocol for neonates with HIE eligible for therapeutic hypothermia . . . 894
4.1.2. Background scale for assessing neonatal encephalopathy by EEG or aEEG . . . 894
4.1.2.1. Background scale for EEG (see Fig. 1) . . . 894
4.1.2.2. Background scale for aEEG (see Fig. 2) . . . 895
4.1.2.3. Notes regarding the application of EEG/aEEG background scale for HIE . . . 896
4.1.3. Monitoring protocol for neonates with moderate-severe HIE undergoing TH . . . 897
4.2. Epileptic seizures . . . 897
4.2.1. Clinical suspicion of epileptic seizures . . . 897
4.2.2. Neurophysiological assessment protocol for suspected epileptic seizures . . . 898
4.2.3. Neurophysiological monitoring protocol for the assessment of response to antiseizure medication . . . 898
4.3. Neurological high-risk conditions . . . 898
4.3.1. Technique and timing to monitor neonates at high risk . . . 898
4.3.2. Time monitoring specifications for neonates at high risk . . . 898
4.4. Clinical indications without urgent clinical question . . . 898
4.4.1. Neurophysiological assessment of electrocortical organisation in neonates without urgent indication . . . 898
4.5. Organisational measures to promote neuromonitoring in NICUs . . . 898
4.6. Legal implications related to the brain monitoring . . . 899
5. Discussion . . . 899
6. Conclusions . . . 900
Declaration of Competing Interest . . . 900
Acknowledgements . . . 900
Appendix A. Supplementary material . . . 900
References . . . 900

1. Introduction

Conventional video-electroencephalography (vEEG) is considered the Gold Standard technique for continuous neurophysiological brain monitoring in neonates (Shellhaas et al., 2011). However, there are still practical barriers for its round-the-clock implementation in most neonatal intensive care units (NICUs) (Boylan et al., 2010, 2013; Hellström-Westas, 2018; Dilena et al., 2019). Few NICUs have the equipment, personnel and expertise to perform long-term continuous vEEG. Therefore, in the last decades, amplitude-integrated EEG (aEEG), previously referred to as Cerebral Function Monitor (CFM), has become popular as a simplified method to perform a continuous brain monitoring based on few channels (usually from 1 to 3 channels) (Boylan et al., 2013). Developed by Maynard et al., in the 60′s (Maynard et al., 1969; Prior et al., 1971) and initially used for monitoring post anoxic and posttraumatic coma in adults, the CFM, as analogical equipment, entered the NICUs in the late 70′s. The current modern digital versions keep the original CFM user-friendly concept, but the CFM-like signal, that is now called aEEG, is digitally derived from the EEG trace. Two or three EEG derivations (usually the P3-P4, C3-P3, C4-P4) are continuously recorded and displayed as aEEG traces together with the corresponding raw EEG traces or electrode impedances by easy touchscreen commands. This technique has been proven to be useful for neonatal encephalopathy, and for the identification of recurrent seizures and status epilepticus (Hellström-Westas, 2018). Modern aEEG monitors may incorporate automatic seizure detection algorithms (SDA) that may help seizure detection, although supervision by clinicians is always needed (Mathieson et al., 2016). The aEEG has the merit of having broadly spread continuous monitoring of the background EEG brain activity as a sign of neurological wellbeing in high-risk newborn infants (Hellström-Westas et al., 2008). In addition, in some clinical situations, this kind of restricted recording is an elective choice (Backman et al., 2018), as may occur in case of vulnerable very low birth weight prematures or in neonates with head trauma (with higher risks related to manipulation, skin maceration and infections). The main limitation of aEEG is its lower sensitivity and specificity for assessing background activity and detecting seizures compared to vEEG (Boylan et al., 2013). The risk of misinterpretation of some findings with aEEG cannot be underestimated. It depends either on the intrinsic limits of the technique or on the personnel expertise. This is why in highly equipped NICUs where a full long-term vEEG may be applied, the neonatologist continuously monitors the neonate, focusing on the aEEG trace and catching a glance at the relevant variations, whereas the EEG expert checks vEEG periodically and when requested by the neonatologist (Backman et al., 2018).

In 2011, the American Clinical Neurophysiology Society's (ACNS) published the Guidelines on Continuous EEG Monitoring in Neonates (Shellhaas et al., 2011), and in 2013 the related standardised EEG terminology and categorisation (Tsuchida et al., 2013). In 2018, a Swedish consensus on recording, interpretation, and reporting of neonatal continuous aEEG was published (Backman et al., 2018). These are important reference recommendations for EEG/aEEG monitoring implementation in neonates, but clear indications on how to complement vEEG and aEEG, and the various adaptations for the different clinical settings are not yet available.

For this purpose, the Italian Neonatal Seizure Collaborative Network (INNESCO) felt the need to work on a protocol for a flexible combined use of vEEG and aEEG suitable for both the NICUs with limited resources, and the Neuro-NICUs with advanced neurocritical care programs.

After a comprehensive literature review, herein, we present our consensus for the use of vEEG and aEEG for the common clinical scenarios in the several NICUs with different levels of complexity. The related consensus statement on the technical standards for the vEEG and aEEG use is detailed in the Supplementary Material (Appendix).

2. Materials and methods

The Italian Neonatal Seizure Collaborative Network (INNESCO), endorsed by the Italian League Against Epilepsy, the Italian Society of Paediatric Neurology, the Italian Society of Clinical Neurophysiology, the Italian Society of Child Neuropsychiatry, the Italian Society of Neonatology, and the Italian Association of Technicians of Neurophysiology, decided to establish a consensus protocol for the complementation of conventional vEEG and aEEG for neonatal brain monitoring for the principal clinical indications where the techniques have been proven useful. The work was developed in four areas as indicated below (paragraphs from 2.1 to 2.4).

2.1. Review of the surveys on neonatal EEG and aEEG practices around the world

In January 2018 and January 2020 we performed a search on the database PUBMED, MEDLINE and EMBASE for survey articles on EEG and aEEG published after 2005 and written in English, using the following terms: 'Infant, Newborn' AND ('Electroencephalography' OR 'amplitude-integrated EEG') AND ('Health Care Survey' OR 'Survey and questionnaire' OR 'Interviews'). We selected 18 articles (Lang et al., 2007; Filan et al., 2007; Bassan et al., 2008; Kapetanakis et al., 2009; Ponnusamy et al., 2010; Vento et al., 2010; Boylan et al., 2010; Allen et al., 2011; Hagmann et al., 2011; Joolay et al., 2012; Glass et al., 2012; Harris et al., 2014; Shah et al., 2015; Gerstl et al., 2015; Wusthoff et al., 2018; Sharpe et al., 2019; Buttle et al., 2019; Dilena et al., 2019) (see Table 1).

2.2. Review of the evidence regarding the contribution of EEG and aEEG to the management of neonatal diseases

In January 2018 and January 2020 we performed a search on the database PUBMED, MEDLINE and EMBASE to find systematic review articles published after 2009 in English with the following terms: 'Electroencephalography OR amplitude-integrated EEG' AND 'Infant, newborn' AND 'systematic review'. Upon evaluating titles and abstracts, 20 articles (Slaughter et al., 2013; Van Laerhoven et al., 2013; Jacobs et al., 2013; Pichler et al., 2014; Pisani et al., 2015, 2020; Rakshasbhuvankar et al., 2015; Sánchez Fernández et al., 2015; Hellström-Westas et al., 2015; Awal et al., 2016; Pisani and Spagnoli, 2016b; Del Río et al., 2016; Ergenekon, 2016; Chandrasekaran et al., 2017; Magalhães et al., 2017; Mebius et al., 2017; Finn et al., 2017; Fogtmann et al., 2017; Massey et al., 2018; Kong et al., 2018) (see Table 2) were selected.

2.3. Review of guidelines on neonatal EEG and aEEG

In January 2018 and January 2020 we performed a search on the database PUBMED, MEDLINE and EMBASE to select the available guidelines on neonatal EEG and aEEG with the following terms: ('Electroencephalography' OR 'amplitude-integrated EEG') AND 'Infant, newborn' AND ('guideline' OR 'consensus'). Seven articles (Guérit et al., 2009; Shellhaas et al., 2011; Tsuchida et al., 2013; André-Obadia et al., 2015; Kuratani et al., 2016; Backman et al., 2018; Bonifacio and Van Meurs, 2019) were selected (*see* Table 3).

Table 1
Review of survey articles on neonatal EEG and aEEG practices in NICUs around the world.

Author Year	Topics of Survey	Participant; Country	Access to EEG or aEEG	EEG use	aEEG use
Lang et al., 2007	TH management for HIE	Directors of NICUs; USA		N = 20 - Continuous: 10%; - Pre and post: 40%; - - Pre and intermittent 50%	Not mentioned in the study
Filan et al., 2007	Attitudes on a scenario of HIE	Neonatologists; Australia (77%), New Zealand	N = 95 EEG 92% aEEG 76%	N = 94; 59%	N = 94; 62%
Bassan et al., 2008	Attitudes on neonatal seizure management	Neonatologists and Neurologist; Israel		N = 102 *For seizure diagnosis* Neonatologists 97% Neurologists 93.7% *Monitoring for HIE* Neonatologists 70.5 Neurologists 40%	aEEG not commonly used in Israel at the time of study
Kapetanakis et al., 2009	Web-based questionnaire on HIE management	Leads of neonatal units; UK		N = 125, 70% Level I units 31% Level II units 57% Level III units 88%	N Total = 125, 58% Level I units: 23% Level II units: 32% Level III: 86%
Vento et al., 2010	Survey on protocols for neonatal seizures	Neonatologists of tertiary NICUs; Europe	N = 13 aEEG: 100% EEG 100%	N = 13 100% (as "sequential multichannel EEG")	N = 13 100% (as continuous aEEG monitoring)
Ponnusamy et al., 2010	Phone survey on availability of CFM and TH devices	Senior nurses of neonatal units; UK	N = 214; 41% Level I 13% Leve II 33% Level III 87%		
Boylan et al., 2010	Web-based survey on the EEG/aEEG use in NICUs	Neonatologists, Neurologists, Neurophysiologists; Europe, USA and Canada, Others	N = 206 90.3%	N = 187 - EEG only 27.3% -Both EEG and aEEG 50.8%	N = 187 - aEEG only 21.9 % -Both EEG and aEEG 50.8%
Allen et al., 2011	Questionnaire on TH for HIE	Lead of Neonatal Units, Ireland	EEG: 6/6 aEEG: 5/6		
Glass et al., 2012	Web-based questionnaire on practices in preterm and term neonates with seizures	Neurologists Neonatologists; USA, Canada, UK, Europe, Others		*N preterm = 188, Term = 182* *Seizure diagnosis with EEG* Preterm 58%, Term 58,2% *with EEG or aEEG* Preterm 34%, Term 33% *N preterm = 187, Term = 182* *Monitoring At-Risk Newborns with EEG* Preterm 17.1%, Term 23.6% *with both EEG and aEEG* Preterm 14.5%, Term 18.7%	*N preterm = 188, Term = 182* *Seizure diagnosis with aEEG* Preterm 1.1%, Term 1.1% *with EEG or aEEG* Preterm 34%, Term 33% *N preterm = 187, Term = 182* *Monitoring At-Risk Newborns with aEEG* Preterm 21.9%, Term 24.2% *with both EEG and aEEG* Preterm 14.5%, Term 18.7%
Hagmann et al., 2011	Survey on TH practices in HIE	Neonatologists; Switzerland	N = 11 NICU aEEG 100%; EEG 100%, but 31% having access only during office hours.	N = 11 Between day 1–3: 75%; Between day 3–7: 25%	N = 11 Continous aEEG during cooling and re-warming time: 64%; Intermittent aEEG: 9%; During cooling time: 18%; Depending on aEEG availability: 9%.
Joolay et al., 2012	A web-based survey regarding opinions and practice of TH for HIE	Neonatologists and Paediatricians treating neonates; South Africa (SA)		N = 93 EEG: 18.3% Both EEG and aEEG: 6.5%	N = 93 aEEG: 35.5% EEG or aEEG monitoring: 6.5%

(*continued on next page*)

Table 1 (*continued*)

Author Year	Topics of Survey	Participant; Country	Access to EEG or aEEG	EEG use	aEEG use
Harris et al., 2014	A web-based survey on TH for management for HIE	Medical Directors of NICUs; USA	N = 158 Continuous Monitoring: 41.1% Pre and post-TH: 19% Pre and intermittent 22.8%, EEG not performed 17%	N = 109 Preferred monitoring EEG 49.5%	N = 109 Preferred monitoring aEEG 50.5%
Gerstl et al., 2015	A Survey TH management for HIE	Neonatologists and clinical heads neonatal units; Austria	N = 19 aEEG 89% cEEG 100%		N = 19 Continuous aEEG monitoring during HT: 81%
Shah et al., 2015	Online survey current aEEG use in NICUs	Neonatologists; USA		Continuous EEG capability 12%	N = 630 *All Units 55%*; Accademic Units 61%; Community Units 46%
Wusthoff et al., 2018	Online survey on services related to TH for HIE	Neonatologists, Neurologists; California (USA)	N = 42 Yes, 88.1% No = 11.9%	N = 42 EEG 9.5% Both aEEG and EEG 50%	N = 42 aEEG 31% Both aEEG and EEG 50%
Sharpe et al., 2019	Phone Interviews to the professionals involved in advanced NICU enrolling patients for the NEOLEV2 trial for neonatal seizures	Neonatologists Neurologists, study coordinators EEG technicians in a pharmacological trial study using continuous videoEEG monitoring with remote access review; USA, New Zealand		N = 25 Interviews At 1 of 5 five sites two-channel aEEG/EEG remained the standard of clinical care outside the study. VideoEEG monitoring remains unfeasible in many clinical contexts	N = 25 Interviews; Remote review of cEEG monitoring was operational at 2 of 5 sites before commencing the study. Then clinical practice evolved so that long-term cEEG became routine at 4 of 5 sites outside the study.
Buttle et al., 2019	Electronic questionnaire on continuous EEG/aEEG monitoring in NICUs	Neonatologists and neurologists accross 25 different sites; Canada			N = 87 *EEG monitoring use (in the form of EEG or aEEG)*: Neurologists 97%, Neonatologists 92% *For seizure detection and HIE* neonatologists prefer aEEG, neurologists cEEG. 53% interested in education sessions on neonatal EEG
Dilena et al., 2019	Web-base questionnaire on neonatal seizure management	Paediatric Neurologists consultant of tertiary NICUs; Italy	N = 19 - aEEG 100 % (anytime) - cEEG 100%, but only during office hours 47%		N = 19 *Preferred monitoring* Continuous cEEG combined with aEEG: 84% Continuous two-channel aEEG/EEG combined with sequential standard cEEG: 16%
Unpublished INNESCO Project Data	Emailed interviews in January 2018 on access to EEG/aEEG in tertiary NICUs	Neonatologists and paediatric neurologists working in tertiary NICUs; Italy	N = 37 NICUs aEEG access: 97% (anytime) cEEG 100%, but 33% only during office hours		

EEG, Electroencephalography; aEEG, amplitude-integrated EEG; cEEG, conventional Electroencephalography; HIE, Hypoxic-ischemic encephalopathy; TH, Therapeutic hypothermia; NICU, Neonatal intensive care unit.

2.4. Discussions among the INNESCO members and consensus statement development

From the end of 2017 to January 2020 open discussions took places in 9 meetings among the members of INNESCO Working Group. Discussions were based on the evidence coming from the literature review and comparisons between exemplificative clinical scenarios presented by various centres with different clinical practices and variable level of complexity. Pros and cons of each model have been weighted up according to the specific features of the centre and the clinical indication. Building on this work, a first written proposal of a consensus statement on neonatal EEG

Table 2
Overview of reviews on the evidences regarding the contribute of EEG and aEEG in neonatal management.

First Author, year	Aim of review	Conclusions regarding EEG/aEEG use
Van Laerhoven et al., 2013	Prognostic Tests in Term Neonates with HIE	Important role of aEEG, EEG, VEP, MRI for prognosis of HIE outcome
Slaughter et al., 2013	Pharmacological treatment of neonatal seizures diagnosed by EEG/aEEG	Limited evidence regarding the best pharmacologic treatment for neonatal seizures, but able to inform on a reference treatment protocol, based on EEG diagnosis and monitoring
Jacobs et al., 2013	TH for neonatal HIE	Reduction in death or major disability among cooled infants with intermediate aEEG findings at baseline and trend towards reduction in infants with severe aEEG findings at baseline. Reduction in major disability but no significant decrease in mortality in cooled infants with either intermediate or severe aEEG findings
Pichler et al., 2014	Physiological monitoring of the brain during immediate postnatal transition	aEEG might be part of the tools evaluating the brain status in post-natal transition, but for a routine recommendation further clinical trials are needed
Hellström-Westas et al., 2015	Management practices on neonatal seizures	Methods for seizure diagnosis and availability of EEG varied. There is an urgent need for more evidence-based studies to guide neonatal seizure management
Rakshasbhuvankar et al., 2015	Comparison studies of aEEG versus EEG for diagnosis of neonatal seizures	When "aEEG with raw trace" was used, median sensitivity was 76% (range: 71–85), and specificity 85% (range: 39–96). aEEG has relatively low and variable sensitivity and specificity, so cannot be recommended as the mainstay for diagnosis and management of neonatal seizures instead of EEG*
Pisani et al., 2015	Incidence of epilepsy after neonatal seizures	Estimates on epilepsy after neonatal seizures vary widely depending on selection criteria and length of the follow-up. Among these factors, it depends if the seizures are confirmed by EEG or not.
Awal et al., 2016	Background features of EEG in term neonates with HIE predicting outcome	Burst suppression, low voltage and flat trace in the EEG of term neonates with HIE most accurately predict long term neurodevelopmental outcome.
Del Río et al., 2016	Predictive value of aEEG in HIE for neurodevelopmental outcome	aEEG background activity, as recorded during the first 72 hours after birth, has a strong predictive value in infants with HIE, so continuous monitoring it is a helpful guide when counselling parents about neurological outcome
Ergenekon, 2016	Therapeutic hypothermia for HIE in NICU	aEEG/EEG are used for diagnosis of HIE severity, to evaluate treatment effects and guide management
Pisani and Spagnoli, 2016a,b	Outcome and outcome predictors in neonatal seizures	EEG and aEEG background pattern are significantly associated with neurologic outcome in newborns with neonatal seizures
Chandrasekaran et al., 2017	Predictive value of aEEG after rescue hypothermic neuroprotection for HIE	A persistently abnormal aEEG at 48 h or more is associated with an adverse outcome. Conversely, a normal 6 h aEEG has a good negative predictive value
Fogtmann et al., 2017	Prognostic accuracy of EEG and aEEG for neurodevelopmental outcome in Preterm Infants	aEEG or EEG within the first 7 days of life in preterm infants may have potential as a predictor for neurodevelopmental outcome. We need high-quality studies for confirmation. Meanwhile, the prognostic value of aEEG and EEG should be used only as a scientific tool.
Mebius et al., 2017	Prognostic value of various brain findings for neurodevelopmental outcome in Congenital Heart Diseases (CHD)	EEG and aEEG abnormal cerebral findings are associated with neurodevelopmental impairment in neonates with CHD.
Finn et al., 2017	Neonatal EEG use as biomarker in delivery room (DR)	EEG monitoring is possible in the DR and may provide objective measures of neurological function. Further feasibility studies are required.
Magalhães et al., 2017	aEGG in very low-birth-weight preterm	Further studies are needed to definitively establish the role of aEEG in the evaluation of preterm infants
Massey et al., 2018	Electroencephalographic monitoring for seizure identification and prognosis in term neonates.	Continuous conventional EEG monitoring is the reference standard for neonatal seizure identification, but it is labor intensive, expensive, and requires the expertise of an electroencephalographer. Thus, aEEG are often used, albeit imperfectly, if conventional EEG is not feasible.
Kong et al., 2018	Predictive value of EEG for cognition in very preterm infants	Background EEG features can predict cognitive outcomes in preterm infants. Reported findings were however too heterogeneous to determine which EEG features are best at predicting cognitive outcome
Pisani et al., 2020	Mortality risk and neurological outcomes in preterms with seizures	Severely abnormal background EEG/aEEG in preterm with NS is associated with unfavourable outcome
Editorials on the above indicated reviews		
Sánchez Fernández et al., 2015	Comments on the Review of Rakshasbhuvankar et al., 2015*	The presented data * suggest that aEEG is a good screening tool. While the gold standard remains cEEG, it may not be feasible in every neonate around the world immediately. Future cost-effectiveness and outcome studies on the yield of cEEG and aEEG may help delineate further which option is best for individual neonates in different settings

EEG, Electroencephalography; vEEG, video-electroencephalography; aEEG, amplitude-integrated EEG. cEEG, conventional Electroencephalography; VEP, visual evoked potentials; MRI, Magnetic Resonance Imaging; HIE, Hypoxic-ischemic encephalopathy; TH, Therapeutic hypothermia.

Table 3
Review of guideline and consensus statement articles on neonatal EEG and aEEG.

First Author, year	Topic of the Guideline
Guérit et al., 2009	Consensus on the use of neurophysiological tests (EEG, EP, ENMG) in the intensive care unit (ICU)
Shellhaas et al., 2011	American Clinical Neurophysiology Society's Guideline on Continuous EEG Monitoring in Neonates
Tsuchida et al., 2013	American clinical neurophysiology society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates
André-Obadia et al., 2015	French recommendations on EEG
Kuratani et al., 2016	American Clinical Neurophysiology Society Guideline: Minimum Technical Standards for Pediatric EEG
Backman et al., 2018	Swedish consensus reached on recording, interpretation and reporting of neonatal continuous simplified EEG that is supported by aEEG analysis
Bonifacio and Van Meurs, 2019	Neonatal Neurocritical Care for All at Risk Neonates

EEG, Electroencephalography; aEEG, amplitude-integrated EEG; EP, Evoked Potentials; ENMG, electroneuromyography; ICU, Intensive Care Unit.

and aEEG was presented to INNESCO members in the meetings and gradually improved with the interdisciplinary contribution of the members representing the different types of NICUs and the different involved professionals. The consensus statement was finally approved by all the scientific societies supporting our collaborative network.

3. Results: Literature review

3.1. Review of the surveys on neonatal EEG and aEEG practices

Among the 18 survey studies available (Table 1) nine were focused on the use of EEG/aEEG in newborns with hypoxic-ischemic encephalopathy (HIE) (Filan et al., 2007; Lang et al., 2007; Kapetanakis et al., 2009; Allen et al., 2011; Hagmann et al., 2011; Joolay et al., 2012; Harris et al., 2014; Gerstl et al., 2015; Wusthoff et al., 2018), five reported about EEG/aEEG in neonatal seizures (NS) (Bassan et al., 2008; Vento et al., 2010; Glass et al., 2012; Dilena et al., 2019; Sharpe et al., 2019) and four were based on the availability/use of EEG/aEEG for all clinical indications in neonatal units (Boylan et al., 2010; Ponnusamy et al., 2010; Shah et al., 2015; Buttle et al., 2019). The surveys published on neonatal EEG and aEEG practices around the world are summarised in the following paragraph.

3.1.1. Surveys on EEG/aEEG use for neonates with HIE

A survey conducted in 2005 in the USA (Lang et al., 2007) showed that among 441 surveyed NICU chiefs only 20 responded to the question regarding the brain monitoring protocols adopted in neonates undergoing therapeutic hypothermia (TH): EEG was used continuously by 10% of the centres, at baseline and after TH by 40%, and at baseline and intermittently throughout TH by 50%. The survey was repeated in 2011 (Harris et al., 2014), and among 797 surveyed NICU chiefs 158 responded to the question regarding EEG protocols during TH: 41.1% declared to use continuous EEG monitoring, 19% baseline and post-TH brain monitoring, 22.8% baseline and intermittent monitoring throughout TH and 17.1% did not perform EEG monitoring. One-hundred and nine respondents were almost equally divided in choosing EEG (49.5%) or aEEG (50.5%) as their preferred monitoring tool.

Later, in California (USA) (Wusthoff et al., 2018), a survey, based on an online questionnaire investigating about the minimum standard of available tools for the neonates with HIE treated by TH revealed that 50% of the centres used both aEEG and EEG, 31% used aEEG alone, and only 9.5% used only EEG. aEEG was considered as a critical minimum standard tool for the management of acute HIE by 70.4% of respondents.

In Australia and New Zealand, (Filan et al., 2007) among 95 neonatologists, 92% declared the availability of EEG in their centres, and 76% aEEG. Moreover, in a hypothetic scenario of a neonate born with perinatal HIE developing clinical seizures at 8 hours of life, 59% of them would perform an EEG and 62% an aEEG (the sum of percentages exceed 100% as a part of participants would use both EEG and aEEG). A different situation was reported in South Africa (considered a low income country) (Joolay et al., 2012), where 18.3% declared the use of EEG, 35.5% of aEEG and only 6.5% of both.

In the UK (2007) (Kapetanakis et al., 2009), in a period when TH use for the treatment of neonatal HIE was still increasing, the EEG was being used by 70% (Unit level I: 31%; II: 57%; III: 88%) and aEEG by 58% (Unit level I: 23%; II: 32%: III: 86%). In Ireland (2010), among the units participating in a web-questionnaire (Allen et al., 2011), only 6 responded to questions regarding EEG: five used both aEEG and EEG, and one used only EEG. In Switzerland (Hagmann et al., 2011), both equipment types were available for the surveyed NICUs, but only 31% had access to EEG during office hours. aEEG monitoring was continuous during cooling and re-warming in 64% of NICUs, intermittent in 9%, only during cooling in 18%, and depending on aEEG availability in 9% of the Units.

In 2013, among the 19 Austrian neonatal Units applying TH for neonates with HIE (Gerstl et al., 2015), 100 % used EEG and 89% aEEG. Continuous aEEG monitoring was performed by 81%, which were mainly level III units.

3.1.2. Surveys on EEG/aEEG in neonatal seizures (NS)

Among 102 Israeli doctors that participated in a survey on management of NS in 2006 (Bassan et al., 2008), EEG was used by more than 90%, while in a case of HIE, EEG monitoring was performed by 70.5 % of the neonatologists, and 40% of neurologists. There was limited use of aEEG in Israel at the time.

The combination of sequential multichannel EEG together with continuous aEEG monitoring was considered to be the best monitoring protocol for NS by a group of 13 members of the European Society for Paediatric Research (Vento et al., 2010). However, in the same period, an international questionnaire with 193 respondents (Glass et al., 2012) showed that for NS diagnosis, about 58% used EEG, only 1.1% used aEEG, and 33% used both. Recently, Canadian doctors (Buttle et al., 2019) have confirmed that neonatologists prefer aEEG even for seizure detection. However, the unavailability of around-the-clock EEG was also seen in Italy where Dilena et al., (Dilena et al., 2019) reported that among 19 NICUs treating NS, EEG access out of office hours was available only in 53% of them. Nevertheless, the preferred method for monitoring neonatal seizures by paediatric neurologists was continuous EEG combined with aEEG for 84% of respondents, and continuous aEEG combined with sequential standard duration EEGs performed in the following days for 16%.

3.1.3. Surveys on availability/use of EEG/aEEG for all indications in neonatal units

By a phone survey in the UK in 2009 (Ponnusamy et al., 2010), the availability of aEEG was reported in 41% of the 214 interviewed centres. Similar results were seen in USA (Shah et al., 2015) where aEEG use was reported at 55% of all neonatal Units (academic units 61%, community units 46%). Only 55% of the participants had attended a formal course or hospital training in aEEG. Furthermore,

an international web-based survey (Boylan et al., 2010) revealed that only 51 % used both EEG and aEEG, with the EEG interpreted mainly by neurophysiologists (72%).

Our Working Group (INNESCO) performed by email a survey in January 2018 on EEG facilities in the 37 Italian NICUs (data not published). aEEG was available anytime in 97% of those Units treating neonates with TH, but EEG out of office hours was available in only 33% of respondents. Similar results were seen by others in Europe (Hagmann et al., 2011).

3.2. Evidence regarding the contribution of EEG and aEEG in neonatal diseases

Among the 20 review articles identified (Table 2) six were on the use of EEG/aEEG in HIE (Jacobs et al., 2013; Van Laerhoven et al., 2013; Awal et al., 2016; Del Río et al., 2016; Ergenekon, 2016; Chandrasekaran et al., 2017), eight on neonatal seizures (Slaughter et al., 2013; Sánchez Fernández et al., 2015; Hellström-Westas et al., 2015; Pisani et al., 2015, 2020; Rakshasbhuvankar et al., 2015; Pisani and Spagnoli, 2016b; Massey et al., 2018), three on preterm outcome prediction (Fogtmann et al., 2017; Magalhães et al., 2017; Kong et al., 2018), two on postnatal transition/resuscitation (Pichler et al., 2014; Finn et al., 2017), and one on monitoring neonates at high risk (Mebius et al., 2017).

3.2.1. Hypoxic-ischemic encephalopathy (HIE)

aEEG or EEG are used for the diagnosis of HIE severity within 6 hours of life in order to guide management and eligibility for therapeutic hypothermia (TH) (Jacobs et al., 2013; Ergenekon, 2016). Furthermore, they play an important role in prognosis (Van Laerhoven et al., 2013). In fact, burst suppression, low voltage, and flat trace in the EEGs of term neonates with HIE most accurately predict long term adverse neurodevelopmental outcome (Awal et al., 2016). However, the aEEG background activity monitored during the first 72 hours of life also has a strong predictive value for neurological outcome in infants with HIE undergoing TH (Del Río et al., 2016). In cooled babies, the persistence of severely abnormal aEEG at 48 h or more was associated with an adverse outcome, whereas in a historical series of HIE neonates who were not cooled, this association was seen even with earlier abnormal aEEGs recorded at 24–36 hours (Del Río et al., 2016). Conversely, a normal 6 h aEEG has a good negative predictive value (Chandrasekaran et al., 2017). A very recently published systematic review (Ouwehand et al., 2020) confirms that aEEG at 36 h is among the most predictive test of adverse (neurodevelopmental) outcomes in cooled neonates with HIE. Two main classifications have been used to evaluate the severity of the encephalopathy by aEEG in the studies: the ‘simple scale’ proposed by Al Naqeb (Al Naqeeb et al., 1999) based on the amplitude margins, and the ‘advanced’ scale proposed by Hellström-Westas (Hellström-Westas and Rosén, 2006), based both on amplitude margins and background pattern recognition. Many other scales based on different rating systems have been used for EEG (Walsh et al., 2011).

The main power of the aEEG relies on being a rapid decision-making tool for neonates with HIE candidate to TH where time factor is crucial. However, aEEG has accuracy lower than EEG both in background recognition with a risk of false negatives (Marics et al., 2013) and in detecting seizures (Rakshasbhuvankar et al., 2015). In newborns with HIE, a higher seizure burden was associated with poor outcome (Miller et al., 2002; Kharoshankaya et al., 2016). The periods at higher risk of seizures seem to be the first 24–48 hours and the first hours after rewarming (Shah et al., 2014; Mahfooz et al., 2017).

3.2.2. Neonatal seizures (NS)

NS are a common phenomenon in neonates, particularly in critically ill neonates or neonates with high neurological risk (Lanska et al., 1995; Ronen et al., 1999; Saliba et al., 1999; Pisani et al., 2018). A high proportion of epileptic seizures has poor or no clinical manifestations especially in critically ill neonates or after antiepileptic drug treatment (Clancy et al., 1988; Murray et al., 2008; Nash et al., 2011; Mizrahi and Hrachovy, 2015). It has been estimated that only half of clinical seizures are correctly classified by inspection both by doctors or other healthcare professionals as NICU nurses (Malone et al., 2009). Correct identification was even lower, only 32% (n = 44/137), for subtle seizures, whereas the rate was 66% (n = 90/137) for clonic seizures. Correct identification rates for nonseizure movements were: 55.8% (n = 76 of 137) for nonspecific movements, 55.5% (n = 76 of 137) for nonseizure sleep myoclonus, and 29.6% (n = 40 of 137) for nonseizure clonus. The interobserver agreement for doctors was 0.21 compared to 0.29 for other health care professionals. The agreement with correct responses for doctors was 0.09 compared to 0.02 for other health care professionals.

Methods for NS diagnosis and availability of EEG vary among centres, so there is an urgent need for more evidence-based studies to guide neonatal seizure management (Hellström-Westas et al., 2015). Continuous conventional EEG monitoring is the reference standard for neonatal seizure identification and monitoring (Shellhaas et al., 2011), but it is labor intensive, expensive, and requires the expertise and availability of technicians and electroencephalographers. Thus, aEEG is often used, albeit imperfectly, when conventional EEG is not feasible (Massey et al., 2018). When aEEG with raw trace was used in comparison with conventional EEG as a standard reference, the median sensitivity among different studies was 76% (range: 71–85), and the specificity 85% (range: 39–96) (Rakshasbhuvankar et al., 2015). aEEG has shown greatly variable sensitivity and specificity among different groups, so according to this review, it cannot be recommended as the mainstay for diagnosis and management of neonatal seizures instead of EEG (Rakshasbhuvankar et al., 2015). If on one hand the gold standard remains conventional EEG, aEEG will on the other hand remain a useful screening tool for high-risk neonates and a precious complementary tool to EEG for neonates with seizures, since continuous conventional EEG is not feasible in every NICU and for every neonate (Sánchez Fernández et al., 2015). The time to start EEG recording and the time of periodic EEG monitoring review by expert electroencephalographers varies among different NICUs, so even in centres who perform continuous EEG monitoring it is difficult to timely recognize neonatal seizures (Rennie et al., 2019). Future cost-effectiveness and outcome studies on the yield of EEG and aEEG may help to better delineate which option is best for individual neonates in different NICU settings (Sánchez Fernández et al., 2015). Using the aEEG, seizures with low amplitude, brief duration, or location far from aEEG electrodes are less likely to be detected (Boylan et al., 2013). The absence of the typical seizure spatial evolution (as it is typically seen in multichannel EEG), is another important limit of aEEG. Therefore, EEG should always be requested when there is any doubt with aEEG (Boylan et al., 2013). The aEEG sensitivity appears higher using at least two channels (Van Rooij et al., 2010), so this technical setting should be preferred as the default option. Central and parietal locations seem to have higher sensitivity than frontal electrodes in detecting seizures (Shellhaas et al., 2007; Wusthoff et al., 2009).

EEG and aEEG provide irreplaceable information on the specific type of electroclinical seizure, the background activity, and the presence of focal anomalies that address the etiology, guiding the following diagnostic work-up and therapeutic management. Also, in this respect, the EEG is superior to aEEG (Boylan et al., 2013). Typical examples of neonatal conditions without neuroimaging

clues with distinctive EEG and sometimes also aEEG features and needing a targeted therapeutic approach, are genetic disorders such as pyridoxine deficiency (Pearl, 2016) or channelopathies (such as KCNQ2 and SCN2A mutations) (Pisano et al., 2015; Sands et al., 2016; Dilena et al., 2017; Vilan et al., 2017; Wolff et al., 2017; Nunes et al., 2019). Finally, the EEG and aEEG are precious outcome predictors in newborns with seizures: the EEG or aEEG severely abnormal background activity is associated with increased risk of neurodevelopmental outcome and chronic epilepsy both in preterm and term infants (Pisani et al., 2015, 2020; Pisani and Spagnoli, 2016b).

3.2.3. aEEG/EEG in neonates at high neurological risk

aEEG and EEG within the first 7 days of life in preterm infants seem to be good predictors of neurodevelopmental outcome. However, further studies are needed to confirm this (Fogtmann et al., 2017). Meanwhile, the prognostic value of aEEG and EEG should be used only as a scientific tool (Fogtmann et al., 2017). Background EEG features can predict cognitive outcomes in preterm infants, but reported findings are too heterogeneous to determine which EEG features are best at predicting cognitive outcome (Kong et al., 2018). Existing reports suggest aEEG as a screening tool for periventricular haemorrhage and white matter lesions in preterm newborn infants, as it may be helpful and even show changes earlier than other methods (Magalhães et al., 2017). However, the role of the aEEG as predictor of the outcome in the very low-birth-weight preterm infants is still uncertain (Magalhães et al., 2017) and this is partly due to the different inclusion criteria used in the published studies.

EEG and aEEG abnormal cerebral findings are associated with neurodevelopmental impairment also in neonates with congenital heart diseases (Mebius et al., 2017). Abnormal brain activity is an early, bedside marker of new brain injury in neonates undergoing cardiac surgery (Claessens et al., 2018). Not only ictal discharges, but also an abnormal background pattern, should be considered a clear sign of underlying brain pathology.

3.2.4. Postnatal transition/resuscitation

aEEG might be one of the tools that are useful in evaluating the brain status in post-natal transition. However, for a routine recommendation, further clinical studies are needed (Pichler et al., 2014). EEG monitoring is possible in the delivery room and may provide objective measures of neurological function, but further feasibility studies are required (Finn et al., 2017).

3.3. Review of guideline articles on neonatal EEG and aEEG

Among the available guidelines on neonatal EEG and aEEG (Table 3) the first published work is a consensus statement on the use of neurophysiological tests (EEG, Evoked potentials, electroneuromyography) in adult and paediatric intensive care units of all ages (Guérit et al., 2009). The limitation of this work it is that it poorly focuses on the specific neonatal needs.

Very important reference articles for the gold standard neonatal EEG monitoring are those provided by the American Clinical Neurophysiology Society (ACNS) (Shellhaas et al., 2011; Tsuchida et al., 2013), although applicability issues are not faced and flexible adaptations for the different levels of care and different NICU resource availability are not reported. Some specifications concerning the concept of minimum technical standards for paediatric and neonatal EEG are found in the article of Kuratani et al., of 2016 (Kuratani et al., 2016).

There are also the French recommendations on electroencephalography targeted for all ages including newborns (André-Obadia et al., 2015). However, the document did not focus on the needs of NICUs.

Backman et al., (Backman et al., 2018) made interesting advances on aEEG standards, reaching a consensus among neonatologists and clinical neurophysiologists in Sweden to optimise simplified neonatal continuous aEEG recordings based on the recommendations previously published by the ACNS. Their work shows that with simplified aEEG/EEG procedures, it is possible to provide an overview of the development of electrocerebral activity in sick infants with limited resource costs. The protocol can be applied not only to the limited channel aEEG, but also to the multichannel continuous vEEG setting combined with some aEEG derivations. However, this document does not offer a comprehensive set of alternative EEG/aEEG recommendations (methods and timing) applicable to the diagnosis and monitoring of the principal neonatal conditions from a minimum set of options to the gold standard of care adaptable to the local resources.

4. Results: Consensus statement on EEG and aEEG assessment and monitoring

Our consensus statement on neonatal EEG and aEEG is divided in the following paragraphs: hypoxic-ischemic encephalopathy, seizures, high-risk neonatal conditions, clinical indications without urgent clinical question. A practical synopsis of our recommendations is provided in Table 4.

4.1. Hypoxic-ischemic encephalopathy

4.1.1. Neurophysiological assessment protocol for neonates with HIE eligible for therapeutic hypothermia

A) **Gold Standard:** vEEG for at least 30 minutes.
B) **Alternative Option**: aEEG for at least 30 minutes.

Note: Whenever there are interpretative doubts with aEEG, especially in case of discordance with the clinical features and decisive impact on clinical decisions, vEEG should be requested.

4.1.2. Background scale for assessing neonatal encephalopathy by EEG or aEEG

Among the different available scales, we first relied on the scale for EEG proposed by Murray et al., (Murray et al., 2009) and the scale for aEEG proposed for Hellstrom-Westas (Hellström-Westas and Rosén, 2006), as they are based on a careful background recognition.

We then decided it was important for the application of our protocol to have a simple rating system common for EEG and aEEG and easily suitable for therapeutic decisions (indication to TH) and prognostic evaluations. The common scoring system we propose here has the advantage of making EEG and aEEG evaluations comparable in the same patient in consecutive evaluations or among different patients for both clinical and research purposes. It is based on 4 points from normal/slight abnormal (score 0) to very severely abnormal (score 3).

4.1.2.1. Background scale for EEG (see Fig. 1). 0 = Normal or slightly abnormal EEG (N): continuous background pattern with normal physiologic features according to the current gestational age and recorded behavioral states (subscore N +); or mild abnormal EEG: continuous background pattern with slightly abnormal activity, such as mild asymmetry, mild voltage depression, or poorly defined sleep-wake cycle (SWC) (subscore N-);.

1 = Moderately abnormal EEG (M): discontinuous activity with inter-burst interval (IBI) of < 10 s, no clear SWC;

Table 4
Summary table of the consensus protocol for neonatal vEEG and aEEG and list of neonatal high-risk conditions.

1. Hypoxic-Ischemic Encephalopathy (HIE)

ENCEPHALOPATHY GRADING BEFORE TH
GOLD STANDARD METHOD: vEEG $\geq$ 30 minutes
ALTERNATIVE METHOD: aEEG $\geq$ 30 minutes
When there are doubts, request vEEG
MONITORING DURING TH
GOLD STANDARD METHOD: continuous vEEG
In case of storage memory limitations, switch the video recording off after the first 60–90 minutes; restart it in case of paroxysmal episodes needing definition.
ALTERNATIVE METHOD: continuous aEEG
MONITORING DURATION
Monitor during all TH period (72 hours) and during the rewarming day (a total monitoring of 96 hours).
N.B. The first 24 hours and the rewarming hours are higher risk hours for seizures. Continuous monitoring provides valuable information on prognosis. If there are doubts at aEEG, especially in case of decisive impact on clinical decisions, vEEG should be requested and performed as soon as possible. In any case, at least a standard vEEG is recommended after rewarming.

2. Suspected Seizures

SEIZURE DIAGNOSIS
GOLD STANDARD METHOD: Continuous vEEG for the time needed to register paroxysmal episodes (up to 24 hours).
ALTERNATIVE METHOD: Standard vEEG for at least 60–90 minutes, followed by aEEG (up to 24 hours).
Whenever vEEG cannot be initiated in a short time, start aEEG immediately. Assessment will be completed by vEEG as soon as possible
SEIZURE MONITORING AFTER DIAGNOSIS
GOLD STANDARD: Continuous vEEG combined with aEEG for 24 h from the last seizure.
In case of storage memory limitations, switch the video recording off after the first 60–90 minutes; restart it in case of paroxysmal episodes needing definition
ALTERNATIVE METHOD: Continuous aEEG for at least 24 h and sequential standard vEEG in the following days.
N.B. Whenever there are doubts on aEEG, request standard vEEG.

3. Brain Monitoring in high risk neonates*

GOLD STANDARD: Continuous vEEG combined with aEEG for 24 hours (monitoring time to adjust according to the specific situation)
In case of storage memory limitations, switch the video recording off after the first 60–90 minutes; resume it in case of paroxysmal episodes needing definition
ALTERNATIVE METHOD: aEEG for 24 hours.
N.B. In case of seizures, particularly if uncertain, request vEEG. When seizure are difficult to recognise on aEEG, prolong vEEG for hours or complement aEEG with sequential standard vEEG in the following days until seizure control is reached.

* *LIST OF HIGH-RISK CONDITIONS (in addition to Hypoxic-ischemic encephalopathy)*
- Meningoencephalitis
- Intracranial haemorrhage
- Ischemic stroke
- Sinovenous thrombosis
- Inborn errors of metabolism
- Disorders of vigilance or other signs of central neurological impairment
- Apnea of unknown origin or other paroxysmal vegetative manifestations
- Sepsis and severe infections (chorioamniositis, HSV, etc)
- Cerebral malformations
- Genetic syndrome with cerebral involvement (certain or suspected)
- Cardiac defects requiring surgery
- Severe lung disease
- Extracorporeal Membrane Oxygenation (ECMO)
- Use of sedation or neuromuscular blockers
- Prematurity with very low birth weight

* N.B. Neurophysiological monitoring is decided by the caring physicians on the basis of the specific patient risk estimate, not automatically due to the presence of a listed condition

4. Evaluation of brain activity for all clinical indications without urgent clinical question
GOLD STANDARD: vEEG for 60–90 minutes
N.B. aEEG is not recommended. When brain activity needs to be well studied, a simplified method such as aEEG is not appropriate to recognise minimal changes or EEG typical features.

EEG, Electroencephalography; vEEG, video-electroencephalography; aEEG, amplitude-integrated EEG. HIE, Hypoxic-ischemic encephalopathy; TH, Therapeutic hypothermia.

2 = Severely abnormal EEG (S): discontinuous activity with IBI of 10–60 seconds, very severe background attenuation of < 10 μV, no SWC;

3 = Very severely abnormal EEG (VS): inactive EEG or very severe discontinuity with IBI of > 60 s.

4.1.2.2. Background scale for aEEG (see Fig. 2). 0 = Normal or slightly abnormal aEEG (N): continuous activity with aEEG lower (minimum) amplitude around 5 and 10 μV and maximum amplitude 10–25 (50) μV, with specific values adjusted for gestational age and behavioral state. The sub score N + or N- described with EEG is more difficult to distinguish with aEEG in the first hours after birth, but with a sufficient prolonged monitoring a distinction could be made by the recognition of a well-defined or poorly defined sleep-wake cycle (SWC) .

1 = Moderately abnormal aEEG (M): discontinuous background with inferior margin of aEEG below 5 μV, and superior margin above 10 μV;

2 = Severely abnormal aEEG (S): Burst-suppression aEEG with a marked discontinuous background with no variable amplitude inferior margin, at around 0–2 μV and bursts with amplitude often > 25 μV (BS) or low voltage continuous aEEG around-below 5 μV (LV).

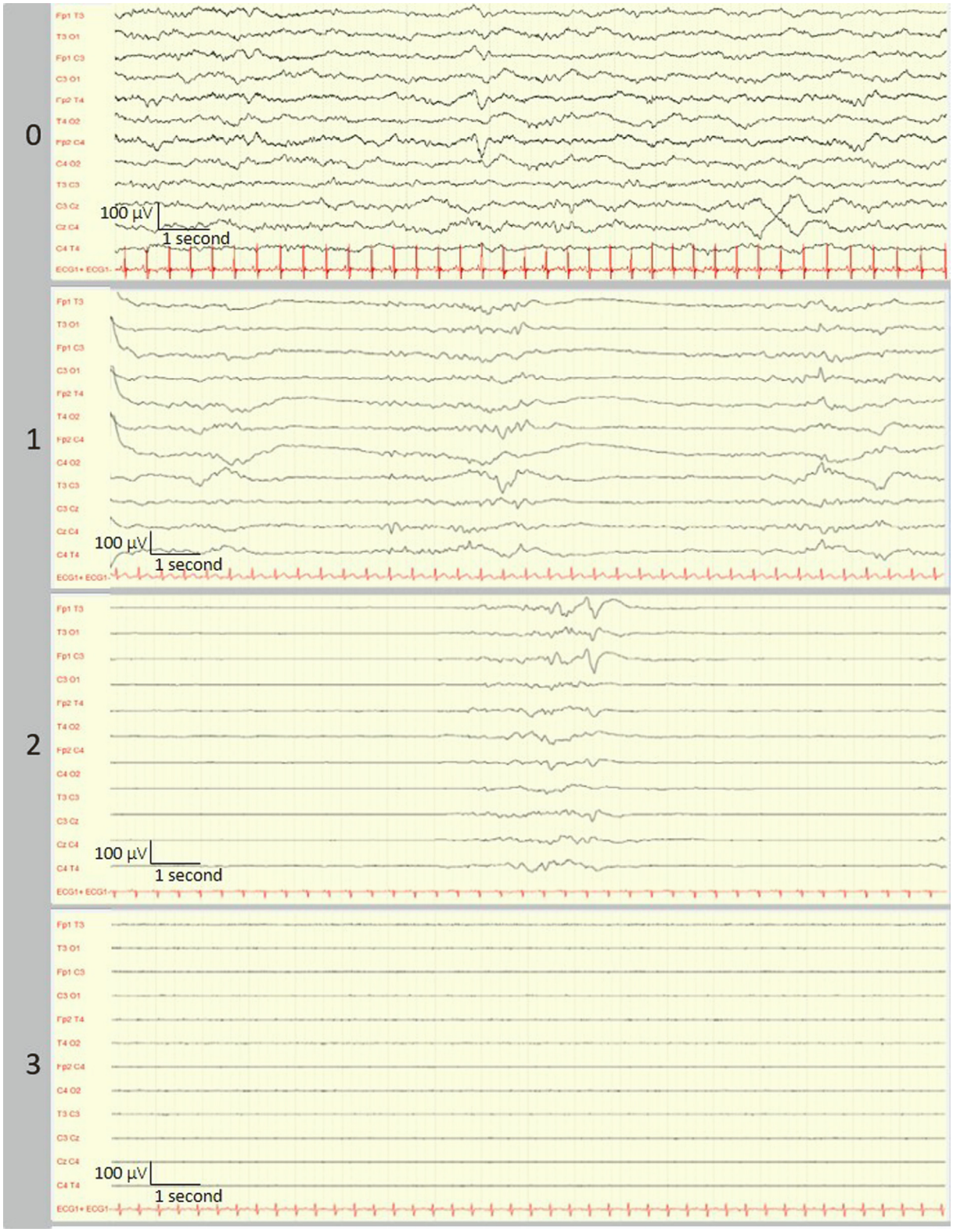


Fig. 1. EEG examples of the INNESCO background scale score for grading neonatal encephalopathy. 0, normal or slightly abnormal EEG (N); 1, moderately abnormal EEG (M); 2, severely abnormal EEG (S); 3 very severely abnormal EEG (VS). EEG, Electroencephalography.

3 = Very severely abnormal (VS): flat aEEG or mainly flat with rare bursts.

4.1.2.3. Notes regarding the application of EEG/aEEG background scale for HIE. Neonates with acute HIE having moderate to very severe EEG or aEEG abnormalities (score 1, 2 or 3) should receive therapeutic hypothermia (TH) within 6 hours of life. Seizures are uncommon at the baseline EEG or aEEG, whereas they are more common during acute HIE monitoring. When present at baseline, seizures are a sign of a brain injury that occurred several hours

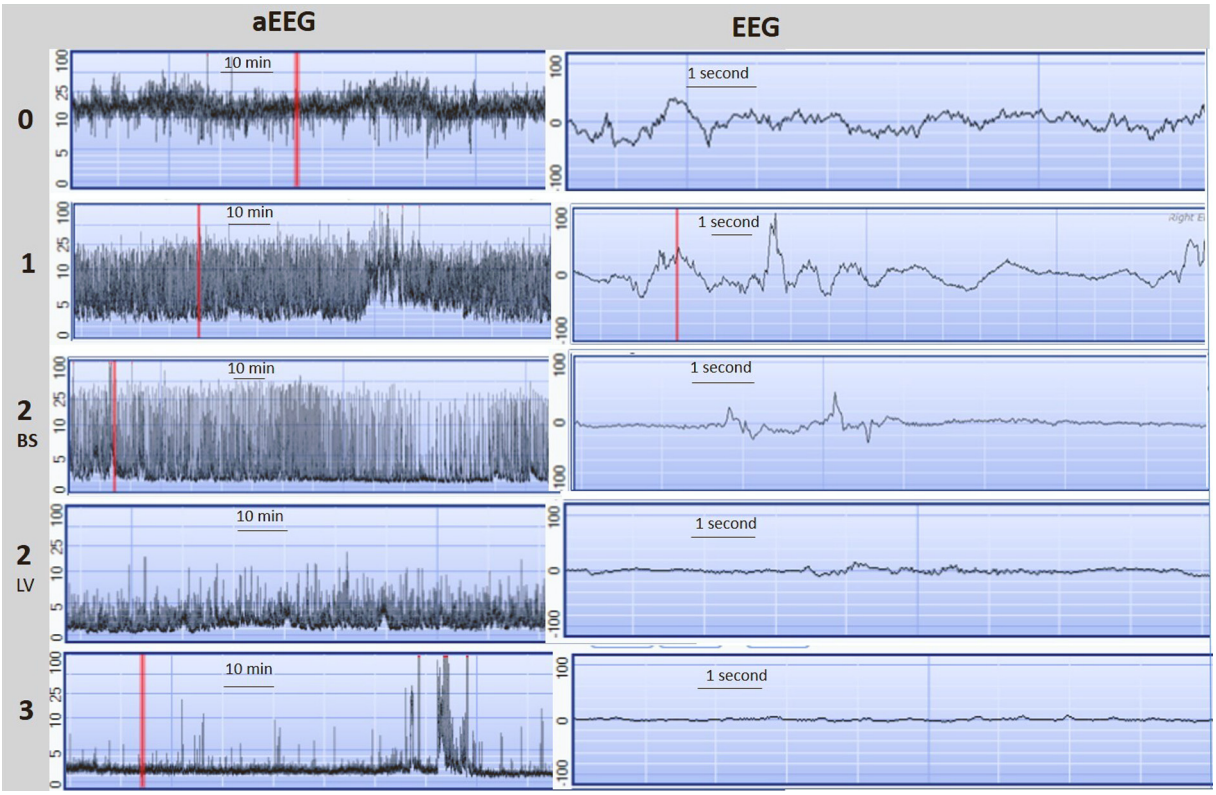


Fig. 2. aEEG examples of the INNESCO background scale score for grading neonatal encephalopathy. In left column are the aEEG examples, whereas in the right column are the corresponding EEG traces. 0, normal (N); 1, moderately abnormal (M) with discontinuous pattern; 2, severely abnormal (S) with the burst-suppression pattern variant (BS) and the low voltage continuous pattern variant (LV); 3, very severely abnormal (VS), with flat trace (or inactive trace). EEG, Electroencephalography; vEEG, video-electroencephalography; aEEG, amplitude-integrated EEG.

before birth. In contrast to single or recurrent seizures, status epilepticus (SE) may impede correct EEG or aEEG background evaluation. So, SE should be promptly recognised and indicated separately ('SE'), and background scoring is better applied after SE control. The description of aEEG/EEG background score evolution up to the rewarming day contributes to the prognosis definition (according to the timing of amplitude recovery – within 48 hours or after - and sleep-wake cycle recovery – within 96 hours or after-).

The evaluation of aEEG should be performed on the interhemispheric trace (P3-P4), ensuring to have a correct inter-electrode distance, low impedances, and no significant interfering biological artifacts as muscle activity and high frequency oscillation may affect the lower margin and cause the so called drift of the baseline. aEEG findings should be always verified on the corresponding EEG trace to avoid misinterpretations.

4.1.3. Monitoring protocol for neonates with moderate-severe HIE undergoing TH

A) Gold Standard: continuous vEEG associated with two derived aEEG trend channels during the three days of hypothermia and the rewarming day.

As there may be problems with continuous video recordings (limited memory space) in long-term monitoring, video may be switched off after the first 60–90 minutes and switched on whenever significant episodes occur.

B) Alternative Option: continuous aEEG during hypothermia and the rewarming day. Whenever there are interpretative doubts on aEEG, especially in case of decisive impact on clinical decisions as any suspected seizures, vEEG should be performed as soon as possible.

In any case at least one standard vEEG after rewarming is recommended to analyse the background activity or disclose unusual features that may help in personalizing the plan of future interventions in the specific patient. In fact, some authors have shown that rewarming affects the background EEG activity of neonates with HIE submitted to TH, and this seems to indicate some degree of neurological deterioration related to the evolution of the brain injury with different features between moderate and severe HIE (Birca et al., 2016).

4.2. Epileptic seizures

4.2.1. Clinical suspicion of epileptic seizures

Epileptic seizure should be suspected in cases of neonates with paroxysmal manifestations that persist after either holding, repositioning or awaking the newborns. Suspected manifestations may be the following:

- Motor manifestations such as focal or multifocal clonic jerks or tonic posturing;
- Paroxysmal and sustained dystonic posture;
- Myoclonic jerks: generalized, focal, segmental, erratic;
- Ocular deviations or nystagmus;
- Motor automatism such as tongue protrusion or lip smacking, automatic atypical suction, automatic limb movements such as pedaling or boxing;
- Stereotyped movements of sudden onset without external stimuli with a repetitive or periodic evolution;
- Vegetative instability of unknown origin (apneas without a clear obstructive origin, recurrent cyanosis, flushing, tachycardia, rapid changes of the blood pressure, pallor).

4.2.2. Neurophysiological assessment protocol for suspected epileptic seizures

A) **Gold standard:** vEEG associated with two derived hemispheric trend channels (aEEG being the most commonly used EEG trend signal in NICU) for the time needed to register the paroxysmal episodes needing definition (usually up to 24 hours).
B) **Alternative Option**: vEEG for 60–90 minutes (or more hours whenever possible) followed by aEEG (up to 24 hours). When it is not possible to immediately perform vEEG, aEEG should be immediately started and neurophysiological assessment will be completed as soon as possible with a standard vEEG.

4.2.3. Neurophysiological monitoring protocol for the assessment of response to antiseizure medication

A) **Gold Standard:** continuous vEEG associated with at least two derived aEEG trend channels for at least 24 hours from the last seizure. As there may be problems with long video recordings (limited storage space), video registration may be switched off after the initial assessment (the first 60–90 minutes) and switched on whenever significant episodes occur.
B) **Alternative Option:** continuous aEEG for 24 hours. Whenever there are interpretative doubts, vEEG should be requested and performed as soon as possible.

Note: in cases of epileptic seizures with electrical features that are difficult to recognise on aEEG (for example short or low-amplitude seizures, or focal seizures far from standard electrode positions, or contaminated by artifacts) continuous vEEG monitoring is preferred. Whenever it is not possible, standard duration vEEG (60–90 minutes) may identify the specific active epileptic focus/foci, helping to customise the aEEG electrode position for continuous monitoring (Bourez-Swart et al., 2009).

4.3. Neurological high-risk conditions

Neurophysiological brain monitoring should be considered in neonates at high risk of brain injury. The decision to start monitoring a neonate is not taken automatically for the mere presence of a certain condition, but it is a clinical judgement based on the specific risk estimate for the patient. See high risk neonatal conditions in Table 4.

4.3.1. Technique and timing to monitor neonates at high risk

A) Gold Standard: Continuous vEEG associated with at least two derived aEEG trend channels for at least 24 hours.

Note: as there may be problems with long vEEG recordings (limited storage space), video registration may be switched off after the initial assessment (the first 60–90 minutes) and switched on whenever significant episodes occur.

B) Alternative Option: aEEG for 24 hours. Whenever there are interpretative doubts, vEEG should be requested and performed as soon as possible.

Note: If vEEG or aEEG continuous monitoring is not possible for more than 60–90 minutes, standard repeated vEEG examinations in consecutive days should be performed.

4.3.2. Time monitoring specifications for neonates at high risk

In the neonates at high risk, brain monitoring could be performed for a period longer than 24 hours when requested by the specific clinical situation. For example, after cardiac surgery, increased seizure risk is spread in the time range from 10 to 36 hours. However, clinicians can decide to reduce the presumed 24-hour monitoring time in cases where the specific risk in a certain patient is estimated low on the basis of clinical updates and baseline EEG or aEEG assessment.

4.4. Clinical indications without urgent clinical question

Some brain disorders identified at birth may be due to fetal developmental brain disorders or remote fetal acquired brain injuries. EEG features at birth depends on the severity, timing, and evolution of the specific brain disorders (André et al., 2010; Pavlidis et al., 2017).

During the chronic evolution of a remote prenatal acute brain injury, many abnormalities typical of the acute stage (as EEG activity depression) tend to disappear. EEG abnormalities of the chronic stages are often characterised by a dysmature or disorganised background (Lamblin et al., 1999; André et al., 2010; Pavlidis et al., 2017). Background abnormalities may also be found in cases of metabolic or structural encephalopathy. In case of significant focal brain lesions, slow focal or paroxysmal abnormalities, and asymmetry of physiological graphoelements or background activity may be observed. In case of cerebral malformation as cortical dysplasia, unusually large and/or fast activity can also be encountered (Dalla Bernardina et al., 1996). These neurophysiological findings, together with clinical and other laboratory and instrumental features (brain ultrasound, brain MRI) contribute to addressing the etiology, treatment and prognosis. In future EEG computerised automatic analysis could increase the capacity to detect and quantify these alterations for diagnostic and prognostic purposes.

4.4.1. Neurophysiological assessment of electrocortical organisation in neonates without urgent indication

A) **Gold Standard:** vEEG for 60–90 minutes.

Note: In the absence of urgent indications, aEEG is not an appropriate method for a careful evaluation of electrocortical background activity and identification of normal and abnormal focal activities and graphoelements. Alterations are often mild and aEEG easily misses them. Complete sleep-wake cycles should always be registered by vEEG for a thorough evaluation of possible stage-dependent alterations. Therefore, vEEG registration should be prolonged for the time needed to register all the sleep-wake cycles. If seizures are observed during this EEG assessment, the neurophysiological monitoring protocol presented for seizures should be applied.

4.5. Organisational measures to promote neuromonitoring in NICUs

Based on epidemiological considerations among the INNESCO working Group, it was assumed that almost 1% of neonates might need neuromonitoring (aEEG or vEEG). Therefore, continuous neurophysiological monitoring should be available in all level NICUs.

A reduced number of neonates may necessitate an advanced neurocritical care involving continuous vEEG available around the clock together with advanced neuroradiological, neurological, neurosurgical consultation. These advanced neurocritical care facilities should be available at least in the regional NICU Hubs to manage the more complicated neurological patients that often converge in these centres.

The following organisational measures may be used to reach the goals of the present proposal:

- Ensuring availability of around-the-clock equipment for at least the minimal neurophysiological monitoring with aEEG devices having aEEG/EEG channels and seizure detection algorithms (SDA) used by trained personnel in all NICUs;
- Ensuring that all the NICUs not having autonomous vEEG facility collaborate with Clinical Neurophysiology Services. This collaboration should be well established in order to have an efficient availability of equipment, technicians and specialists for interpreting neonatal vEEG at least during the day hours;
- Identification of regional NICU Hubs for advanced neonatal neurocritical care programs where both vEEG and aEEG long-term monitoring (with the related equipment and expert personnel) may be available around the clock;
- Promotion of teleneurophysiology to have the possibility of remote-access to neuromonitoring inside the institution and among different institutions (promoting professional relationship between Spoke and Hub NICU centres and their neurophysiological services by telemedicine technologies);
- Promotion of multicentre networks of neurophysiologists specialising in vEEG to develop vEEG on call shifts available to different centres around the clock;
- Periodic training programs on aEEG and vEEG for all NICU staff with attention to involvement of the entire multidisciplinary team: neonatologists, paediatric neurologists, neurophysiologists, technicians and nurses. Online video teaching modules can be also used to facilitate this task.

4.6. Legal implications related to the brain monitoring

The timely identification of relevant pathological events by neurophysiological techniques (aEEG or vEEG) depends on the applied neuromonitoring model (specific techniques used and competent personnel shifts).

Parents should be informed that aEEG and vEEG use has improved neonatal care and prognosis compared to clinical care without any neurophysiological monitoring.

No technique has however demonstrated 100% accuracy in the real-life context. There are complex situations where some electrical and clinical findings may be correctly interpreted a posteriori when the stereotyped nature is confirmed over time with repeated or prolonged aEEG or vEEG registrations. Treatments can also reduce the most typical features. Sometimes a review conducted hours or days after the aEEG or vEEG recordings by specialists may evidence previously undiagnosed events. Also, in cases where neurophysiological diagnosis has not been prompt, the caring team and parents should remember that the availability of neurophysiological monitoring is helpful for a following better treatment and prognostication.

5. Discussion

There are consistent differences in the specific neurophysiological assessment and monitoring practices in the NICUs around the world, but in the last years, there has been an undoubtable trend toward a higher implementation of EEG and aEEG both as diagnostic and monitoring tools.

Two reasons have determined these changes. First, after TH was established as the standard of care for HIE between 2005 and 2010, recourse to aEEG or EEG as neurophysiological assessment tools before and during cooling was largely accepted by most NICUs as the reference standard of care in USA (Wusthoff et al., 2018) and in European countries (Hagmann et al., 2011; Gerstl et al., 2015).

The second important reason is the increased awareness of the importance of EEG and aEEG for diagnosis, management, and prognosis of neonates with seizures and those at high neurological risk among paediatric neurologists and neonatologists (Boylan et al., 2010; Vento et al., 2010; Shah et al., 2015; Dilena et al., 2019). Furthermore, although aEEG and EEG monitoring is currently more popular than 20 years ago, few neonatologists feel confident in interpreting EEG or aEEG (Boylan et al., 2010; Shah et al., 2015). Availability of competent round-the-clock personnel to record and interpret continuous vEEG is still limited to a small number of neuro-oriented NICUs around the world (Buttle et al., 2019). EEG is mostly provided by neurophysiologists or paediatric neurologists and usually needs technicians for recording. As a consequence, the aEEG is considered to be a user-friendly alternative to EEG, directly provided by neonatologists and promptly available, has enormously spread in the previous years, becoming a basic standard of continuous neuromonitoring in most NICUs in developed countries. However, the consequences of poor training in aEEG management should be seriously considered and not underestimated in terms of inappropriate clinical decisions. A survey (Shah et al., 2015) showed that only 9% of respondent neonatologists felt confident interpreting aEEG traces, and only 55% of them attended a formal course or hospital training. Attendance of a formal course and the collaboration with neonatal EEG experts to review cases with challenging recordings is recommended to improve the operator confidence. Online video teaching modules should be used to facilitate the task (Bonifacio and Van Meurs 2019).

The data coming from the above indicated survey articles and the related discussions within our national network similar to the situation shown by literature around the world have convinced us that some gaps need intervention. First of all, there is a need for applicable guidelines that may be easily adapted to the local and regional health care network resources. The second important issue is the educational training. Periodic training programs are necessary for the entire neonatal staff. They should be performed by and for all the neonatal neurocritical monitoring multidisciplinary team members (neonatologists, paediatric neurologists /neurophysiologists, nurses and technicians). The third issue is the need to implement national health care strategies to establish around-the-clock neurophysiological facilities to adapt according to the specific NICU role in the neonatal health care regional network (Hub-and-Spoke model). Availability of around-the-clock continuous EEG facilities (both vEEG and aEEG equipment, technicians, neonatal EEG experts, EEG remote review, neurology consultation) should be implemented in every regional referral NICU (Hub), or in the NeuroNICUs, where the neonates with more severe neurological problems are concentrated. However, not all neonates needing neuromonitoring can be transferred to Neuro-NICUs. A minimum standard of neurocritical care (aEEG continuous monitoring, daily vEEG services) should therefore be available in every tertiary NICU (Spoke), that should possibly have access to teleconsultation with the Hub neurological services when needed. To address the current gap, it is crucial to promote a strong collaboration among NICUs of the same network and their supporting services offering neonatal EEG and neurological/neurophysiological consultation with the aim to build an efficient local and regional interdisciplinary team, taking advantage of tele-neurophysiology technologies.

INNESCO working group discussions on the contribution of aEEG and EEG use in neonates with HIE have highlighted that EEG or aEEG should be used:

1) To establish the severity of HIE and confirm indication to TH at baseline (within 6 hours from birth);
2) To monitor brain function and establish the prognosis;
3) For early identification and prompt treatment of epileptic seizures.

Many NICUs of our network perform aEEG monitoring during hypothermia and rewarming, and complete with conventional

EEG as soon as possible, and when needed for clinical doubts. Few NICUs in our network use systematically prolonged continuous vEEG monitoring for all the TH period as indicated by other neurocritical care programs (Bashir et al., 2016). At the moment few centres in our network also add other neurophysiological tests as evoked potentials to improve prognostication (Suppiej et al., 2010; Lori et al., 2011, 2017; Cainelli et al., 2018).

On the topic of neonatal seizures, our network discussed the limits of the conventional definition of electrographic seizure as a sudden and abnormal discharge characterised by an electric repetitive pattern with amplitude > 2 μV and duration more than 10 seconds, with a typical evolution in frequency, morphology, and amplitude during the seizure (Clancy et al., 1988). It was also highlighted that discharges < 10 seconds should be observed with great attention as they are associated with a risk of developing seizures. Some typical seizures have a shorter duration than 10 seconds. For example epileptic spasms (duration 0.5–2 seconds) and epileptic myoclonus (duration less than 100 ms). Also, some atypical patterns in aEEG should be remembered. If most seizures are characterised at aEEG by a steep increase of the inferior / superior margin with a hump-shape for a single seizure or a sawtooth-shape for highly recurrent seizures (Hellström-Westas et al., 2008), in some rare conditions (as in KCNQ2 epileptic encephalopathy) seizures have a different aspect with a shape of an inverted hump (Vilan et al., 2017).

Concerning the neonates at high risk, our network recognised the potential of aEEG or EEG within the first 7 days of life for preterms as a predictor of outcome, but since this practice is very costly and no high-quality studies are still available (Fogtmann et al., 2017), no clinical recommendation can be provided at the moment. As no systematic reviews specifically addressing the topic of EEG/aEEG monitoring role in other category of high-risk neonates were available, we performed additional discussions based on the clinical experience and reference library articles of our network members. Electrographic seizures with poor manifestation have been recognised as very common in critically ill neonates with many kinds of acute encephalopathy (Abend et al., 2013). Many neonatal categories have been described as being at high risk for seizures such as neonates with stroke (risk of seizures 90%,), meningitis (risk 85%), neonates undergoing extracorporeal membrane oxygenation (risk 10–30%), or those with congenital heart disease, metabolic disorders such as hypoglycaemia and inborn errors of metabolism (Abend et al., 2013). Poor seizure clinical manifestations are particularly frequent in premature babies with intraventricular haemorrhage (IVH) especially with GA < 32 weeks (Spagnoli et al., 2018). Acquired etiologies include central nervous system or systemic infections, brain haemorrhage, ischemic stroke, trauma, transient metabolic diseases (i.e. hypoglycaemia in low birth weight infants, hypocalcaemia, hypomagnesaemia, sodium imbalance in very low birth weight neonates, drug withdrawal or poisoning) (Spagnoli et al., 2018). In the population of neonates at high risk of seizures and neurodevelopmental compromise, it is useful to apply neuromonitoring tools and multidisciplinary care including continuous vEEG or aEEG (Bonifacio et al., 2011; Pisani and Spagnoli, 2016a). To ensure a good diagnostic accuracy, continuous aEEG should be used together with repeated standard multichannel vEEG in the setting of a multi-disciplinary approach (Vento et al., 2010; Hellström-Westas et al., 2015).

6. Conclusions

The neurophysiological protocol proposed here is an expression of a comprehensive multidisciplinary working group that met for two years and half to find a synthesis between different approaches, recognising pros and cons of each choice in different clinical contexts and the value of a clever complementary use of vEEG and aEEG.

In the difficult task of establishing the best, cost-effective neurophysiologic monitoring protocol for neonates, protocol feasibility and applicability in the specific local setting with variable resources for the different clinical indications and the specific patient features need to be considered in addition to the sensitivity and specificity of the alternative techniques.

This consensus document is not intended as a mandatory standard of care, but as a structured set of alternative recommendations applicable according to the specific centre and patient features. It intends to promote the best possible standard of care in the current clinical practice outside research NICU or NeuroNICUs in patients with different clinical profiles. This will be made possible by a careful complementary use of the available techniques, the collaboration of the available professional competencies (locally or by telemedicine) within and between different collaborating centres on the basis of an effective multidisciplinary approach.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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