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Scoping Review on the Diagnosis, Prognosis, and Treatment of Pediatric Disorders of Consciousness

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Abstract

Background and Objectives. Comprehensive guidelines for diagnosis, prognosis, and treatments of disorders of consciousness (DoCs) in pediatric patients have not yet been released. We aim to summarize available evidence for DoCs with >14 days duration, to support the future development of guidelines for children aged 6 months to 18 years.

Methods. This scoping review was reported based on PRISMA-ScR guidelines. A systematic search identified records from 4 databases: PubMed, Embase, Cochrane Library, and Web of Science. Abstracts received 3-blind reviews. Corresponding full-text articles rated as “in-scope” and reporting data not published in any other retained article (i.e., no double reporting) were identified and assigned to 5 thematic evaluating teams. Full-text articles were reviewed using a double-blind standardized form. Level of evidence was graded, and summative statements were generated.

Results. On November 9, 2022, 2167 documents had been identified; 132 articles were retained, of which 33 (25%) were published over the last 5 years. Overall, 2161 individuals met the inclusion criteria; female patients were 527 of 1554 (33.9%) cases included, whose sex was identifiable. Of 132 articles, 57 (43.2%) were single case reports, and only 5 (3.8%) clinical trials; the level of evidence was prevalently low (80/132; 60.6%). Most studies included neurobehavioral measures (84/127; 66.1%), and neuroimaging (81/127; 63.8%); 59 (46.5%) were mainly related to diagnosis, 56 (44.1%) to prognosis, and 44 (34.6%) to treatment. Most frequently used neurobehavioral tools included the Coma Recovery Scale-Revised, Coma/Near Coma Scale, Level of Cognitive Functioning Assessment Scale and Post-Acute Level of Consciousness scale. Electroencephalography, event related potentials, structural computerized tomography and Magnetic Resonance Imaging were the most frequently used instrumental techniques. In 29/53 (54.7%) cases DoC improvement was observed, which was associated to treatment with amantadine.

Discussion. The literature on pediatric DoCs is mainly observational, and clinical details are either inconsistently presented or absent. Conclusions drawn from many studies convey insubstantial evidence, and have limited validity, and low potential for translation in clinical practice. Despite these limitations, our work summarizes the extant literature and constitutes a base for future guidelines related to diagnosis, prognosis and treatment of pediatric DoCs.

Keywords. Pediatric disorders of consciousness; unresponsive wakefulness syndrome/ vegetative state; minimally conscious state; diagnosis; treatment; prognosis; children; adolescents.

Introduction

Disorders of Consciousness (DoCs) including coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious state (MCS) have been predominantly described in adults. Coma is a state of unresponsiveness in which the eyes are closed and there is no arousal upon stimulation¹. VS/UWS is characterized by periods of wakefulness without awareness of self and/or environment.² MCS includes minimal but reproducible behavioral signs of consciousness,³ without (MCS-) or with some evidence of language function (MCS+) (see definitions in eAppendix 1 of Supplement). DoCs result from insult and disruption to brain systems that regulate arousal and awareness. A DoC for ≥ 28 days after brain insult or disruption is described as a prolonged DoC.⁴

In the last few years literature has been summarized and guidelines developed for diagnosis, prognosis, and treatment of patients with prolonged DoCs. Guidelines were developed by groups in the United States,⁴ United Kingdom,⁵ and Europe.⁶ These guidelines provide little support for evaluation and management of pediatric DoCs, for whom dedicated literature is lacking overall. The European and UK guidelines were based entirely on adults. While Giacino and colleagues included pediatric literature in their systematic review,⁴ only 3/18 recommendations focused on children. One provides indications for clinical practice, and two recommend counselling to families on the lack of prognostic and therapeutic evidence.

Studying children with DoCs presents multiple challenges due to small sample sizes at single sites and heterogeneity in age and etiology of injury. Assessment of young children with DoCs is difficult, due to immature nervous systems and limited repertoire of developmental skills.^{7,8} Although existing literature on DoCs has focused primarily on adults, in 2022, a systematic search⁹ on neuroimaging and neurophysiological methods for diagnosis and prognosis of children with DoCs found preliminary evidence for application of event-related potentials to support diagnosis. A commentary also reviewed treatments available to this population.¹⁰

In this context, a working group of expert members of the Special Interest Group on DoC of the International Brain Injury Association (IBIA-DoC SIG, <https://www.internationalbrain.org/membership/groups/disorders-of-consciousness->

special-interest-group) conducted a scoping review on diagnosis, outcome/prognosis, and treatment of pediatric DoCs. The aim was to identify and summarize existing literature on diagnosis, assessment tools, prognostic factors, and treatment approaches for pediatric DoCs. Analyzing the scope of this literature is a preliminary step in development of evidence-based guidelines on evaluation and management of pediatric DoCs.

Materials and Methods

Primary and secondary outcomes

Primary outcomes include systematic identification and summary of published evidence describing diagnostic and outcome/prognostic methods of assessment and therapeutic management of children with DoCs, and generation of summative statements. We considered DoCs lasting for ≥ 14 days (rather than 28 days⁴) to maximize inclusion of available cases and cohorts, given the paucity of literature on pediatric DoCs.¹¹ We considered peer-reviewed published documents including novel data describing children and adolescents aged between 6 months and 18 years at onset of a neurological injury or insult resulting in DoC. Secondary outcome is the identification and description of levels of evidence associated with reported results in selected documents. This scoping review was reported in accordance with PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines.¹¹

Eligibility criteria

Full-text articles had to include novel data from children and adolescents (i) aged 6 months through 18 years at onset of DoC, (ii) with DoC (including terms such as coma, VS/UWS, MCS, emergence from MCS [eMCS] or $GCS \leq 8$), (iii) with DoC duration ≥ 14 days, and (iv) with non-neurodegenerative conditions.

Search strategy and selection criteria

To identify potentially relevant studies, four equivalent logic searches were performed in 4 databases (PubMed, Embase, the Cochrane Library, and Web of Science) on September 28, 2019 (Sintax is available in eAppendix 2 of Supplement). Searches included terms related to DoCs (e.g., vegetative state), age (e.g., child, adolescent), and assessment tool or treatment (e.g., electroencephalography). They

comprised terms disused in the field (e.g., apallic state). We considered the logic union \cup (i.e., all documents in unique copy) of the studies. Relevant references from previous recommendations for DoCs in adults⁴ were double-checked, for quality control. Two additional identical searches were repeated in the 4 databases on August 15, 2021 (manuscript preparation), and on November 9, 2022 (manuscript revision), to identify recent studies (Figure 1).

Data identification, screening, and eligibility verification

Three-blind abstract reviewers identified in-scope documents, by verification of eligibility criteria. Full-text articles were assigned to one of 5 thematic teams. Themes were identified a-priori, based on previous independent work^{6,12} and logic search terms: diagnosis, prognosis, neurobehavioral techniques, neuroimaging, and neurophysiology techniques. Team members received preliminary training on inclusion/exclusion criteria, data collection process, and double-blind procedure before starting the review process (Methods details are available in eAppendix 3 of Supplement). Each full-text article was reviewed double-blind using a standardized abstraction form. Disagreements were resolved conservatively by consensus. For selected studies (i.e., eligible studies satisfying inclusion criteria), data were collected double-blind including the study design and aim, patients' demographic information at group/subgroup/individual level, diagnosis, clinical assessment and support needed, treatment, behavioral, imaging, neurophysiological, and biological examinations, conclusions of the study, sources of bias and evidence (eAppendix 4). For relevant articles, QUADAS-2¹³ and PROBAST^{14,15} checklists were completed. Full-text articles written in Italian, French, Portuguese, Japanese, Russian, Spanish were reviewed by one expert only. Each informative document was graded per level of evidence according to Cochrane framework, and associated to high/medium/low evidence based on abstraction form questions Q67-Q82, QUADAS-2 and PROBAST (Results available at <http://doi.org/doi:10.105281/zenodo.7997317>).

Depending on thematic contents of each article, documents were re-evaluated by one or more teams. Teams were instructed to examine each article aim and main topic of discussion, to identify similarities between articles, and to cluster articles into subthemes (including any subthemes related to treatment). At least one team discussed each retained article, highlighted main observations and conclusions, and

produced a critical summary of articles within each subtheme. Next, each team generated summative statements of clustered literature (eAppendix 3; <http://doi.org/doi:10.105281/zenodo.7997317>); these were subsequently merged by the lead authors, and iteratively reviewed by all authors until consensus. A set of data elements to be reported in pediatric DoCs research was identified through data mining and item discussion until agreement. Detailed description of the search, screening process, data extraction, assignment of articles to themes and subthemes, and framework for generation of summative statements can be found in eAppendices 3 and 4 of supplement.

Level of evidence

For each summative statement, highest level of single-study supporting evidence was rated as high (+++), if supported by >1 controlled clinical trial; medium (++), by >1 robust well-designed cohort/group study; and low (+), by case studies, series, or studies with high risk of bias only (Adapted from¹⁶, Tables 1-3). Number of supporting documents and an *evidence score* were calculated.

Standard Protocol Approvals, Registrations, and Patient Consents

Ethics approval was not required because of the nature of the study (no human or animal subjects).

Data availability

Data generated in this study are provided as supplemental information.

According to UK research councils' Common Principles on Data Policy, and according to Wellcome Trust's Policy on data, software and materials management and sharing, all data supporting this study are openly available at <http://doi.org/doi:10.105281/zenodo.7997317>.

Results

Literature identification and selection

Initial search retrieved 776 results from PubMed; 506 from EMBASE; 84 from Cochrane; and 471 from Web of Science. After removal of duplicates *within* and *between* searches, 1486 abstracts were screened. The second search retrieved 102 additional documents, and the third retrieved 579. Overall, the *screening* phase identified 2167 documents (Figure 2; More details are available in eAppendix 5 of Supplement). Articles written in German (n=28), Chinese (n=22), Polish (n=7), Czech (n=3), Croatian, Dutch, Lithuanian, Romanian, and Serbian (n=1 each) were discarded in the screening phase, due to lack of language support by the working group. After blinded review, 132 articles were judged eligible to be retained. The selected group included 1 article in French, 5 in Japanese, 2 in Portuguese, and 2 in Russian.

Literature composition

The list of retained articles is provided in eAppendices 6 of Supplement. Of the 132 retained documents, 25% were published in the last 5 years (33/132) (Details are available in eAppendices 7 and 8). Overall, 2161 individuals met inclusion criteria (eAppendix 7); 33.9% were female patients (527/1554). Of 118 articles clearly reporting cohort age, 19 (16.1%) were on infants and/or toddlers (>6 months; ≤3 years old); 67 (56.8%) children (>3; ≤12 yo), and 32 (27.1%) adolescents (>12 yo). Etiologies included traumatic brain injury (40/132; 30.3%), hypoxic/anoxic brain injury (19; 14.4%), stroke (5; 3.8%), encephalitis of infectious and other causes (20; 15.2%), mixed (36; 27.3%), and other/unclear (12; 9.0%). Fifty-seven (43.2%) were single case reports, and 21.2% reported results from more than 20 cases. Observational studies were 56 (42.4%), and clinical trials were 5 (3.8%). Level of evidence was high in 5 (3.8%), medium in 47 (35.6%), and low in 80 (60.6%) (eAppendix 9).

Five articles were judged non-informative during qualitative synthesis, because conclusions were unrelated to DoCs, or based on cohorts that included cases <14 days. Of the remaining 127 articles, 84 (66.1%) included neurobehavioral measures,

81 (63.8%) included neuroimaging, and 53 (41.7%) neurophysiological measures. Fifty-nine (46.5%) were related to diagnosis, 56 (44.1%) to prognosis, and 44 to treatment (34.6%) (eAppendix 10). Qualitative review by expert teams revealed 6-10 subthemes within each theme (eAppendix 11-16).

Subtheme identification

Seven diagnosis subthemes were identified (eAppendix 11). The largest included articles on multimodal diagnostic approaches that used neurobehavioral assessment combined with neuroimaging and/or neurophysiological methods. Ten prognosis subthemes were identified (eAppendix 12). The largest three investigated etiology, clinical factors, and neurophysiology as predictors of outcomes. The largest treatment subtheme was pharmacology (eAppendix 13).

Main evidence

Neurobehavioral tools used most frequently included the CRS-R, CNCS, LOCFAS and PALOC-s. Among imaging techniques, structural CT and MRI were reported most frequently, although some studies described use of PET, functional MRI, and/or MR Spectroscopy. The neurophysiological technique used most frequently was electroencephalography (EEG). Other methods used included event related potentials (e.g., ERPs, SEPs, BAEPs) and polysomnography (PSG) (eAppendix 14-16 of Supplement).

Sixteen statements were created, including 8 for diagnosis, 6 for prognosis, and 2 for treatment (Tables 1-3). To increase level of evidence in future research on pediatric cases with DoCs, a set of data elements were identified which could guide reporting (Table 4).

Diagnosis

Statement 1. (++) *Definitions of states of consciousness.*

Evidence. (++) Literature investigating children and adolescents with DoCs used definitions of coma, VS/UWS, MCS, and eMCS formulated for adults. Coma is a DoC by the European guidelines,⁶ but is excluded from DoCs spectrum by other recommendations.^{3,4} The classification of VS/UWS and MCS (including MCS- and MCS+) was reported in children older than 6 years of age.^{17,18} Some evidence⁷ also

exists in younger children (mean age=2.7 years). Further research is needed to explore utility and suitability of these terms for the youngest children and those with pre-existing neurodevelopmental disabilities.

Statement 2. (++) *Behavioral assessment.*

Evidence. (++) The CRS-R was used most frequently. It was used in several single case studies, larger studies (^{19,20} and others), and combined with instrumental measurements.²¹ Only one study explored the psychometric properties of the CRS-R in children.²²

Measures with some validation in pediatric DoCs include LOCFAS (^{23–25} and others), the WNSSP,²⁶ and CNCS.^{20,27,28}

Qualitative analysis of behavior was used to characterize DoCs in children,^{7,18} based on accepted characteristics of DoC stages.

Statement 3. (++) *Very young children (<4y).*

Evidence. (++) DoC states were identified in children <4 years of age.⁷

Language skills develop rapidly over early childhood in typically developing children. In very young children thought to be in MCS, visual fixation and pursuit are commonly observed, while intelligible verbalizations and command following occur rarely.^{7,28} Age-appropriate salience, familiarity, and emotional relevance of stimuli have also been considered. When employing neurobehavioral assessment tools designed and validated on adult cohorts with very young children, some children in MCS may be inaccurately classified due to limited language development and sensorimotor limitations.⁷

Statement 4. (++) *Structural imaging.*

Evidence. We define *structural imaging* as all instrumental approaches, specialized for visualization, qualitative, and quantitative analysis of anatomical properties of the brain, including their deviation from a normative (e.g., atrophy, anatomical lesions, etc.). Acutely, structural neuroimaging was widely used to identify etiology, perform differential diagnosis, and investigate brain injury evolution²⁹; and also in

combination with neurophysiological examination.³⁰ (++) Few studies used neuroimaging to formulate a DoC diagnosis, or to characterize DoC of ≥ 14 days. After traumatic DoC diagnosis, structural neuroimaging was used to describe (partial) preservation of structures, pathophysiology, and brain areas where recovery of function can be considered.³¹ In research, structural neuroimaging was shown to assist in identifying neuroanatomical correlates of pediatric DoCs at group-level, including time-evolving relation between secondary neural damage and behavioral changes.³²

Statement 5. (++) *Electroencephalography and evoked potentials.*

Evidence. (++) In children with VS/UWS, EEG were used to confirm consciousness status when wide cortical damage presented with brain stem preservation,³³ to detect residual cortical activity and connectivity, revealing potential for improvement, and to study common DoCs complications, such as epileptic abnormalities.³⁴

Stimulation paradigms combined with ERP recordings were used to assess responsiveness in children with DoCs.²¹ Among these, auditory *oddball* (presentation of sequential repetitive stimuli, infrequently interrupted by a deviant stimulus) provided an alternative to language-based stimulation when there was doubt on the individual's capability to access instructions, commands, or language content. In general, a stimulus that is salient, emotionally relevant, and familiar increases likelihood to generate cortical electrophysiological response.³⁰ Semantic paradigms combined with ERPs assess conscious processing of words. P300 component was observed in healthy controls, and in about 50% of MCS cases, but not in pediatric VS/UWS.²¹ Presence of P300, and later mismatch negativity (MMN) component, is regarded as an indicator of high consciousness level and as predictive of favorable outcome.

Among ERPs, SEPs have been proposed as reliable instrumental biomarkers in post-acute pediatric DoCs, although they might not be observable nor repeatable in the entirety of healthy children.^{17,21} ERP paradigms in pediatric DoCs are limited by frequent movement artifacts, which sometimes require correction. The large number of repetitions necessary to obtain a reliable trace of neural responses can

occasionally cause unacceptably long acquisition times for examination, due to the patients' quick fatigability, short arousal, and frequent attention fluctuations. Sensory deficits caused by damage to sensory pathways can be an additional impeding factor.²¹

Statement 6. (++) Polysomnography.

Evidence. (++) DoCs are associated with severe alterations in sleep duration and architecture, and decreased complexity of the polysomnographic pattern.³⁵ PSG was proposed to assist in differential diagnosis of VS/UWS from hypothalamic dysfunction such as hypothalamic-induced lethargy,^{19,35} to identify temporal SWA profiles¹⁹ and the (re)appearance of sleep spindles,³⁵ and to document transitions between DoCs levels.

PSG can identify REM sleep presence, which is considered sign that conscious experience (i.e., lucid dreams) is possible.³⁵

Sleep architectures are not always representative of behavioral diagnoses, and misclassifications are estimated at 22%.¹⁹ Fluctuation between VS/UWS and MCS can be potential confounding variable; also, medications (e.g., anti-seizure) can alter sleep pattern and microstructure.³⁵ Although some sleep features might be concealed or distorted due to medications,³⁵ PSG monitoring is proposed for assessing ability of the brain to stabilize in specific stages, to switch between stages,³⁵ and to generate figures and microstructures indicative of underlying integrity of specific circuits.¹⁹ At emergence from coma, this ability can evolve quickly and it was shown to anticipate the corresponding behavioral evidence in some cases.³⁶

Scoring of PSG of children with DoCs can be qualitatively performed through the Sleep Patterns for Pediatric Unresponsive Wakefulness Syndrome (SPPUWS) tool.³⁵

No studies reported on PSG use in intensive care units (ICUs) in pediatric DoCs, probably due to technique unwieldiness, need of time-consuming expert visual review, and interference of pharmacological sedation and ICU environmental factors.

Statement 7. (++) Functional imaging.

Evidence. (++) Severe brain hypoperfusion at PET and SPECT is a marker of decreased arousal and responsiveness in post-acute and chronic phases.³⁷ VS/UWS in children is characterized by generalized (chronic) decreased metabolic activity in the brain, including reduction in glucose uptake at PET.³⁸

In children with unclear DoCs states, 18F-positron emission tomography (FDG-PET) was used to demonstrate persistent global reduction of cerebral glucose metabolism, as evidence of VS/UWS.³⁸ However, there is no sufficient evidence that FDG-PET alone can be used to reliably confirm a clinical diagnosis of VS/UWS in children in post-acute or chronic phases.

Also, FDG-PET and SPECT were proposed to assist monitoring of brain metabolism after pioneering treatments for pediatric DoCs,³⁴ to detect possible functional changes or recovery.

No evidence was found for use of Near Infrared Spectroscopy in pediatric DoCs, possibly due to several factors, including general inability of photons to reach the deep structures of the brain (>4cm underneath the scalp) in individuals other than newborns, risk of invalid measures due to hydrocephalus, and limited validity of current homogeneous spherical models of brain tissue in presence of focal anatomical lesions.

Statement 8. (++) *Maximization of arousal and responsiveness.*

Evidence. (++) Literature has pointed out the need of robust and reliable stimulation to maximize arousal, including stimulation saliency³⁹ attending to the child's position, choosing optimal times of day for assessment,⁴⁰ employing trained and experienced staff in structured assessments scoring,²⁶ and using serial assessment (≥ 3) to characterize DoCs.^{23,40} Using only the best (positive) observations has implications in cautious and optimistic determination of prognosis.²¹

Delivery of long assessment sessions has been reported to induce patient fatigue, resulting in false negative results which are not reflective of inability to respond, but rather related to the reversible patient's exhaustion.²¹ Tasks based on different modalities (i.e., visual, auditory, and tactile) have been used to overcome potential

damages to specific sensory pathways and maximize the chance to instrumentally observe neural activation, which in some circumstances is indicative of consciousness.^{17,21}

Outcome and Prognosis

Statement 9. (+++/++) *Modulators of outcome.*

Evidence. (+++) Several cohort studies (n=127,⁴¹ n=86²³, and others) and smaller case series compared outcomes of children with TBI to those with other etiologies (anoxic injury only, or mixed etiology including anoxia, infection, status epilepticus, and stroke). Children with TBI had better outcomes than those with other etiologies. Anoxic brain injury has been associated with worse outcomes. Two studies included a common sub-group of 26 individuals.

(++) Among clinical predictors of prognosis, literature investigated effects of age,^{25,27,42} location and extent of brain lesions, presence of epilepsy and instability of vital parameters on neurological outcome. Findings were either not conclusive or contradictory.

Statement 10. (++) *Early recovery.*

Evidence. (++) One cohort study⁴² (n=56) and one case series (n=3) of children with anoxic injury showed that shorter length of DoCs (60-90 days) was associated with better outcome. Other cohort studies showed that early neurobehavioral assessments (<3 months) were related to long-term state of consciousness (at 6 months; n=92)²⁸, and predictive of DoCs 5 years post-injury (n=124).²⁵

Several predictors of prognosis were reported: time to follow commands (i.e., days from injury until patients follows commands or until a GCS motor score of 6),⁴³ responsiveness at admission,²⁷ and social and motor responsiveness.⁴² Among 11 behavioral predictors, response to stimuli, execution of commands, and evidence of awareness of self <3 months after injury were most strongly linked to positive prognosis.²⁵

Statement 11. (++) *Late recovery.*

Evidence. (++) Rare cases of late emergence from VS/UWS or MCS are reported >12 months from TBI and >6 months from non-TBI. One study⁴⁴ showed that 4/27 patients with DoC for ≥ 90 days developed consistent verbal communication 3-14 years after injury. Six additional case reports (e.g.,³²) documented late recovery from DoC (9 months to 7 years). All 10 cases were >13 years of age at injury, with TBI etiology in 7/10. Another study showed that a minority of individuals with DoC manifested significant functional recovery between one year after injury and later follow-up (2-12 years).¹⁸ Among factors proposed to favor recovery from DoCs >1 year were older age, TBI etiology, appropriate nursing care, protracted intensive rehabilitation, successful seizure management, and complication resolution (eg., infections, cranioplasty).

Statement 12. (++) *Neuroimaging.*

Evidence. (++) In children with DoCs >14 days, structural imaging was employed to assess brain atrophy, deep nuclei lesions and secondary white matter damage, and to predict neurological deficit.³⁰ In pediatric VS/UWS and MCS, severity of clinical disability correlates with white matter tract abnormalities, as well as reduced fractional anisotropy and increased diffusivity in corpus callosum and superior cerebellar peduncles.⁴⁵ Tracking of white matter tracts using diffusion tensor imaging presents technical challenges in children <24 months, and needs to be methodologically addressed.⁴⁵

Chronic brain hypoperfusion after injury was found to relate to outcome, with severe hypoperfusion interpreted as lack of sufficient metabolic support to enable emergence from VS/UWS.^{37,38} While some pediatric normative data are available, identification of intra-individual standard reference regions for fully quantitative PET computation is still debated.

Statement 13. (++) *Electroencephalography and evoked potentials.*

Evidence. (++) BAEP and SEP abnormalities are indicators of brainstem and/or encephalic damage, and point at poor prognosis, especially in anoxic children.⁴⁶

Although used acutely, ERPs are less common but potentially equally useful to establish outcome in post-acute settings (≥ 14 days). Absence of cortical component N20 on bilateral SEPs was observed in relation to wide cortical lesions with preserved N13 brainstem component and generally poor outcome at 6 months,⁴⁶ although a few comatose children showed progression to mild or moderate neurological deficits.⁴⁷ Absence of MMN from auditory evoked potentials was also considered unfavorable feature in VS/UWS, and especially in MCS. Combined use of EEG and evoked potentials was seen to improve the outcome prediction in comparison with use of just one modality.⁴⁶

Statement 14. (++) *Polysomnography.*

Evidence. (++) Reappearance of sleep spindles and REM sleep after coma indicates integrity of supporting neural circuits and increases likelihood of transition from VS/UWS to the MCS and eMCS.^{35,36}

Differential EEG activity during sleep and wake was observed to be related to later recovery from pediatric VS/UWS⁴⁶, particularly in the beta band³⁶, and to anticipate later neurobehavioral scores.³⁶ Reduction in parietal slow wave activity (SWA) build-up was more frequent in individuals with DoCs, and lowest in those with poorest outcome.¹⁹ From early childhood to late adolescence the location of maximal SWA undergoes a shift from posterior towards anterior brain regions.¹⁹

Several factors hamper prognosis using PSG. Epilepsy and pharmaceuticals can distort sleep macro- and microstructure, and spasticity can cause multiple awakenings during the night.¹⁹

Treatment

Statement 15. (++)/+) *Pharmacology.*

Evidence. (++) Dopamine agonists were employed to promote recovery of function in the mesocircuit after pediatric DoCs, and their administration reported in 9 articles (2 small clinical trials; 2 small cohort studies^{48,49}). Overall, amantadine was administered to 53 children; 6 also received pramipexole and 2 methylphenidate. In 29/53 (54.7%) cases, DoC improvement was observed after treatment; in 9/53 (17.0%) improvement was unclear. Neurobiological functions supporting amantadine effectiveness are still partially unknown.

(+) Zolpidem, a pharmaceutical with GABAergic effect, was administered to 6 children, in 3 independent studies. Only 1/6 had some DoC improvement during treatment, mainly attributed to an associated immunotherapy, 2 had unclear benefit, and 3 had no observable benefit from zolpidem. Zolpidem was also tested as adjunctive treatment to accelerate recovery and rehabilitation results in a case of anti-N-methyl-D-aspartate receptor encephalitis after tumor removal and immunotherapy, with clinically significant response.⁵⁰

Statement 16. (+) *Non-pharmacological interventions.*

Evidence. (+) In one series and one single case, benefits of multisensory stimulation and utility of long delayed intensive rehabilitation programs were discussed for slow-to-recover children with DoCs, and in relation to neuromotor and neurocognitive domains. Regenerative treatments employing cell transplantation were reported for 9 patients. Assistive technologies to improve communication in home environment, median nerve stimulation, and traditional medicine therapies were also tested on single cases (eAppendix 13).

Discussion

This review systematically examines all evidence published prior November 9, 2022 on pediatric DoCs. It relies on definitions of coma, VS/UWS, MCS, and emergence

from MCS previously adopted^{3,4} (More details available in eAppendix 1). Minimal duration of DoC of ≥ 14 days from severe brain injury, and prognosis is an outcome prediction thereafter. Strengths include 7-language systematic literature review, by experts from 10 countries, and diverse specialties. Literature was examined to find potential bias. 132 articles were pooled, and evidence described into summative statements to inform the clinics. An increase in published studies was noted over the recent years. Most retained reports were single cases, series, or small observational studies. Studies with stronger designs mostly provided a single case or small subset that met criteria for inclusion. Strength of evidence was low, and it was not possible to draw conclusions from many individual studies retained. Despite this, systematic pooling of results enabled identification of subthemes and replicated findings. Several statements related to diagnosis, outcomes/prognosis, and treatment were identified, to potentially focus future research endeavors. Statements might be used along with expert opinion to create guidelines and inform practice.

Limitations and Future Directions

Inclusion and exclusion criteria were applied consistently throughout the article evaluation and across teams; however, at times interpretation was challenging. We included cases with DoCs lasting ≥ 14 days, differently from current recommendations for the general population with DoCs, requiring length ≥ 28 days;⁴ this pragmatic choice maximized inclusion and evidence, yet resulted in few uncertain cases for whom DoC duration could not be clearly extracted, and in differences between teams, with possible overinclusion. Information about time when individuals transitioned from coma to UWS was rarely reported. Sedative administration was not reported in most cases, which caused uncertainty around the exclusion of cases for whom coma was pharmacologically-induced. Also, while we included children ≥ 6 months and older, our inclusion criteria did not specify whether this was age at event or at study, which also was interpreted differently across teams. That said, few studies investigated neonates and infants under 6 months of age. For large studies having a subgroup of children with DoCs, demographic and clinical information was only extracted for the relevant subgroup; however, demographics were not always reported for subgroups, which were often small or

even single cases, and in few cases we could not rely on the general conclusions driven from the entire cohort. Lastly, despite being systematic, this review is not a single-patient meta-analysis. Large cohort studies did not provide sufficient details to conduct analyses at individual level, which would introduce further bias towards low evidence case studies and series, or would require correspondence with the authors.

To increase level of evidence, a minimal information set should be reported in future scientific literature: 1) age at event, 2) age at study, 3) GCS at event, 4) etiology, 5) at least two assessments of state of consciousness, ideally using a standardized behavioral measure (e.g., CRS-R), and possibly at admission and discharge from rehabilitation, 6) occurrence or absence of a) epilepsy, b) craniotomy/decompressive surgery, and c) paroxysmal activity, 7) medications, and 8) rehabilitation received (Table 4). Negative findings should be reported. Whenever possible, length of DoC should be documented, and children with DoCs ≥ 14 days should be analyzed separately from those with shorter DoC. Lastly, if appropriate, a measure of global functioning (such as the Functional Independence Measure for Children – WeeFIM, and/or the Disability Rating Scale - DRS) should be reported.

Conclusions

Literature on pediatric DoCs is mainly observational, and clinical details are either inconsistently presented or absent. Conclusions drawn from many studies convey insubstantial evidence, have limited validity, and low potential for translation in clinical practice. Despite these limitations, several statements related to diagnosis, outcomes/prognosis, and treatment were identified that can inform future research. Together with expert opinion, our work constitutes a base for future guidelines on the management of pediatric DoCs.

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Table 1. Summative statements on “Diagnosis”. Single-study supporting evidence was rated as high (+++) if supported by at least one controlled clinical trial, medium (++) if supported by at least one robust well-designed cohort/group study, and low (+) if only supported by case studies, series, or studies with high risk of bias. The total number of documents contributing to each statement is indicated. In the columns related to high, medium, and low evidence, the numbers outside brackets indicate the number of articles reporting high, medium and low evidence in support of the specific statement; the numbers inside brackets indicate the number of articles reporting high, medium and low evidence related to the specific aims or objectives of those papers. The corresponding documents are charted in the study open Data at <http://doi.org/doi:10.105281/zenodo.7997317>. An evidence score is also calculated according to the formula in eAppendix 3.

Diagnosis			N. of docum	High evidenc	Medium evidenc	Low evidenc	Score
1	++	<i>All states of consciousness previously defined in adults using behavioral assessment including coma, VS/UWS, MCS and further subdivision in MCS- and MCS+, and eMCS have been reported in pediatrics.</i>	29	0 (1)	8 (12)	21 (16)	0.160
2	++	<i>A range of standardized behavioral assessment methodologies have been used to characterize the behavioral phenotype of pediatric DoC, although they have limited validation.</i>	29	0 (2)	10 (17)	19 (10)	0.166
3	++	<i>For the determination of DoC in very young children (<4y), assessment of visual and motor skills was shown to be the most applicable, and assessment of language-based skills was shown to be the least applicable.</i>	4	0 (0)	1 (3)	3 (1)	0.024
4	++	<i>Structural imaging (CT, sMRI, DTI) has been used to describe the etiology, location(s), extent, and evolution of brain injury. (++) However, less evidence exists</i>	68	0 (1)	7 (13)	61 (54)	0.349

		<i>on the use of structural neuroimaging to investigate the cause of DoC, its anatomical underpinnings, and its severity, and to complement behavioral assessment in children to better classify the DoC.</i>					
5	++	<i>Electrophysiological methods (EEG, ERPs) have been used to detect residual activity, conductivity, and connectivity of the neuronal circuitry in children with DoCs, and to complement behavioral assessment during diagnosis.</i>	28	0 (2)	5 (6)	23 (20)	0.159
6	++	<i>To assist in the diagnosis of DoC, PSG has been used in the post-acute and chronic phases to identify and characterize altered sleep architecture, which is common condition in pediatric individuals with DoC ≥ 14 days. Also, PSG has been used at the emergence from a coma, to monitor the progressive re-structuring of the circadian rhythm over time, including wake periods and sleep stages, and particularly REM (re)appearance.</i>	6	0 (0)	4 (4)	2 (2)	0.035
7	++	<i>The use of functional imaging (PET, SPECT) can inform on the metabolic and functional activity in the brain, thus complementing behavioral assessment when diagnosing DoCs in children.</i>	11	0 (0)	1 (1)	10 (10)	0.065
8	++	<i>Strategies to maximize arousal and responsiveness when conducting behavioral and instrumental assessment in children have been described, that include child's positioning, time of day, number of assessments performed (repetitions), relevant sensory pathway identification, type and salience of stimuli, length of session, and expertise of staff. Given variability in responding and the high possibility of interfering factors, the use of best (positive) observations have been used to diagnose the state of DoC.</i>	14	0 (0)	3 (5)	11 (9)	0.072

Table 2. Summative statements on “Prognosis”.

Outcome and Prognosis			N. of contrib	High evidenc	Medium evidenc	Low evidenc	Score
9	+++ / ++	<i>(+++)</i> Etiology has an association with outcome. Children with traumatic brain injury have better outcomes than children with other etiologies, especially anoxic brain injury. <i>(++)</i> Also, associations with outcome were studied for several demographic and clinical characteristics, although some findings are not conclusive.	41	2 (3)	14 (18)	25 (20)	0.491
10	++	<i>Earlier recovery of consciousness has been associated with better clinical evolution and long-term neurological outcome.</i>	12	0 (0)	9 (9)	3 (3)	0.071
11	++	<i>Although infrequent, cases of late recovery from VS/UWS and MCS are reported.</i>	9	0 (0)	3 (4)	6 (5)	0.050
12	++	<i>Worse prognosis is associated with neuroimaging findings: lesions in the deep nuclei and/or brainstem, moderate or severe atrophy, and (diffuse) white matter damage, manifesting through decreased fractional anisotropy and increased diffusivity at DTI. Functional and metabolic imaging have been applied to test whether the brain metabolic uptake can inform on potentiality or likelihood of emergence from DoC; however, no definite criteria are available.</i>	18	0 (0)	4 (5)	14 (13)	0.100
13	++	<i>The neurophysiological evaluation, including EEG, BAEPs, SEPs, and ERPs (i.e. P300 and MMN), has been used to assist post-acute prognostication.</i>	13	0 (2)	7 (5)	6 (6)	0.085
14	++	<i>PSG has shown electrophysiological patterns predictive of preserved neurological function. It has been used in the post-acute disease, and in conjunction with other information, to define prognosis, and to direct the pharmacological therapy and rehabilitation of states of reduced consciousness.</i>	4	0 (0)	3 (4)	1 (0)	0.014

Table 3. Summative statements on “Treatment”.

Treatment			N. of contrib	High evidenc	Medium evidenc	Low evidenc	Score
15	++/+	<i>(++) The safety, tolerability, and efficacy of amantadine have been described in children. Dosage variability was high. In half of the pediatric cases reporting outcome after amantadine treatment, DoC improvement was observed concurrent with treatment. (+) Other pharmacologic interventions used for adults with DoCs have been occasionally reported in children (e.g., Zolpidem).</i>	13	0 (2)	5 (5)	8 (6)	0.080
16	+	<i>Few non-pharmacological treatments have been documented for children with DoC, among which rehabilitation, regenerative medicine, and instrumental and technology-assisted therapies. However, evidence for their efficacy is low.</i>	16	0 (0)	0 (0)	16 (16)	0.032

Table 4. Data elements for research reporting on pediatric cases with a Disorder of Consciousness.

	Essential data elements	
	Age at injury Age at assessment, Duration of Disorder of Consciousness previous to study assessment, Level of consciousness Tool, guidelines or criteria employed for DoC assessment	
	Core data elements	Should be reported if available
Clinical management in acute	Sex Etiology or cause of injury Glasgow Coma Score at rescue or A&E Days from injury to eye opening (or days of coma if more appropriate)	Glasgow Coma Score items at rescue or A&E Time to follow commands Neurophysiological abnormalities at Brainstem Auditory Evoked Potentials (BAEPs) and/or Somatosensory Evoked Potentials (SEP) Radiological abnormalities at Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), including brain hemorrhage, midline shift, focal damages, and spine involvement Medical complications. Surgical interventions
Data at admission to rehabilitation center, trial or treatment	Age at study Glasgow Outcome Score at admission Disorder of Consciousness at admission One neuropsychological evaluation (e.g., CRS-R,	

	<p>C/NCS, LOCFAS)</p> <p>Motor disorder at admission</p> <p>Presence of spasticity, hyper/hypotonia and hyper/hyporeflexia</p>	
<p>Data during rehabilitation / rehabilitation center in-stay</p>	<p>Need of respiration assistance</p> <p>Need of feeding assistance</p> <p>Need of surgery (e.g., craniotomies, shunting)</p> <p>Insurgence of sympathetic paroxysmal activity or instability of vital parameters</p> <p>Insurgence of epilepsy</p> <p>Insurgence of infections</p> <p>Insurgence of metabolic diseases (e.g., diabetes)</p> <p>Treatments, including non-pharmacologic</p>	<p>Neurophysiological abnormalities at awake electroencephalography (EEG)</p> <p>Neurophysiological abnormalities at Event Related Potentials (ERPs)</p>
<p>Data at discharge from rehabilitation center or termination of treatment</p>	<p>Glasgow Outcome Score at discharge</p> <p>Disorder of Consciousness at discharge</p> <p>One neuropsychological evaluation (e.g., CRS-R, C/NCS, LOCFAS)</p> <p>Motor disorder at discharge</p> <p>Presence of spasticity, hyper/hypotonia and hyper/hyporeflexia</p>	<p>Radiological abnormalities at Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), including focal damages, white matter damage, atrophy, and hydrocephalus</p>

	Data on sphincters control	
Data at follow-up	<p>Age at follow-up</p> <p>One neuropsychological evaluation (e.g., CRS-R, C/NCS, LOCFAS)</p> <p>Motor disorder at follow-up</p>	<p>Neurophysiological abnormalities at awake electroencephalography (EEG)</p> <p>Radiological abnormalities at Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), including focal damages, white matter damage, atrophy, and hydrocephalus</p>

ACCEPTED

List of abbreviations.

¹H-MRS: 1H-Magnetic Resonance Spectroscopy

BAEP(s): Brainstem Auditory Evoked Potential(s)

CALS: Cognitive and Linguistic Scale

CNCS: Coma Near Coma Scale

CPC: Cerebral Performance Category

CRS-P: Coma Recovery scale – Pediatric version

CRS-R: Coma Recovery scale - Revised

CT: Computed Tomography

DoC(s): Disorder(s) of Consciousness

DRS: Disability Rating Scale

DTI: Diffusion Tensor Imaging

EEG: Electroencephalography

eMCS: emerged from Minimally Conscious State

EMG: Electromyography

EQUATOR: Enhancing the QUALity and Transparency Of health Research (<https://www.equator-network.org>)

ERP(s): Evoked Response Potential(s)

FDG-PET: fluorodeoxyglucose positron emission tomography

GABAergic: which affects the neurotransmitter γ -aminobutyric acid

GCS: Glasgow Coma Scale or Glasgow Coma (Scale) score

GOS: Glasgow Outcome Score

GRADE: Grading of Recommendations Assessment, Development and Evaluation

IBIA-DoC SIG: Special interest Group on Disorders of Consciousness of the International Brain Injury

ICU: Intensive Care Unit

LOCFAS: Level of Cognitive Functioning Assessment Scale

MCS: Minimally Conscious State

MCS-: Minimally Conscious State minus (i.e., with language comprehension and production deficit)

MCS+: Minimally Conscious State plus (i.e., with some language abilities)

MMN: mismatch negativity (cortical component of Event Related Potential)

MR(I): Magnetic Resonance (Imaging)

NAA/Cre: N-AcetylAspartate / Creatinine ratio

PALOC-s: Post Acute Level of Consciousness - scale

PET: Positron Emission Tomography

PRISMA-ScR: Preferred Reporting Items for Systematic reviews and MetaAnalyses - extension for Scoping Reviews
(<https://www.equator-network.org/reporting-guidelines/prisma-scr/>)

PROBAST: Prediction Model Risk of Bias Assessment Tool (checklist)

PSG: polysomnography

qEEG: Quantitative Electroencephalography

QUADAS-2: The Quality Assessment of Diagnostic Accuracy Studies 2 (checklist)

REM: Rapid Eye Movement (sleep phase)

SEP(s): Somatosensory Evoked Potential(s)

sMRI: structural Magnetic Resonance Imaging

SPECT: Single Photon Emission Computed Tomography

SPPUWS: Sleep Patterns for Pediatric Unresponsive Wakefulness Syndrome

SWA: electroencephalographic Slow Wave Activity

TBI: Traumatic Brain Injury

UWS: Unresponsive Wakefulness Syndrome

VEP: Visual Evoked Potentials

VS: Vegetative State

WeeFIM: Functional Independence Measure for Children

WNSSP: Western Neuro Sensory Stimulation Profile

¹H-MRS: 1H-Magnetic Resonance Spectroscopy

Figure 1. Workflow illustrating the generation of themes, subthemes, and statements through the study. The IBIA DoC-SIG Diagnosis and Prognosis Subgroup conceptualized the study, and established 5 themes a-priori, based on the previous work and recommendations for the general population with DoCs and based on the terms included into the database search. Three systematic searches were repeated during the study, with four different databases interrogated at any search. Subthemes were iteratively generated, which informed the statements formulation.

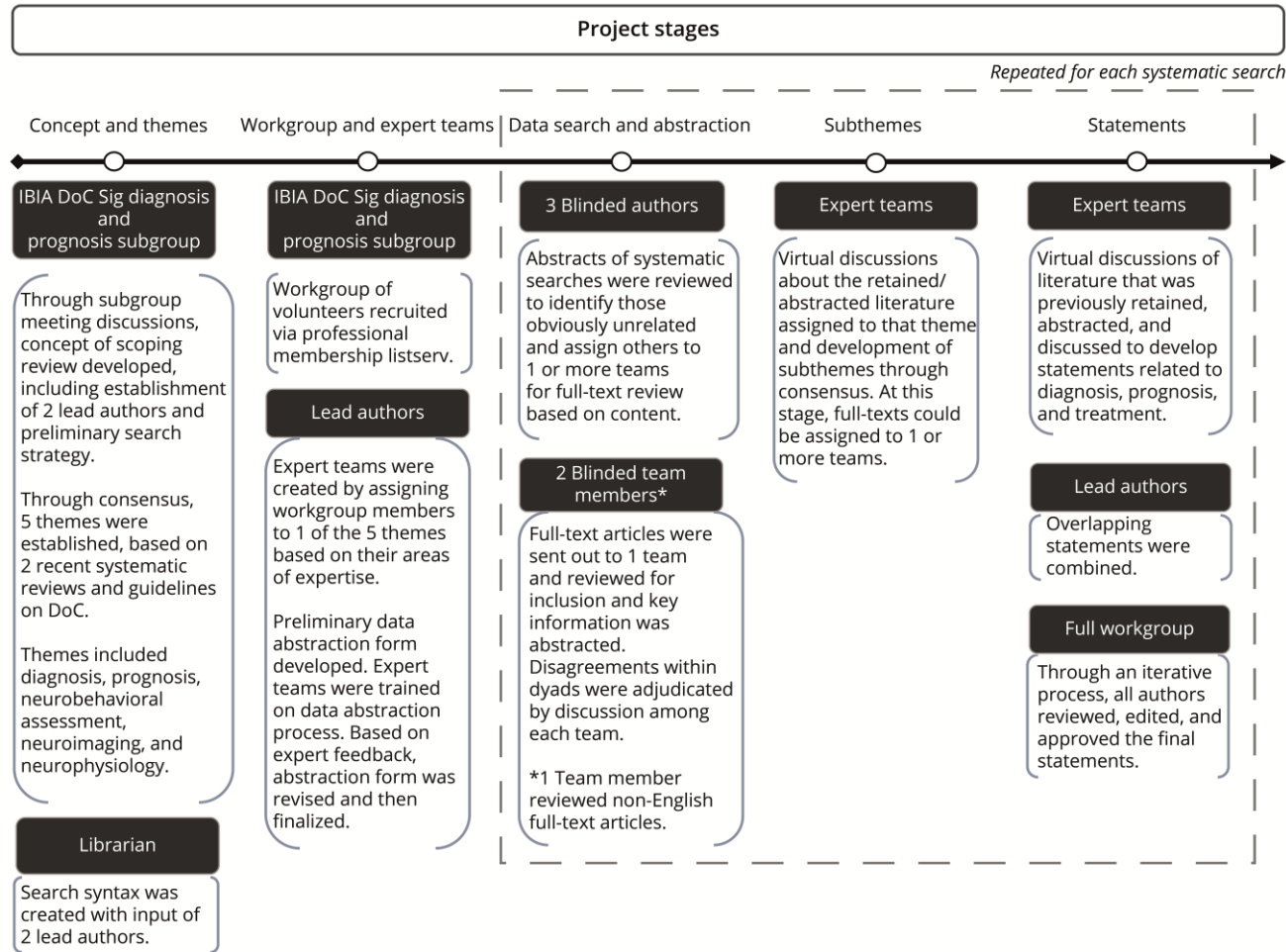
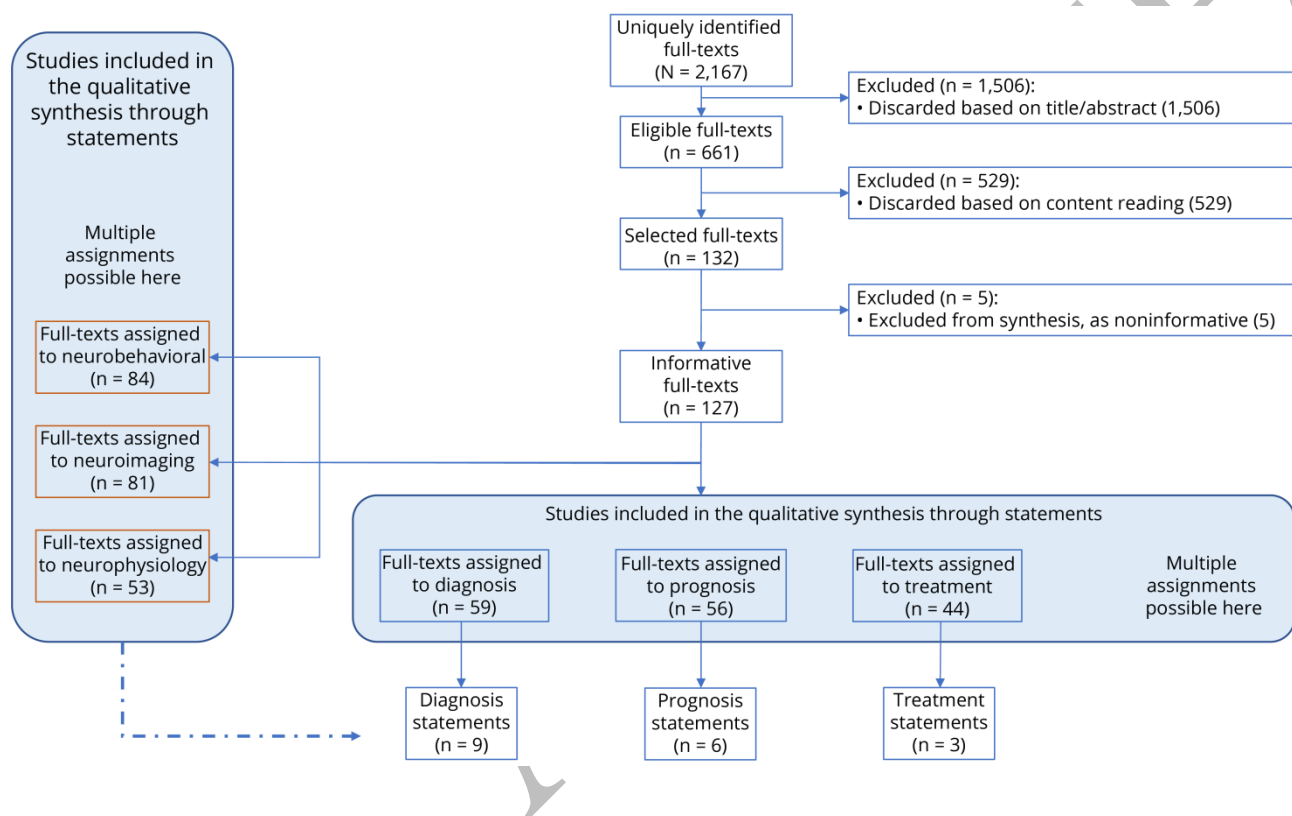


Figure 2. Flowchart illustrating the extraction of evidence on the diagnosis, prognosis, treatment, and techniques employed in the care of pediatric patients with DoCs. The selected full-texts (n=132, of which n=127 informative) were in most cases reviewed by more than one team of experts, as relevant to more than one topic. Full-texts were reviewed for information about clinical aim (diagnosis, prognosis and/or treatment), and for the techniques used (behavioral tests, neuroimaging, neurophysiological exam).



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