ISAQUE NILTON DOS SANTOS

IATROGENIC WITHDRAWAL SYNDROME IN CRITICALLY ILL NEONATES: A REVIEW OF MECHANISMS, ASSESSMENT, MANAGEMENT, AND PREVENTION

Paper presented to the Federal University of Santa Catarina, as a requirement for the completion of the Undergraduate Course in Medicine.

Florianópolis

Federal University of Santa Catarina

2022

ISAQUE NILTON DOS SANTOS

IATROGENIC WITHDRAWAL SYNDROME IN CRITICALLY ILL NEONATES: A REVIEW OF MECHANISMS, ASSESSMENT, MANAGEMENT, AND PREVENTION

Paper presented to the Federal University of Santa Catarina, as a requirement for the completion of the Undergraduate Course in Medicine.

Collegiate chairman: Prof. PhD. MD. Edevard José de Araujo

Professor supervisor: Prof. PhD. Helena Iturvides Cimarosti

Joint supervisor: MD. Carolina Teixeira Goulart Peano

Florianópolis

Federal University of Santa Catarina

2022

Iatrogenic Withdrawal Syndrome in Critically Ill Neonates: A Review of Mechanisms, Assessment, Management, and Prevention

Isaque Nilton dos Santos[1,2], M.D. Carolina Teixeira Goulart Peano[1,2], MSc. Ericks Sousa Soares[1,2] and PhD. Helena Iturvides Cimarosti[1,2,3*]

[1]Department of Pharmacology, School of Biological Sciences, Federal University of Santa Catarina (UFSC), Florianópolis, Santa Catarina, Brazil.

[2]Postgraduate Program in Pharmacology, UFSC, Florianópolis, Brazil.

[3]Postgraduate Program in Neuroscience, UFSC, Florianópolis, Brazil.

*Corresponding author:

Prof. Dr. Helena I. Cimarosti

Address: Departamento de Farmacologia, Centro de Ciências Biológicas – CCB, Universidade Federal de Santa Catarina – UFSC, Campus Trindade, Florianópolis, 88040-900, Santa Catarina, Brasil.

E-mail addresses: isaque.nilton@grad.ufsc.br (I.N.S.); carolina.peano@ufsc.br (C.T.G.P); ericks.sousa@posgrad.ufsc.br (E.S.S.); helena.cimarosti@ufsc.br (H.I.C.).

Abstract

Considering that neonatal pain is a relevant matter given its implications and consequences, many neonates, particularly those undergoing critical care, are subjected to analgo-sedation therapies, which commonly includes treatment with opioids and benzodiazepines. These drugs, however, can induce tolerance and dependency, leading to the development of the so-called iatrogenic withdrawal syndrome (IWS) which is observed following discontinuation of these therapeutic agents particularly when utilized for a prolonged period of time (≥ 5 days). IWS consists of signs and symptoms manifested especially in young children, such as term and premature newborns in the neonatal intensive care unit (NICU), who are less capable of metabolizing and eliminating these drugs, compared to older patients. In this study, we review assessment tools that were developed to identify, evaluate and manage children affected by IWS. The studies reviewed demonstrate that optimal management of IWS includes consideration of alternate routes of drug administration, the need for adequate time for drug tapering, and also the presence of planned rescue therapy when encountering cases refractory to ongoing management. Equally important is prevention of IWS which can be accomplished with the implementation of drug rotation protocols and, adherence to evidenced based guidelines which facilitate an overall decline in the use and duration of opioids and benzodiazepines. Finally, our review strongly supports the need for more research on IWS in neonates given their increased susceptibility and sparse published data for this age group.

Keywords: analgo-sedation; benzodiazepine; neonatal; opioid; withdrawal.

Introduction

In the past, health care professionals believed that neonates would not feel pain as their nervous system was still immature and under development.[1] However, over the years, it has been observed that newborns are more sensitive to pain than older children and adults due to increased excitability of nociceptive pathways and a lack of a robust modulatory system.[2] In addition, neonates, particularly those that are preterm requiring neonatal intensive care (NICU), are routinely exposed to procedures that induce pain, such as blood sampling, mechanical ventilation, and surgery.[3]

Despite being subject to these painful stimuli, newborns are non-verbal and have limited ability to express or indicate common characteristics of pain. As a result, researchers have developed tools to facilitate neonatal pain assessment based on their behavior, serial vital signs, and facial expression.[4] The goal is to balance analgesia and sedative requirements while minimizing acute and potential long-term consequences such as inadequate recovery, unfavorable developmental outcomes, and ineffective pain management[3,5] Consequently, more effective analgesia and sedation management is required in the NICU.

Despite providing clear benefits for newborns, analgo-sedation must be handled with caution as it is also associated with known risks such as hypotension, respiratory depression, and paralytic ileus.[6] Another important issue is that of neonatal withdrawal to both analgesic and sedative medications commonly used in the NICU, either of which can lead to abstinence or dependency in newborn infants.[7] These effects are well described through the use of the term, iatrogenic withdrawal syndrome (IWS).

The provision of neonatal pain control is an important issue for NICU patients which requires judicious use of medications with known potential side effects such as IWS. As a result, we present the findings from our review of IWS in neonates in which we focus on its epidemiology, etiology, diagnosis, management, and prevention. Our goal is to provide health

care professionals, especially pediatric intensivists, with an updated, valuable and evidence based overview of IWS management in newborns to facilitate their ongoing care leading to optimal patient outcomes.

Definition

IWS can be defined as a collection of signs and symptoms that follow the sudden discontinuation of drugs, such as opioids and/or benzodiazepines, in patients that are physically dependent on these agents. Dependency and tolerance usually occur after prolonged drug exposure, most commonly described as following 5 days of continuous infusion. Subsequently, withdrawal symptoms may be apparent within 1 hour up to 2 days following drug discontinuation.[8] In addition, it must be differentiated from neonatal abstinence syndrome (NAS) which refers to drug dependency in newborns (≤ 28 days) that were exposed to those drugs during the prenatal period and not after birth.[7]

Neonates suffering from IWS can exhibit symptoms that are related to central nervous system (CNS) overstimulation, dysregulation of the autonomic system, and gastrointestinal disturbances.[7] Furthermore, withdrawal symptoms can bring negative consequences for newborns such as prolonged drug exposure leading to extended NICU and possible hospital length of stay following transfer from the NICU to the PICU or pediatric ward.[7]

Epidemiology

There is currently sparse evidence in the literature that describes the frequency of IWS specifically in neonatal patients. However, some studies suggest that, for opioid analgesia, the younger the patient, the greater the risk of dependency.[9] Among pediatric patients in general, the incidence of IWS also varies depending on the duration of analgo-sedation. It is estimated that it affects around 50% of patients that receive drug infusion for ≥ 24 hours and may reach 80-100% when drug administration lasts more than 5 days.[10]

A systematic review from 2019 gathered studies showing the prevalence of IWS ranges from 7.5% to 100% of hospitalized pediatric patients.[11] The authors aptly explain that this variability likely results from differences in IWS definition, methods to determine its occurrence, weaning protocols, and the heterologous nature of study populations.[11] The variability of IWS prevalence is commonly described in the literature and was noted in another review in which IWS was identified in 5% to 87% of pediatric patients of all ages.[12]

Pathogenesis

Opioid-derived drugs such as morphine, fentanyl, and methadone are important components of IWS. Opioids are potent analgesics not uncommonly used to relieve pain in neonates. Their effects are facilitated by their binding to several types of membrane opioid receptors (e.g. mu, kappa, and delta) which are located not only in the CNS but in the related ascending and descending pain pathways as well. When a molecule binds to an opioid receptor in the ascending pain pathway, hyperpolarization of neurons in the spinal cord stimulates postsynaptic potassium channels decreasing their probability of firing action potentials.[9]

In the descending pain pathway, the activation of opioid receptors in the brainstem leads to stimulation of regions responsible for pain modulation, known as the periaqueductal gray and the rostral ventromedial medulla. These regions can inhibit pain by reducing the excitability of neurons in the spinal cord through the release of monoamines such as noradrenaline. In short, the basic effect of administered opioids is to reduce the firing of action potentials that signal pain.[9]

When opioid cessation occurs, several body systems can be affected and manifest the known complication of dependency. An example is the *locus coeruleus* (LC), a structure located at the base of the brain and responsible for autonomic regulation through noradrenergic circuits. Usually, the binding of an opioid to mu receptors reduces the release of noradrenaline by the LC through inhibition of adenylyl cyclase and reduction of AMPc levels. To maintain

homeostasis, the organism increases the production of these molecules and, when withdrawal occurs, these metabolic changes result in increased noradrenaline levels and the consequent autonomic dysregulation seen in IWS, as shown in Figure 1.[13]

Particularly in neonates and preterm infants, opioids may reach high serum concentrations that induce the risk of toxicity and dependency.[14] These risks are enhanced by the reduced hepatic and renal metabolism of drugs in newborns compared to older children or adults, leading to slower elimination and subsequently a longer half-life of opioids seen in this age group.[15] Acute critical illness and any chronic co-morbidities also may contribute to the presence of hepatic and renal impairment and therefore exacerbate the prolonged presence of opioids and their related complications in neonates due to reduced clearance of these agents.[14]

Another drug class that is frequently prescribed to critically ill newborn patients are benzodiazepines such as midazolam, lorazepam, and diazepam whose main goal is provision of required sedation.[16] Although their molecular mechanisms are still not completely understood, it is well accepted that benzodiazepines interact with the gamma amino butyric acid (GABA)-A receptor.[17]

GABA is one of the main inhibitory neurotransmitters in the CNS, found mostly in the cerebral cortex and limbic system where it reduces neuronal excitability.[17] GABA binds to three different receptors (A, B, and C); benzodiazepines interact with the A-type receptors. GABA-A receptors are ligand-gated chloride-selective ion channels and exhibit an allosteric site on which benzodiazepines exert a positive effect. This means that drugs such as midazolam will produce sedation by increasing the neuroinhibitory effect of the bond between GABA and its type-A receptor resulting in reducing general neuronal excitability.[17]

Long-term exposure to benzodiazepines can also cause physical dependency and lead to withdrawal symptoms. The exact mechanism by which this takes place remains uncertain, but it is thought that dependency is related to development of tolerance.[18] Prolonged use of

benzodiazepines may cause changes in the structure, localization, and function of GABA-A receptors, which ultimately may require a higher dose of medication to achieve the same therapeutic result. Known as drug tolerance, this effect may also be responsible for the development of dependency and consequent withdrawal symptoms upon discontinuation of benzodiazepine therapy, as represented in Figure 2.[18]

Benzodiazepine pharmacokinetics, in neonates and preterm infants, are similar to that of opioids where immature hepatic and renal pathways lead to reduced elimination rates and subsequently longer drug half-lifes.[14] Interestingly, midazolam has been noted by some authors to have great variability of drug clearance based on gestational age with higher midazolam clearance in neonates born after 39 weeks of gestation.[14,19]

Assessment

A precise diagnosis of IWS may be very difficult to make since patients are usually in an intensive care setting, where many of their symptoms can be misinterpreted due to their overlap with other conditions and interventions.[7,8] In addition, newborns in the NICU may be submitted to more than one drug that may cause withdrawal symptoms.[11] Overall, the literature describes a wide variety of IWS associated symptomatology to include CNS-related symptoms (e.g. agitation, insomnia, and increased muscle tone), autonomic system dysregulation (e.g. tachypnea and sweating) and, gastrointestinal disturbances (e.g. diarrhea and vomiting).[11]

In consideration of the variety of medications and symptoms that are related to IWS great efforts have been made to develop standardized methods for assessing withdrawal symptoms that have led to validated assessment tools. The most commonly used tools are the Opioid and Benzodiazepine Withdrawal Score (OBWS), the Withdrawal Assessment Tool-1 (WAT-1), and the Sophia Observation Withdrawal Symptoms scale (SOS).[10] Although they

were not developed exclusively for neonatal patients, the WAT-1 and SOS did include neonates in their development.

OBWS[20] consists of a checklist of 21 items, 16 of which are related to drug withdrawal. This tool is used to assess the frequency and severity of withdrawal symptoms. It was first developed in 1998, but was updated in a 2004 study by the same authors.[20] In this study, nurses were asked to assess a group of 15 children aged 6 weeks to 28 months who had been exposed to opioid and/or benzodiazepine therapy for longer than 5 days. The OBWS was performed every 4 hours for approximately 2 days after the discontinuation of these drugs. The score ranges from 0 to 21 and, a cutoff of > 8 is considered presence of withdrawal with an associated sensitivity and specificity of 0.50 and 0.87, respectively.[20]

WAT-1[21] is a symptom assessment scale developed in 2007 and used to monitor withdrawal symptoms in pediatric patients exposed to opioids and benzodiazepines. It was designed to be performed twice a day, which facilitates its use in clinical practice.[22] Its developers evaluated 19 symptoms, derived in part from OBWS, and came up with an 11-item scale resulting in a score range of 0 to 12. A cutoff value of WAT-1 ≥ 3 has a sensitivity of 0.872 and, a specificity of 0.880.[21] In a study involving 40 pediatric patients (newborns to 18 years of age) undergoing mechanical ventilation and analgo-sedation, the prevalence of IWS using the WAT-1 tool was 95% without a protocol for proper tapering of drugs.[23]

The SOS scale[24] was introduced in 2009 to create a more valid and reliable assessment tool and, was constructed in four steps. First, an extensive literature review was used to develop a list of 24 signs and symptoms related to analgo-sedation withdrawal.[25] Then, a prospective observational study was conducted on a group of critically ill pediatric patients aged ≤ 16 years old who underwent weaning of midazolam and/or opioids. Bedside nurses utilized the list to record the occurrence of the signs and symptoms related to withdrawal and data was analyzed. The authors then sought expert opinion from which an assessment tool was created

reflecting those symptoms considered necessary for inclusion by the consulted experts.[24] Finally, they created a scale that ranges from 0 to 15 with a cutoff value of ≥4, resulting in sensitivity and specificity of 0.83 and 0.93, respectively.[26] According to Duceppe and colleagues (2019), studies that used SOS in pediatric patients have found IWS frequencies that range from 18% to 100%, while the ones using WAT-1 presented frequencies ranging from 37% to 77%.[11]

Another well-known scale used to assess withdrawal symptoms is the Finnegan's Neonatal Abstinence Score (FNAS)[27]. Although it was developed to evaluate patients exposed to drugs in the prenatal period, it also focuses on newborn infants and includes symptoms such as the hyperactive Moro-reflex, which were not included in the other scales.[25] The limitations of the FNAS include its purpose, which does not include recognition of IWS[27] and, its dated conception in 1975 leading to the use of modified versions to overcome its outdated nature.[9] In addition, it was designed to evaluate neonates born to mothers addicted to opioids, not the use of benzodiazepines thereby limiting its use in the management of IWS.[25,27] Therefore, despite its application to assess IWS in prior studies[11,25], FNAS may not be well suited for this use.

In the presence of these scales, a recently published guideline (2022) recommends the use of either WAT-1 or SOS to assess IWS.[28] When comparing these two scales, clear advantages and disadvantages become apparent. WAT-1 is focused on older infants and children and is superior for evaluation and management of opioid withdrawal. In comparison, SOS is designed to assess children up to 16 years of age and is best used for evaluation and management of benzodiazepine withdrawal.[21,24] Furthermore, WAT-1 involves verbal stimulation of patients which may not be well suited for newborns and, SOS assessment involves only observational criteria, which presents limitations relevant to the age of the patient.[21,24]

Management

Once patients have been assessed with a proper scoring tool, it is also important to know how to manage infants with withdrawal symptoms. The literature describes a variety of drugs used for the dual role of pharmacological treatment and prevention. The most commonly used drugs to manage IWS patients are clonidine, methadone, and dexmedetomidine. The best specific agent depends on whether IWS stems from opioid use alone or the combination of opioids and benzodiazepines.[10]

Considering that the molecular mechanisms underlying IWS depend on drug-receptor interactions, its management should focus on an agent(s) that act on the same receptor(s) as the analgesic or sedative agent that led to IWS.[28] As expected, a recent review indicated that methadone was the most commonly used agent to manage withdrawal related to opiate use.[16] The benefits of this medication include both intravenous and oral administration and long half-life.[28,29] The recommended transition is from intravenous opioid therapy to oral methadone with dose adjustment to achieve the same analgesic effect.[16] Once the transition is initiated the methadone dose should then be reduced by 10-20% each day[29] facilitating a longer taper period to prevent withdrawal symptoms.[28] Protocols using methadone to promote opioid weaning have shown a decrease in IWS occurrence utilizing an adjusted methadone dose (based on previous duration and intensity of opioid exposure) which has been shown to be effective in clinical trials.[30]

As for benzodiazepines, there is little information available regarding how to treat related IWS because they are commonly used in conjunction with opioid analgesic agents in the intensive care unit leading to mixed effects.[16] Lorazepam, diazepam, and midazolam are the agents of choice that can be used as benzodiazepine weaning agents[16]; however, lorazepam is commonly described in the literature due to its prolonged duration of action. The technique is

similar to that recommended for opioid weaning in that a transition from an intravenous infusion to oral administration should be initiated with subsequent gradual daily reduction in drug dosage.[28] Regardless of the medications and technique used for managing IWS it should be accompanied by serial withdrawal assessment to evaluate treatment success.[28,29]

When referring to the duration of weaning, the literature is unclear on an exact period of time. Options described by authors include a treatment period proportional to the time the infant has been exposed to analgo-sedation, while others suggest a short fixed period of time up to 10 days.[31] In addition, some authors provide a practical guide on how to make the transition from intravenous drugs to oral administration. For example, the fentanyl dose (mcg/kg/hr) should be multiplied by 0.05-0.1 to achieve the appropriate methadone dose (mg/kg/daily), which should then be divided into every 6-hour administration.[29,31] A similar conversion can be made for midazolam, by multiplying its dose by 0.5-1 to achieve the appropriate daily lorazepam dosage, which should also be divided into every 6-hour administration.[31]

Alpha-2 agonists, such as dexmedetomidine, can also be used for analgo-sedation purposes during intensive care. This medication acts on both the LC and the dorsal horn of the spinal cord providing both sedative and analgesic effects.[32] For this reason, it can be used concurrently with opioid therapy and also to prevent withdrawal symptoms.[33] As with other commonly used analgo-sedation, prolonged dexmedetomidine infusion may also cause dependency; therefore, a weaning protocol should also be taken into consideration.[32] The tapering of dexmedetomidine can accomplished by multiplying its hourly dose by 5 to arrive at a converted daily dose of clonidine, whose benefit is that it also is an oral alpha-2 agonist that may then be administered orally every 4 hours.[31] The methods of conversion for all analgo-sedative agents described in this review are summarized in Table 1.

Another facet to consider in the management of IWS is the duration of intravenous analgo-sedative infusions as highlighted by Sanavia, et al.[34] If the drug is utilized for less than

5 days, the infusion should be rapidly reduced (50% per day) and the symptoms treated with oral methadone 0.1–0.2 mg/kg/6 hr and oral clorazepate 0.5–2 mg/kg/8 hr. However, if the drug exposure lasts for more than 5 days, a gradual reduction of infusion is suggested (20% per day), with prophylaxis during weaning and, management of withdrawal symptoms by utilizing oral clonidine 1–4 mcg/6–8 hr and, dexmedetomidine 0.2–0.75 mcg/kg/hr, as shown in Table 2.[34]

Prevention

To avoid IWS in neonates, it is necessary to establish a proper weaning protocol. Our review found that, studies that utilized a standardized protocol observed fewer withdrawal events, through a reduction in length of exposure to analgo-sedation therapy and, therefore the predominant risk associated with the occurrence of IWS. Of note, was that successful weaning was dependent on strict protocol adherence.[16]

The implementation of a drug rotation protocol can prevent IWS occurrences. The main goal of drug rotation is the reduction of the length of time receptors are exposed to the same drug facilitating a decrease in patient tolerance and dependency. Sanavia, et al conducted a prospective observational study over four years that analyzed 100 children (1 month to 16 years old) who required continuous infusion of analgo-sedative agents for >4 days while managed in the intensive care unit setting during which the SOS scale was utilized to assess withdrawal symptoms while conducting a drug rotation protocol that alternated use of opioid and non-opioid agents and, benzodiazepine and non-benzodiazepine agents to achieve adequate analgesic and sedative therapy, respectively. The underlying goal was to use alternative means of drug therapy to limit exposure to prolonged use of drugs known to associated with high risk of IWS.[34] The primary analgesic agents used were fentanyl and remifentanil with ketamine and metamizole used as their analgesic alternatives. Likewise, the primary sedative drug was midazolam with propofol and dexmedetomidine used as its

sedative alternative. With the knowledge that drug infusions lasting longer than 5 days increase the risk of IWS, the investigators also instituted a weaning protocol where the duration of each rotation was limited to four days. The results were interpreted as a reduction in the odds ratio for the incidence of IWS that was approximately 10 fold lower in those children managed with protocolized drug rotation thereby proving the efficacy of the protocol.[34] The protocol is outlined in Table 3.

A recent study from McPherson, et al, in 2021 also summarizes the evidence for IWS and, highlights practical approaches to reduce the risk of this complication. Their conclusion also supports the use of an opioid rotation protocol to avoid tolerance and withdrawal through transition of fentanyl to morphine and hydromorphone. They recommended an approach in which fentanyl is replaced by morphine multiplying its dose by 10-20 and, in the next rotation, morphine is replaced by hydromorphone dividing its dose by 7. In both transitions, the dosage should be reduced by approximately 25% to prevent cross-tolerance.[31] This technique is outlined in Table 4.

Another option to prevent the occurrence of IWS is to consider efforts to reduce the use of the analgesic and sedative agents that precipitate the presence of IWS in the NICU. Rana, et al utilized a multidisciplinary group at a large pediatric hospital to perform an extensive literature review to include published expert opinions and available guidelines on the practice of neonatal pain and sedation management. Their efforts facilitated the creation of guidelines for analgesic and sedative management for infants undergoing either surgery (major and minor) or mechanical ventilation.[35] The implementation of their guidelines was found to benefit neonates by an observed decrease in opioid and benzodiazepine use without incurring the risk of compromised pain management. The results demonstrated a significant reduction in the cumulative dose of analgo-sedation while maintaining the same level of pain scores. Of particular interest, the authors found that analgesia may be achieved with non-opioid drugs,

such as acetaminophen, or non-pharmaceutical measures that do not precipitate dependency.[35] The incorporation of a partnership with nursing and patient families may further accelerate plans for the successful implementation of strategies to optimize evaluation and management of neonatal analgo-sedation. The comfort provided to families will enhance a better understanding of their child's behavior and prospectively contribute to the success of analgo-sedative pain assessment and management plans.[36]

In the future,, artificial intelligence (AI) may also emerge as a useful technology to improve the evaluation and management of neonatal analgesic and sedative use. AI can potentially reduce the manual workload of collecting subjective information intermittently through the continuous retrieval of data through the use of AI leading to improved recognition and management of neonatal analgo-sedative requirements in critically ill neonates. An example of the proposed use and benefit of AI was described by Salekin, et al (2021), utilizing readily available data such as vital signs, body movement, crying frequency, and facial expressions of neonates. The authors conclusion suggest that, utilizing this data, AI would allow early recognition and management of the newborn's pain through timely implementation of non-opioid agents by neonatologists to facilitate avoidance of IWS and its related complications.[37]

Conclusion

Although the majority of the studies described in this review included patients of ages outside the newborn period, this limitation is explained by the scarcity of available data focusing on IWS in neonates. As previously stated, neonatal pain is an important topic due to evidence indicating that newborns are more susceptible to pain and can suffer from acute and long-term consequences if they do not receive appropriate analgesic therapy. Pain management, particularly in critical care, commonly involves both analgesic and sedative therapies usually managed through the use of opioids and benzodiazepines. Despite clinically

effective analgo-sedation, these agents also present risks which include tolerance and dependency which may lead to the development of IWS.

Even though there is limited information available concerning IWS epidemiology specifically for the neonatal group, data from the general pediatric population shows high prevalence and incidence rates for this problem particularly when drug exposure lasts more than 5 days. This finding supports the development of more extensive research and subsequent widespread distribution of evidenced based education concerning evaluation, recognition, management and prevention of IWS.

Opioids and benzodiazepines are the main drugs responsible for IWS due to their ability to induce changes in the hepatic and renal metabolism that led to reduced elimination and subsequent development of tolerance and dependency in neonates in comparison to older children and adults. Distinct from opioids, benzodiazepine withdrawal effects need to be better understood so that research can elucidate unique treatment options to counter their contribution to IWS.

Regarding currently available assessment tools for evaluating IWS intensivists should be aware of their limitations in order to appropriately determine their best option(s). The FNAS is designed to assess NAS instead of IWS, and considering its date of publication and inherent limitations, it may not be suited for assessment and evaluation of IWS. In contrast, WAT-1 and SOS both offer good sensitivity and specificity but, are limited by their development for pediatric patients of essentially all ages. Overall, despite both being recognized as validated IWS assessment tools, SOS may be more advantageous than WAT-1. As a result, future research efforts should be directed towards the neonatal population to more thoroughly address this shortcoming in the evaluation and management of neonatal IWS.

Most authors agree that IWS management consists basically of a transition from intravenous infusion of opioids and benzodiazepines to oral analogs with a greater half-life, followed by a

protocolized but judicious tapering in order to reduce drug exposure and the related risk of IWS. The prevention of IWS is equally as important and represents an additional effort to reduce the risk of opioid and benzodiazepine withdrawal and subsequent IWS. To this end, the implementation of a drug rotation protocol is recommended to reduce prolonged exposure to these agents and their association to IWS.

In closing, we recommend that neonatologists and pediatric intensivists implement protocolized evaluation and management of IWS with potential future inclusion of AI to reduce the risk of prolonged opioid and benzodiazepine exposure and their association with IWS.

Acknowledgments

This work was supported by grants from the Brazil National Council of Scientific and Technological Development (CNPq), in the form of graduate (I.N.S.) and postgraduate (E.S.S,) studentships, and productivity in research scholarship (H.I.C.).

Conflict of Interest

None declared.

References

1. Fitri SYR, Lusmilasari L, Juffrie M, Rakhmawati W. Pain in Neonates: A Concept Analysis. Anesthesiol Pain Med. 2019;9(4):e92455
2. Walker SM. Neonatal pain. Pediatr Anesth. 2014;24(1):39-48
3. Walker SM. Long-term effects of neonatal pain. Semin Fetal Neonatal Med. 2019;24(4):101005
4. Carter BS, Brunkhorst J. Neonatal pain management. Semin Perinatol. 2017;41(2):111-116
5. Valeri BO, Holsti L, Linhares MBM. Neonatal Pain and Developmental Outcomes in Children Born Preterm: A Systematic Review. Clin J Pain. 2015;31(4):355-362
6. Smits A, van den Anker JN, Allegaert K. Clinical pharmacology of analgosedatives in neonates: ways to improve their safe and effective use. J Pharm Pharmacol. 2017;69(4):350-360
7. LaRosa JM, Aponte-Patel L. Iatrogenic Withdrawal Syndrome: A Review of Pathophysiology, Prevention, and Treatment. Curr Pediatr Rep. 2019;7(1):12-19
8. Harris J, Ramelet AS, van Dijk M, et al. Clinical recommendations for pain, sedation, withdrawal and delirium assessment in critically ill infants and children: an ESPNIC position statement for healthcare professionals. Intensive Care Med. 2016;42(6):972-986
9. Isaac L, van den Hoogen NJ, Habib S, Trang T. Maternal and iatrogenic neonatal opioid withdrawal syndrome: Differences and similarities in recognition, management, and consequences. J Neurosci Res. 2022;100(1):373-395
10. Ávila-Alzate JA, Gómez-Salgado J, Romero-Martín M, Martínez-Isasi S, Navarro-Abal Y, Fernández-García D. Assessment and treatment of the withdrawal syndrome in paediatric intensive care units. Medicine (Baltimore). 2020;99(5): e18502
11. Duceppe MA, Perreault MM, Frenette AJ, et al. Frequency, risk factors and

symptomatology of iatrogenic withdrawal from opioids and benzodiazepines in critically Ill neonates, children and adults: A systematic review of clinical studies. J Clin Pharm Ther. 2019;44(2):148-156

12. Best KM, Boullata JI, Curley MAQ. Risk factors associated with iatrogenic opioid and benzodiazepine withdrawal in critically ill pediatric patients: A systematic review and conceptual model. Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2015;16(2):175-183
13. Pergolizzi Jr JV, Raffa RB, Rosenblatt MH. Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: Current understanding and approaches to management. J Clin Pharm Ther. 2020;45(5):892-903
14. Donato J, Rao K, Lewis T. Pharmacology of Common Analgesic and Sedative Drugs Used in the Neonatal Intensive Care Unit. Clin Perinatol. 2019;46(4):673-692
15. Thigpen JC, Odle BL, Harirforoosh S. Opioids: A Review of Pharmacokinetics and Pharmacodynamics in Neonates, Infants, and Children. Eur J Drug Metab Pharmacokinet. 2019;44(5):591-609
16. Fenn NE, Plake KS. Opioid and Benzodiazepine Weaning in Pediatric Patients: Review of Current Literature. Pharmacotherapy. 2017;37(11):1458-1468
17. Griffin CE, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine Pharmacology and Central Nervous System–Mediated Effects. Ochsner J. 2013;13(2):214-223
18. Gravielle MC. Regulation of GABAA receptors by prolonged exposure to endogenous and exogenous ligands. Neurochem Int. 2018; 118:96-104
19. Jacqz-Aigrain E, Burtin P. Clinical Pharmacokinetics of Sedatives in Neonates. Clin Pharmacokinet. 1996;31(6):423-443
20. Franck LS, Naughton I, Winter I. Opioid and benzodiazepine withdrawal symptoms in paediatric intensive care patients. Intensive Crit Care Nurs. 2004;20(6):344-351

21. Franck LS, Harris SK, Soetenga DJ, Amling JK, Curley MAQ. The Withdrawal Assessment Tool - Version 1 (WAT-1). Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2008;9(6):573-580
22. Franck LS, Scoppettuolo LA, Wypij D, Curley MAQ. Validity and generalizability of the Withdrawal Assessment Tool-1 (WAT-1) for monitoring iatrogenic withdrawal syndrome in pediatric patients. PAIN. 2012;153(1):142-148
23. Dokken M, Rustøen T, Diep LM, et al. Iatrogenic withdrawal syndrome frequently occurs in paediatric intensive care without algorithm for tapering of analgosedation. Acta Anaesthesiol Scand. 2021;65(7):928-935
24. Ista E, van Dijk M, de Hoog M, Tibboel D, Duivenvoorden HJ. Construction of the Sophia Observation withdrawal Symptoms-scale (SOS) for critically ill children. Intensive Care Med. 2009;35(6):1075-1081
25. Ista E, van Dijk M, Gamel C, Tibboel D, de Hoog M. Withdrawal symptoms in children after long-term administration of sedatives and/or analgesics: a literature review. “Assessment remains troublesome.” Intensive Care Med. 2007;33(8):1396-1406
26. Ista E, de Hoog M, Tibboel D, Duivenvoorden HJ, van Dijk M. Psychometric evaluation of the Sophia Observation withdrawal symptoms scale in critically ill children. Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2013;14(8):761-769
27. Finnegan LP, Kron RE, Connaughton JF, Emich JP. Assessment and treatment of abstinence in the infant of the drug-dependent mother. Int J Clin Pharmacol Biopharm. 1975;12(1-2):19-32
28. Smith HAB, Besunder JB, Betters KA, et al. 2022 Society of Critical Care Medicine Clinical Practice Guidelines on Prevention and Management of Pain, Agitation, Neuromuscular Blockade, and Delirium in Critically Ill Pediatric Patients with

Consideration of the ICU Environment and Early Mobility. Pediatr Crit Care Med. 2022;23(2): e74

29. D'Souza G, Wren AA, Almgren C, Ross AC, Marshall A, Golianu B. Pharmacological Strategies for Decreasing Opioid Therapy and Management of Side Effects from Chronic Use. Children. 2018;5(12):163
30. Dervan LA, Yaghmai B, Watson RS, Wolf FM. The use of methadone to facilitate opioid weaning in pediatric critical care patients: a systematic review of the literature and meta-analysis. Paediatr Anaesth. 2017;27(3):228-239
31. McPherson C, Ortinau CM, Vesoulis Z. Practical approaches to sedation and analgesia in the newborn. J Perinatol. 2021;41(3):383-395
32. Haenecour AS, Seto W, Urbain CM, Stephens D, Laussen PC, Balit CR. Prolonged Dexmedetomidine Infusion and Drug Withdrawal in Critically Ill Children. J Pediatr Pharmacol Ther. 2017;22(6):453-460
33. Mondardini MC, Sperotto F, Daverio M, et al. Efficacy and safety of dexmedetomidine for prevention of withdrawal syndrome in the pediatric intensive care unit: protocol for an adaptive, multicenter, randomized, double-blind, placebo-controlled, non-profit clinical trial. Trials. 2019;20(1):710
34. Sanavia E, Mencía S, Lafever SN, Solana MJ, Garcia M, López-Herce J. Sedative and Analgesic Drug Rotation Protocol in Critically Ill Children with Prolonged Sedation: Evaluation of Implementation and Efficacy to Reduce Withdrawal Syndrome*. Pediatr Crit Care Med. 2019;20(12):1111-1117
35. Rana D, Bellflower B, Sahni J, et al. Reduced narcotic and sedative utilization in a NICU after implementation of pain management guidelines. J Perinatol. 2017;37(9):1038-1042
36. Craske J, Carter B, Jarman I, Tume L. Parent's experiences of their child's withdrawal syndrome: a driver for reciprocal nurse-parent partnership in withdrawal assessment.

Intensive Crit Care Nurs. 2019; 50:71-78

37. Salekin MS, Mouton PR, Zamzmi G, et al. Future roles of artificial intelligence in early pain management of newborns. Paediatr Neonatal Pain. 2021;3(3):134-145

Legend to Figures:

Figure 1: Opioids interact with membrane receptors, inhibiting adenylyl cyclase-induced production of AMPc. During prolonged opioid use, homeostatic changes cause an increase in adenylyl cyclase activity, maintaining normal levels of AMPc. However, during opioid withdrawal, there is no inhibition of adenylyl cyclase, which increases AMPc levels. AMPc then stimulates the release of noradrenaline by the locus coeruleus (LC), and consequently, produces autonomic symptoms such as tachypnea and sweating. Protein structures obtained from: SwissModel.expasy.org

Figure 2: Benzodiazepines bind to an allosteric site in GABA-A receptors and modulate their activity positively. Prolonged exposure to benzodiazepines induces changes that lead to the development of tolerance and dependency. These alterations may include a decrease in receptor density, changes in receptor structure that affect benzodiazepine binding, and changes in GABA-A localization, such as the internalization of receptors. Protein structures obtained from: SwissModel.expasy.org

Table 1: Alternatives for analgesic and sedative drug therapy and, conversion of drug therapy from intravenous (IV) to oral dosing.

Reference	Current IV therapy	Oral alternative	Dose adjustment
McPherson et al. (2021)	Fentanyl (mcg/kg/hr)	Morphine (mg/kg/daily dose)	Multiply by 0.1 Administer 4/4 hr
	Fentanyl (mcg/kg/hr)	Methadone (mg/kg/daily dose)	Multiply by 0.05-0.1 Administer 6/6 hr
	Midazolam (mg/kg/hr)	Lorazepam (mg/kg/daily dose)	Multiply by 0.5-1 Administer 6/6 hr
	Dexmedetomidine (mcg/kg/hr)	Clonidine (mcg/kg/daily dose)	Multiply by 5 Administer 4/4 hr
D'Souza et al. (2018)	Morphine (mg/kg/hr)	Methadone (mg/kg/daily dose)	Multiply by 2-8 Administer 6/6 hr
	Fentanyl (mcg/kg/hr)	Methadone (mg/kg/daily dose)	Multiply by 0.05 Administer 6/6 hr

Table 2: Prophylactic and rescue treatments options for IWS according to the duration of drug therapy.

Duration of exposure	Dose reduction	Oral prophylaxis	Rescue treatment
<5 days	Reduce by 50% per day	-	Methadone 0.1-0.2 mg/kg/6 hr ± Clorazepate 0.5-2 mg/kg/8 hr
≥5 days	Reduce by 20% per day	Methadone 0.1-0.2 mg/kg/6 hr ± Clorazepate 0.5-2 mg/kg/8 hr	Clonidine 1-4 mcg/kg/6-8 hr ± Dexmedetomidine 0.2-0.75 mcg/kg/hr

Adapted from Sanavia E, Mencía S, Lafever SN, Solana MJ, Garcia M, López-Herce J. Sedative and Analgesic Drug Rotation Protocol in Critically Ill Children with Prolonged Sedation: Evaluation of Implementation and Efficacy to Reduce Withdrawal Syndrome*. Pediatr Crit Care Med. 2019;20(12):1111-1117

Table 3: Proposed drug rotation protocol for analgesic and sedative medications.

Rotation number	Drug options for analgesia	Drug options for sedation	Rescue treatment
1	Fentanyl 2 mcg/kg/hr (max 4 mcg/kg/hr)	Midazolam 2 mcg/kg/min (max 6 mcg/kg/min)	Clonidine 1-4 mg/k/6 hr oral
2	Ketamine 1 mg/kg/hr (max 2 mg/kg/hr)	Propofol 1 mg/kg/hr (max 4 mg/kg/hr)	Metamizole 6.6 mg/kg/hr IV
3	Remifentanyl 12 mcg/kg/hr (max 30 mcg/kg/hr)	Midazolam 2 mcg/kg/min (max 6 mcg/kg/min)	Clonidine 1-4 mg/k/6 hr oral
4	Metamizole 6.6 mg/kg/hr IV Acetaminophen 15 mg/kg/6 hr oral	Dexmedetomidine 0.75 mcg/kg/hr (max 1.2 mcg/kg/hr)	Morphine chloride 20 mcg/kg/hr IV (max 40 mcg/kg/hr)

Adapted from Sanavia E, Mencía S, Lafever SN, Solana MJ, Garcia M, López-Herce J. Sedative and Analgesic Drug Rotation Protocol in Critically Ill Children with Prolonged Sedation: Evaluation of Implementation and Efficacy to Reduce Withdrawal Syndrome*. Pediatr Crit Care Med. 2019;20(12):1111-1117

Table 4: Options for opioid rotation and guidance for dose conversion.

Rotation number	Opioid agent	Dose adjustment
1	Fentanyl (mcg/kg/hr)	-
2	Morphine (mcg/kg/hr)	Multiply fentanyl dose by 10–20 and reduce by ~25% for cross-tolerance
3	Hydromorphone (mcg/kg/hr)	Divide morphine dose by 7 and reduce by ~25% for cross-tolerance

Adapted from McPherson C, Ortinau CM, Vesoulis Z. Practical approaches to sedation and analgesia in the newborn. J Perinatol. 2021;41(3):383-395

Figure 1

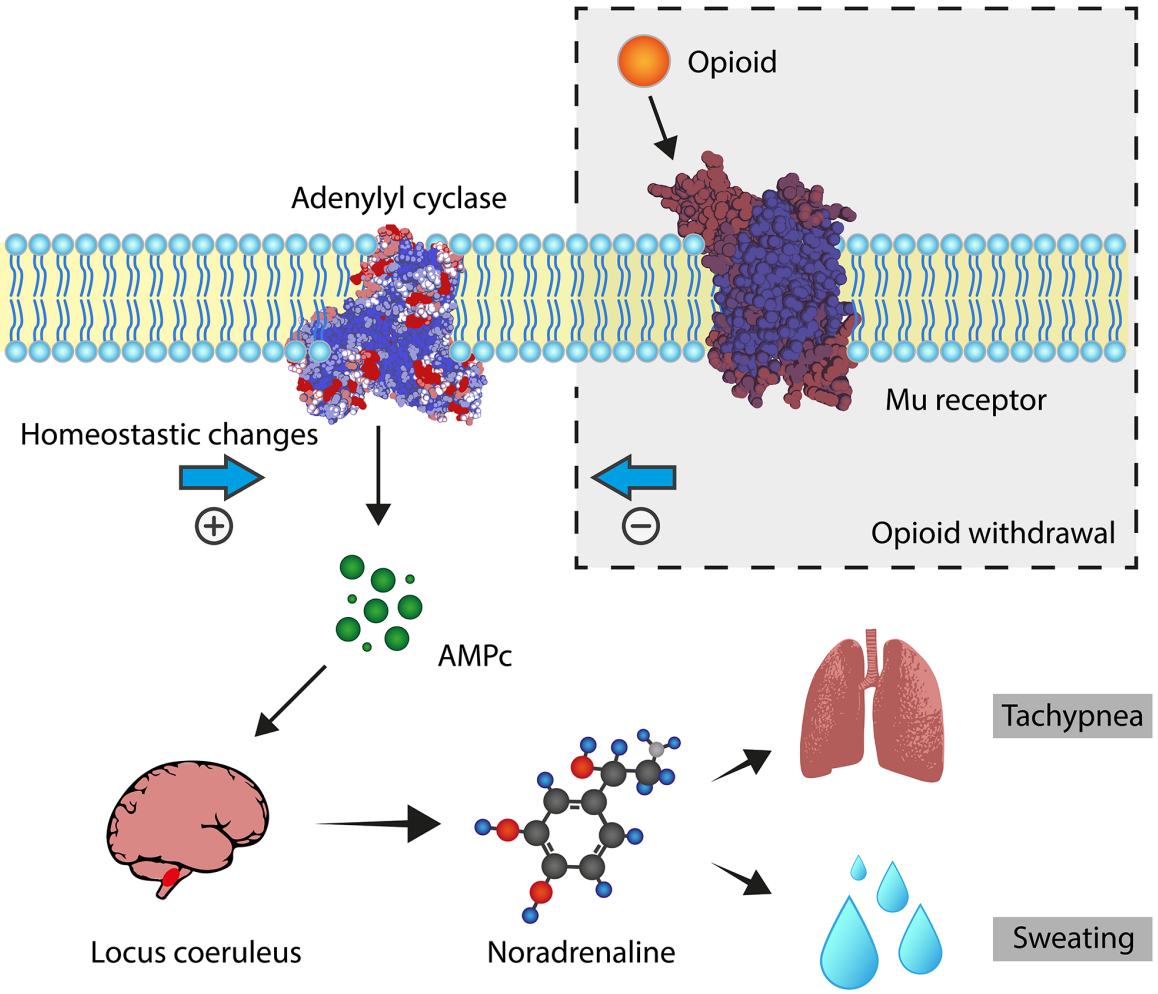
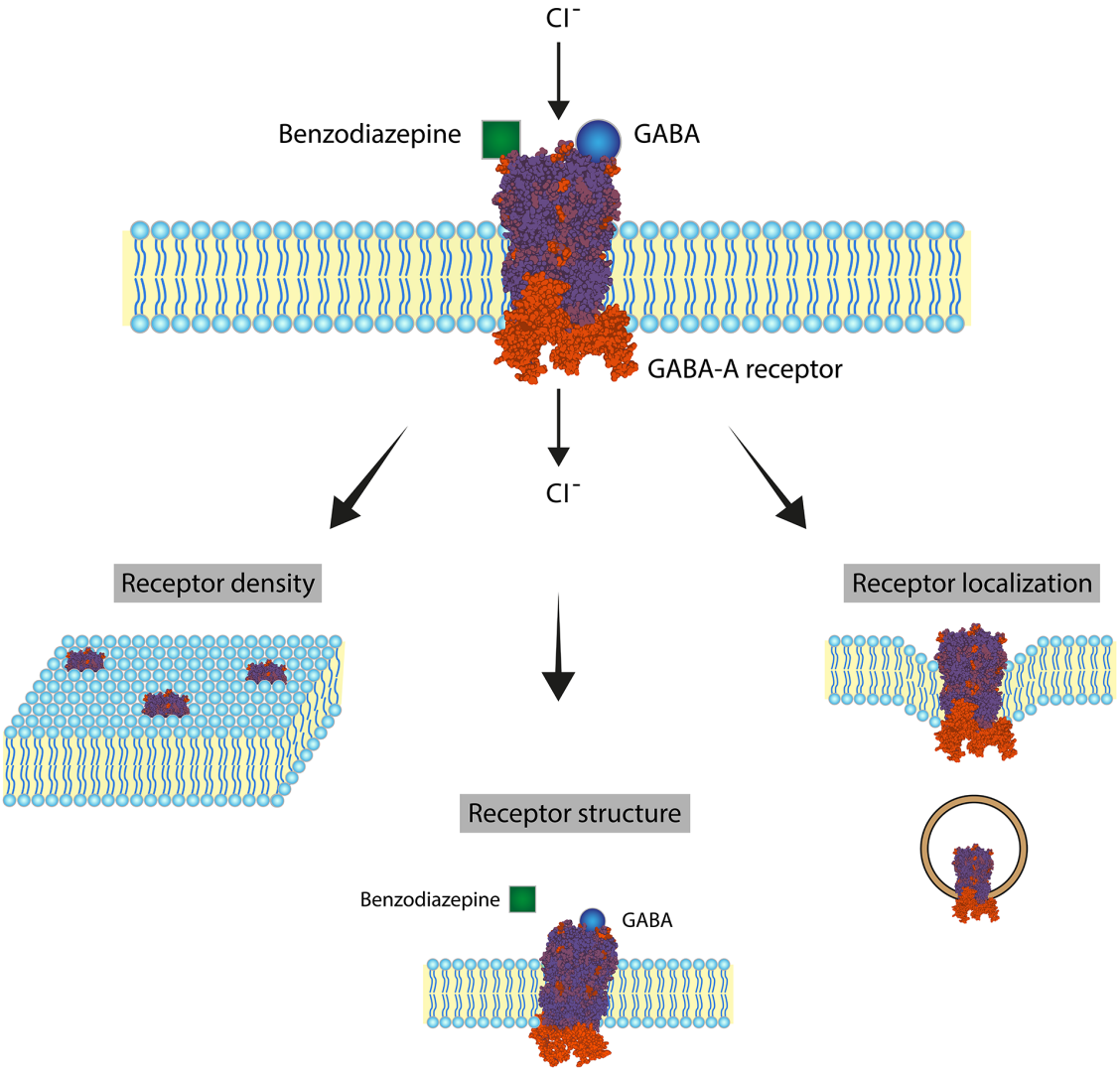

Opioid
Adenylyl cyclase
Mu receptor
Homeostastic changes
Opioid withdrawal
AMPc
Tachypnea
Locus coeruleus
Noradrenaline
Sweating

Figure 2


Cl⁻
Benzodiazepine
GABA
GABA-A receptor
Cl⁻
Receptor density
Receptor localization
Receptor structure
Benzodiazepine
GABA

ATTACHMENT

ADOPTED NORMS

This paper was produced following the standards of manuscript submission described in the Author Instructions guide, in attachment, from the Journal of Pediatric Intensive Care.

Journal of Pediatric Intensive Care
Author Instructions

Thank you for contributing to *Journal of Pediatric Intensive Care*. Please read the instructions carefully and observe all the directions given. Failure to do so may result in unnecessary delays in publishing your article.

SUBMISSION CHECKLIST

All manuscripts must be submitted at the following link:
http://www.editorialmanager.com/jpic

☐ **AUTHOR INFORMATION**
- All authors: full name, degrees, department, affiliation, e-mail address
- Corresponding author: mailing address, telephone number

☐ **MANUSCRIPT FILE**
- Must be digital - hard copy submissions are not accepted

☐ **ABSTRACT AND KEYWORDS**
- See the section Article Types for word limits

☐ **REFERENCES**
- Cited sequentially in AMA style

☐ **FIGURES AND TABLES**
- Cited sequentially and included in the main document

☐ **ART FILES**
- Must be saved separately from the main document

☐ **PERMISSIONS**
- Required if you plan to reproduce content from a published source or include a photograph of a patient
- Patient permission forms available at www.thieme.com/journal-authors

CONTENTS

MANUSCRIPT FORMAT

Article Types

The following graph shows what types of articles are accepted for publication, and what requirement they may have.

Article Type	Abstract Limit	Keywords Limit	Text Words (excluding refs) Limit	Tables/Figures Limit	References Limit
Original Article	Up to 250 words	3 to 6 keywords	Up to 4,000 words	Up to 5 tables/figures	Up to 40 references
Review Article	Up to 250 words	3 to 6 keywords	No limit	No limit	No limit
Case Report	Case reports are no longer published in *Journal of Pediatric Intensive Care*. Authors are encouraged to submit case reports to *Journal of Child Science*.				
Editorial	n/a	n/a	Up to 600 words	n/a	Up to 5 references
Letter to the Editor	n/a	n/a	Up to 600 words	Up to 1 table/figure	Up to 5 references
Book Review	n/a	n/a	Up to 600 words	n/a	n/a
Annual Meeting Abstract	n/a	n/a	No limit	No limit	No limit

General Guidelines

- You must submit a digital copy of your manuscript. Hard copy submissions are not accepted.
- Keep the format of your manuscript simple and clear. We will set your manuscript according to our style—do not try to "design" the document.
- The manuscript, including the title page, abstract and keywords, text, references, figure captions, and tables should be typewritten, double-spaced in 12-point font with 1-inch margins all around and saved as one file.
- Each figure should be saved as its own separate file. Do not embed figures within the manuscript file. This requires special handling by Thieme's Production Department.
- Keep abbreviations to a minimum and be sure to explain all of them the first time they are used in the text.
- The manuscripts should be written in American English.
- The authors should use Système International (SI) measurements. For clarity, nonmetric equivalents may be included in parentheses following the SI measurements.
- Use generic names for drugs. You may cite proprietary names in parentheses along with the name and location of the manufacturer.
- Credit suppliers and manufacturers of equipment, drugs, and other brand-name material mentioned in the manuscript within parentheses, giving the company name and primary location.

MANUSCRIPT FORMAT *continued*

Title Page

- This journal adheres to a single-blinded peer-review policy. The title page should be included in the main document.
- The title page should list the article title and the corresponding author's full name, degree, title, department, affiliation, mailing address, e-mail address, and telephone and fax numbers. It should also list the full name, degree, title, department, and affiliation of every co-author.

Abstract and Keywords

See the section Article Types for word limits.

The abstract should briefly outline the content of the article and any conclusions it may reach. The keywords should be words a reader would be likely to use in searching for the content of the article.

Main Document

- Please clearly distinguish the hierarchy of headings within the manuscript by using capital letters, underline, italic, and bold styles as necessary.
- As needed, use italic, superscripts, subscripts, and boldface, but otherwise do not use multiple fonts and font sizes.
- Do not insert page or section breaks except where noted in the Author Instructions.
- Use hard returns (the Enter key) only at the end of a paragraph, not at the end of a line. Allow lines of text to break automatically in your word-processing software. Do not justify your text.
- Use only one space, not two, after periods.
- Create tables using the Table function in Microsoft Word.

Thieme Editing Services

Thieme offers a language editing service for manuscripts, abstracts and theses in partnership with Enago, a world-leading provider of author services to researchers around the world. Authors can choose from a range of editing services and get their manuscripts edited by Enago's professional medical editors. Authors that wish to use this service will receive a 20% discount on all editing services. To find out more information or get a quote, please visit https://www.enago.com/thieme

Acknowledgments

The source of any financial support received and recognition of personal assistance for the work being published should be indicated at the end of the article, just before the Reference section, under the heading Acknowledgments.

Conflict of Interest

All authors (including corresponding and co-authors associated with the manuscript) must make a formal statement at the time of submission indicating any potential conflict of interest that might constitute an embarrassment to any of the authors if it were not to be declared and were to emerge after publication. Such conflicts might include, but are not limited to, shareholding in or receipt of a grant or consultancy fee from a company whose product features in the submitted manuscript or which manufactures a competing product. Should the article be accepted for publication, this information will be published with the paper.
Types of conflicts include: Consulting, Royalties, Research Support, Institutional Support, Ownership, Stock/Options, Speakers Bureau, and Fellowship Support. Any commercial entity whose products are described, reviewed, evaluated, or compared in the manuscript, except for those disclosed in the Acknowledgments section, are potential conflicts.
This journal follows the guidelines of the International Committee of Medical Journal Editors and an ICMJE disclosure of potential conflicts of interest (COI) form must be submitted for each author at the time of

manuscript submission. Forms must be submitted even if there is no conflict of interest. It is the responsibility of the corresponding author to ensure that all authors adhere to this policy prior to submission.
A conflict of interest statement must also be included in the manuscript after any "Acknowledgements" and "Funding" sections and should summarize all aspects of any conflicts of interest included on the ICMJE form. If there is no conflict of interest, authors must include 'Conflict of Interest: none declared'.
Please click http://www.icmje.org/conflicts-of-interest to download a Conflict of Interest form. The disclosure information is important in article processing. If the provided forms are incomplete or missing, it can cause delays in publishing of article.

Please note: The ICMJE Conflict of Interest forms can only be opened & edited with Adobe Reader.

References

References should be the most recent and pertinent literature available. It is essential that they are complete and thoroughly checked. If the reference information is incomplete, good online sites to search for full details are the National Library of Medicine: www.nlm.nih.gov; Books in Print: www.booksinprint.com; PubMed: www.ncbi.nlm.nih.gov/PubMed/; or individual publisher Web sites.

- References must be listed in AMA style, using Index Medicus journal title abbreviations.
- References follow the article text. Insert a page break between the end of text and the start of references.
- References must be cited sequentially (NOT alphabetically) in the text using superscript numbers.
- By way of exception to AMA style, do not italicize book titles or journal title abbreviations and do not put a period at the end of a reference.
- List all author names, up to and including six names. For more than six authors, list the first three followed by et al.
- References should be styled per the following examples:

1. Citing a journal article:
   Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma-globulin. N Engl J Med 1986;315:341–347

2. Citing a chapter in a book:
   Toma H. Takayasu's arteritis. In: Novick A, Scoble J, Hamilton G, eds. Renal Vascular Disease. Philadelphia: WB Saunders; 1995:47–62

3. Citing a book:
   Stryer L. Biochemistry. 2nd ed. San Francisco: WH Freeman; 1981:559–596

4. Citing a thesis:
   Stern I. Hemorrhagic Complications of Anticoagulant Therapy [Ph.D. dissertation]. Evanston, IL: Northwestern University; 1994

5. Citing a government publication:
   Food and Drug Administration. Jin Bu Huan Herbal Tablets. Rockville, MD: National Press Office; April 15, 1994. Talk Paper T94-22

6. Citing an online article:
   Rosenthal S, Chen R, Hadler S. The safety of acelluler pertussis vaccine vs whole-cell pertussis vaccine [abstract]. Arch Pediatr Adolesc Med [serial online]. 1996;150:457–460. Available at: http://www.ama-assn.org/sci-pubs/journals/archive/ajdc/vol_150/no_5/abstract/htm. Accessed November 10, 1996

7. Citing a symposium article:
   Eisenberg J. Market forces and physician workforce reform: why they may not work. Paper presented at: Annual Meeting of the Association of American Medical Colleges; October 28, 1995; Washington, DC

Figure Captions

- Figures include photographs or radiographs, drawings, graphs, bar charts, flow charts, and pathways, but NOT lists or tables.
- Figures must be cited sequentially in the text. Number all figures (and corresponding figure captions) sequentially in the order they are cited in the text.
- Figure captions should be written after the reference list. Insert a page break between the end of references and the start of figure captions.
- Figure captions should include a description of the figure and/or each lettered part (A, B, etc.) and of any portions of the figure highlighted by arrows, arrowheads, asterisks, etc.
- For a figure borrowed or adapted from another publication (used with permission), add a credit line in parentheses at the end of each figure legend. This credit line should be a complete bibliographic listing of the source publication (as a reference), or other credit line as supplied by the copyright holder. For example (Reprinted with permission from Calfee DR, Wispelwey B. Brain abscess. Semin Neurol 2000;20:357.)

Tables

- Data given in tables should be commented on but not repeated in the text. Be sure that lists or columns of related data are composed in a word-processing program like the rest of the text.
- Do not intersperse tables in the text. Tables should appear after the figure captions. Insert a page break between the end of the figure captions and the start of the tables.
- Tables must be double-spaced and numbered in the same sequence they are cited in the text. A short descriptive title should be provided for each table.
- If a table contains artwork, supply the artwork separately as a digital file.
- For tables borrowed or adapted from another publication (used with permission), add a credit line as the first footnote beneath each table. This credit line should be a complete bibliographical listing of the source publication (as a reference), or other credit line as supplied by the copyright holder. For example, “Reprinted with permission from Calfee DR, Wispelwey B. Brain abscess. Semin Neurol 2000;20:357.” (“Data from . . .” or “Adapted from . . .” may also be used, as appropriate.)
- Other footnotes for tables should be indicated in the table using superscript letters in alphabetical order.
- Any abbreviations used in the table should be explained at the end of the table in a footnote.

DIGITAL ARTWORK PREPARATION

General Guidelines

- It is best to use Adobe Photoshop to create and save images, and Adobe Illustrator for line art and labels.
- Do not submit art created in Microsoft Excel, Word, or PowerPoint. These files cannot be used by the typesetter.
- Save each figure in a separate file.
- Do not compress files.
- All black-and-white and color artwork should be at a resolution of 300 dpi (dots per inch) in TIFF format. Line art should be 1,200 dpi in EPS or TIFF format. Contact the Production Editor at Thieme if you are unsure of the final size.
- It is preferable for figures to be cropped to their final size (approximately 3½ inches for a single column and up to 7 inches for a double column), or larger, and in the correct orientation. If art is submitted smaller and then has to be enlarged, its resolution (dpi) and clarity will decrease.

  Note: Lower resolutions (less than 300 dpi) and JPEG format (.jpg extension) for grayscale and color artwork are strongly discouraged due to the poor quality they yield in printing, which requires 300 dpi resolution for sharp, clear, detailed images. JPEG format, by definition, is a lower resolution (compressed) format designed for quick upload on computer screens.

Black-and-White Art

- Black-and-white artwork can be halftone (or grayscale) photographs, radiographs, drawings, line art, graphs, and flowcharts. Thieme will only accept digital artwork.
- If possible, do not send color art for conversion to black-and-white. Do the conversion yourself so that you can check the results and confirm in advance that no critical details are lost or obscured by the change to black-and-white.
- For best results, line art should be black on a white background. Lines and type should be clean and evenly dark. Avoid screens or cross-hatching, as they can darken or be uneven in printing and lead to unacceptable printing quality.

Color Art

- Color illustrations are expensive to produce and usually cannot be accepted unless the author is willing to cover the additional production costs incurred. Please check with the Editor in Chief or Thieme for details. We will convert color illustrations to black-and-white unless we receive a letter from the author assuming responsibility for the cost of printing color. Upon request, we will provide you with a cost estimate for the color printing.
- All color artwork should be saved in CMYK, not RGB.

Art Labels

- Arrows, asterisks, and arrowheads (or other markers) should be white in dark or black areas and black in light or white areas, and large in size. If not, these highlighting marks may become difficult to see when figures are reduced in size during the typesetting process.
- Use 1-point (or thicker) rules and leader lines.
- Capitalize the first word of each label and all proper nouns. Consider using all capitals if you need a higher level of labels.
- Where there are alternate terms or spellings for a named structure, use the most common one and make sure it is consistent with what is used in the text.
- Avoid using multiple fonts and font sizes for the labels; use only one or two sizes of a serif font.

SUBMISSION PROCEDURE

Submission Procedure

- Consult the checklist on the first page of this document to ensure that you are ready to submit your manuscript.
- Please note: **There are no submission charges to submit your manuscript to this journal.**
- Manuscripts must be submitted electronically at the following link: http://www.editorialmanager.com/jpic
- Always review your manuscript before submitting it. You may stop a submission at any phase and save it to submit later. After submission, you will receive a confirmation email. You can also check the status of your manuscript by logging in to the submission system. The Editor in Chief will inform you via email once a decision has been made.

Preprint Server Statement

Journal of Pediatric Intensive Care encourages the submission of manuscripts that have been deposited in an initial draft version in preprint repositories such as Research Square, arXiv, and medRxiv. Drafts of short conference abstracts or degree theses posted on the website of the degree-granting institution, and draft manuscripts deposited on authors' or institutional websites are also welcome. All other prior publication is forbidden.

During submission, authors should (1) note use of the preprint repository in the cover letter, (2) state what adjustments and/or updates the draft has undergone between deposition and submission and (3) cite the preprint, including the DOI, as a reference in the manuscript.

After submission to the journal, and until a final decision has been made, authors are discouraged from depositing versions of their manuscript as preprints. Upon publication authors should add a link from the preprint to the published article. Twelve months after publication, authors can update the preprint with the accepted manuscript.

Revision Procedure

- Should the editors decide that your article requires a revision, you will need to make the changes via a word-processing program and resubmit it electronically.
- Log In to the submission system and find your article, which will be marked for revision.
- The best way to make revisions to your manuscript is by enabling the Track Changes mode in Microsoft Word, which will automatically highlight and mark up revised text. Please submit both a marked up copy and a clean copy of your revised manuscript to the submission system.
- Your original files will still be available after you upload your revised manuscript, so you should delete any redundant files before completing the submission.
- You will also be provided space in which to respond to the reviewers' and editors' comments. Please be as specific as possible in your response.

PRODUCTION PROCEDURE

Page Proofs

Page proofs will be sent to you via email. The proofs will be in a PDF file format, which should be opened using Acrobat Reader software. You will receive further instructions with your proofs. Take this opportunity to check the typeset text for typographic and related errors. Elective alterations are difficult to accommodate owing to the associated time and expense of introducing them. Therefore, please be sure that when you submit your manuscript, it is accurate, complete, and final.

Article Offprints

You will be able to order offprints of your article in advance of its publication. Details and prices will be sent to you along with the page proofs. Upon publication, the corresponding author will receive a complimentary PDF of their article.

POLICY STATEMENTS

Statement on Liability

The legislation on product liability makes increased demands on the duty of care to be exercised by authors of scientific research and medical publications. This applies in particular to papers and publications containing therapeutic directions or instructions and doses or dosage schedules. We therefore request you to examine with particular care, also in your own interest, the factual correctness of the contents of your manuscript once it has been copyedited and returned to you in the form of galley proofs. The responsibility for the correctness of data and statements made in the manuscript rests entirely with the author.

Definition of Authorship

Authorship credit should be based on criteria established by the International Committee of Medical Journal Editors. Each author should have made the following contributions towards the completion of the manuscript:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data
2. Drafting the article or revising it critically for important intellectual content
3. Final approval of the version to be published

Copyright Statement

Submitted manuscripts must represent original research not previously published nor being considered for publication elsewhere. The editors and Thieme combat plagiarism, double publication, and scientific misconduct with the software CrossCheck powered by iThenticate. Your manuscript may be subject to an investigation and retraction if plagiarism is suspected.

If you plan to reproduce text, tables, or figures from a published source, you must first obtain written permission from the copyright holder (usually the publisher). This is required even if the material is from your own published work. For material never before published and given to you by another person, you must obtain permission from that person. Serious delays to publication can be incurred if permissions are not obtained.

As the author, it is your responsibility to obtain all permissions, pay any permission fees, furnish copies of permissions to Thieme with your manuscript, and include a credit line at the end of the figure caption, beneath the table, or in a text footnote.

Upon publication of an article, all rights are held by the publishers, including the rights to reproduce all or part of any publication. The reproduction of articles or illustrations without prior consent from the publisher is prohibited.

Statement of Ethics

This journal adheres to the ethical standards described by the Committee on Publication Ethics and the International Committee of Medical Journal Editors. Authors are expected to adhere to these standards.

For all manuscripts reporting data from studies involving human or animal participants, formal review and approval, or formal review and waiver (exemption), by an appropriate institutional review board (IRB) or ethics committee is required, as well as any necessary HIPAA consent, and should be described in the Methods section with the full name of the reviewing entity. All clinical trials must be registered in a public trials registry. Denote the registry and registry number.

Patient Permission Policy and Thieme GDPR Policy

You must obtain a signed patient permission form for every patient whose recognizable photograph will be used. If you do not supply this, the identity of the patient must be obscured before the image is published; this could interfere with the instructive value of the photograph.

The personal rights of people who are recognizable on images must be protected. Please provide a written consent form for publication signed by every recognizable person. For persons under 18 years of age / persons supervised, please provide the signature of both parents / the legal guardian / supervisor. A suitable declaration of consent form can be obtained in our authors' lounge. Patient permission forms are available at www.thieme.com/journal-authors

We cannot accept or store illustrations in which personal data of third parties are included. Please submit images in completely anonymous form, free of personal data only! Such data may not only be directly visible in the image (e.g., a patient name or a date of birth in an X-ray image); they can also be included in the metadata of the image, which is accessible with the appropriate software. They may also be obscured by a cropping feature (such as PowerPoint or Word), but can be made visible underneath. If you have questions about data protection regulations, please contact us before submitting your manuscript.

EDITORIAL CONTACTS

Please contact the Editors or Thieme Publishers with any questions.

Editors in Chief
Mark J. Heulitt, MD
Medical Director,
Pediatric Intensive Care Unit and Hospitalist Program,
Spence and Becky Wilson Baptist Hospital,
Memphis, TN 38120
Tel.: +501-258-7404
markheulitt@gmail.com

Huseyin Caksen, MD, PhD
Necmettin Erbakan University, Meram Medical Faculty
Department of Pediatrics,
Divisions of Pediatric Neurology and Genetics
42080 Meram, Konya, Turkey
Tel: +90 332 223 75 46 / Fax: +90 332 223 61 81
huseyincaksen@hotmail.com

Thieme Publishers
jpic@thieme.com

Thieme Publishers – Production Editor
Sudeshna Roy
Thieme Medical and Scientific Publishers Private Limited
A-12, Second Floor, Sector -2,
NOIDA -201301
Uttar Pradesh
India
Email: Sudeshna.Roy@thieme.in
Tel: +91 120 4556600/ Fax: +91 120 4556649

Last Updated: January 2022