

NON-PHARMACOLOGICAL INTERVENTIONS FROM NURSES TO PATIENTS WITH DELIRIUM ADMITTED TO INTENSIVE CARE – AN UPDATE

Intervenções não farmacológicas dos enfermeiros à pessoa com delirium internada em cuidados intensivos – uma atualização

Intervenciones no farmacológicas de enfermeras a personas con delirio ingresadas en cuidados intensivos: una actualización

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ABSTRACT

Background: the person with delirium represents a challenge to health professionals, especially nurses. On the other hand, there are important limitations regarding the pharmacological treatment of this disease. **Objectives:** to identify the efficacy of non-pharmacological interventions in adults with delirium by intensive care nursing. **Methodology:** we carried out an integrative review, using electronic bibliographic databases, namely EBSCO and Pubmed MEDLINE, for articles published between 2018 and 2022. The process of selecting articles was based on the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for systematic reviews. **Results:** nine articles (n=9) were included in the study, of which six correspond to original articles, two to meta-analyses and one systematic review. The non-pharmacological intervention with the greatest available evidence was the multicomponent intervention, although the quality of the studies limits concrete recommendations regarding this approach. **Conclusion:** the evidence points to the fact that a personalization of care in a complex and integrated perspective is the most effective non-pharmacological approach to delirium.

Keywords: nursing care; adult; intensive care; delirium diagnosis.

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RESUMO

Enquadramento: a pessoa com delirium representa um desafio aos profissionais de saúde, nomeadamente aos enfermeiros. Por outro lado, existem limitações importantes quanto ao tratamento farmacológico desta doença. **Objetivos:** identificar a eficácia de intervenções não farmacológicas em adultos com delirium implementadas pelos enfermeiros em cuidados intensivos. **Metodologia:** realizámos uma revisão integrativa, tendo recorrido a bases bibliográficas eletrónicas, nomeadamente EBSCO e Pubmed MEDLINE, para artigos publicados entre 2018 e 2022. O processo de seleção de artigos teve por base as recomendações da PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) para revisões sistemáticas. **Resultados:** foram incluídos no estudo nove artigos (n=9), dos quais seis correspondem a artigos originais, dois a meta-análises e uma revisão sistemática. A intervenção não farmacológica com maior evidência disponível foi a intervenção multicomponente, apesar da qualidade dos estudos limitar recomendações concretas em relação a esta abordagem. **Conclusão:** a evidência aponta para que uma personalização dos cuidados numa perspetiva complexa e integrada seja a abordagem não farmacológica do delirium com maior eficácia. **Palavras-chave:** cuidados de enfermagem; adulto; cuidados intensivos; delirium.

RESUMEN

Marco contextual: la persona con delirium representa un desafío para los profesionales de la salud, especialmente para los enfermeros. Por otro lado, existen limitaciones importantes con respecto al tratamiento farmacológico de esta enfermedad. **Objetivos:** identificar la eficacia de las intervenciones no farmacológicas en adultos con delirium en las enfermerías de cuidados intensivos. **Metodología:** se realizó una revisión integradora, utilizando bases de datos bibliográficas electrónicas, a saber, EBSCO y Pubmed MEDLINE, para artículos publicados entre 2018 y 2022. El proceso de selección de artículos se basó en las recomendaciones de PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) para revisiones sistemáticas. **Resultados:** nueve artículos (n=9) fueron incluidos en el estudio, de los cuales seis corresponden a artículos originales, dos a metanálisis y una revisión sistemática. La intervención no farmacológica con mayor evidencia disponible fue la intervención multicomponente, aunque la calidad de los estudios limita las recomendaciones concretas con respecto a este enfoque. **Conclusión:** la evidencia apunta al hecho de que una personalización de la atención en una perspectiva compleja e integrada es el enfoque no farmacológico más efectivo para el delirium. **Palabras clave:** enfoque no farmacológico; adulto; cuidados intensivos; delirium.

INTRODUCTION

Delirium or acute confusional syndrome is an acute and fluctuating alteration of the mental state characterized by changes in consciousness, disorientation, and attention, among other symptoms (Inouye et al., 2014), including psychomotor agitation, lack of insight into the clinical situation, and consequent lack of cooperation in care provision. It is a potentially life-threatening condition in the absence of proper clinical management since, most of the time, it masks an underlying medical condition.

Acute confusional syndrome is a common complication in patients admitted to Intensive Care Units (ICU), occurring in over 87% of cases in this context (Blevins & DeGennaro, 2018), and is associated with increased length of hospital stay, mortality, and healthcare costs (Barr et al., 2013). Pharmacological treatment of delirium has been widely studied but is not always effective and may be associated with harmful side effects to the patient's clinical condition. Despite its negative impact at different levels, it has only recently been considered an important factor in terms of prognostic evolution (Olmos et al., 2019).

For this reason, there has been a growing focus on the non-pharmacological approach to delirium, especially by the intensive care nursing team. Nurses, as professionals who are in direct contact with the patient for extended periods, play a crucial role in early recognition of the condition. It is also important that the assessment is carried out multiple times a day, considering the fluctuating nature of the disease. It is estimated that delirium goes undetected in 30 to 75% of cases (Blevins & DeGennaro, 2018).

Non-pharmacological approaches may include non-invasive interventions such as (non)verbal

communication, ensuring a calming environment, and promoting a proper sleep-wake cycle (Poole & Ray, 2022). Additionally, other interventions such as music therapy (Khan, 2020), occupational therapy (Álvarez, 2017), and physiotherapy (Rains, 2017) can also be used to prevent and treat delirium in intensive care. The potential of these interventions lies in their ability to be part of a holistic approach focused on the patient's well-being (Keating, 2015). Recent studies have shown promising results. The implementation of delirium prevention and treatment protocols has been associated with a reduction in the incidence and duration of the condition in intensive care settings (Trogrlić Z, 2015). In 2018, a review by Portuguese authors was published on non-pharmacological interventions by nursing staff in intensive care (Bento & Sousa, 2021). However, it mentions limitations in the methodology used regarding the methodological analysis of the included articles, which hinders specific recommendations in clinical practice.

Considering the limitations of previous studies, the authors aimed to review studies published after the work of Bento and Sousa to identify the effectiveness of different non-pharmacological strategies implemented by intensive care nurses with stronger methodological evidence.

METHODS

This study followed the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations (Page et al., 2021).

- Eligibility criteria

The eligibility criteria included: 1) articles in Portuguese or English; 2) individually or cluster-randomized controlled trials, comparative and

observational studies with participants aged 18 years or older, as well as systematic reviews and meta-analyses, published between 2018 and 2022; 3) participants diagnosed with acute confusional syndrome (ACS) during their stay in an ICU; 4) use of a validated tool to quantify delirium progression; 5) implementation of a non-pharmacological intervention directly addressing ACS.

Grey literature articles (e.g., oral communications, conference papers, government documents), qualitative studies, other reviews that were not systematic reviews, and case reports were excluded. Articles where the outcomes of interest were not measured or reported were also excluded. Studies based on the comparator (except if pharmacological), treatment duration, or follow-up period were not excluded.

- Sources of information and search criteria

The PubMed and EBSCOhost - Research Databases platforms were used, which include resources such as CINAHL Complete; Nursing & Allied Health Collection: Comprehensive; Cochrane Central Register of

Controlled Trials; Cochrane Database of Systematic Reviews; Cochrane Methodology Register; Library, Information Science & Technology Abstracts, and MedicLatina. Descriptors were combined in a standardized way to identify relevant works as follows: "delirium" OR "confusional" AND "ICU" OR "intensive care" AND "non-pharmacological" OR "behavioral" OR "behavioural" AND "nurse". The search on both platforms was limited to articles published between 2018 and 2022.

- Selection process and data collection

Two independent reviewers evaluated the titles and abstracts of the studies identified through electronic search using predefined inclusion and exclusion criteria. Studies that met the inclusion criteria were selected for full analysis. Any disagreements between reviewers were resolved through discussion and consensus. The Rayyan® platform was used to aggregate and facilitate the exclusion of duplicates, as well as the inclusion and exclusion of articles. No other tool was used for data collection or processing.

language (n=85); publication year outside 2018 to 2022 (n=25); duplicates (n=688); grey literature (n=762); population [not matching participants aged 18 or older admitted to ICU with ACS] (n=460 studies); pharmacological intervention or others not aligning with the study objective as a comparator variable (n=147); and outcomes of interest not reported (n=146). Nine studies were included in this review.

RESULTS

- Study selection

Following the above-mentioned search strategy, 2422 works were obtained and examined (see Figure 1). Articles were excluded preferably in the following order of exclusion criteria: non-English or Portuguese

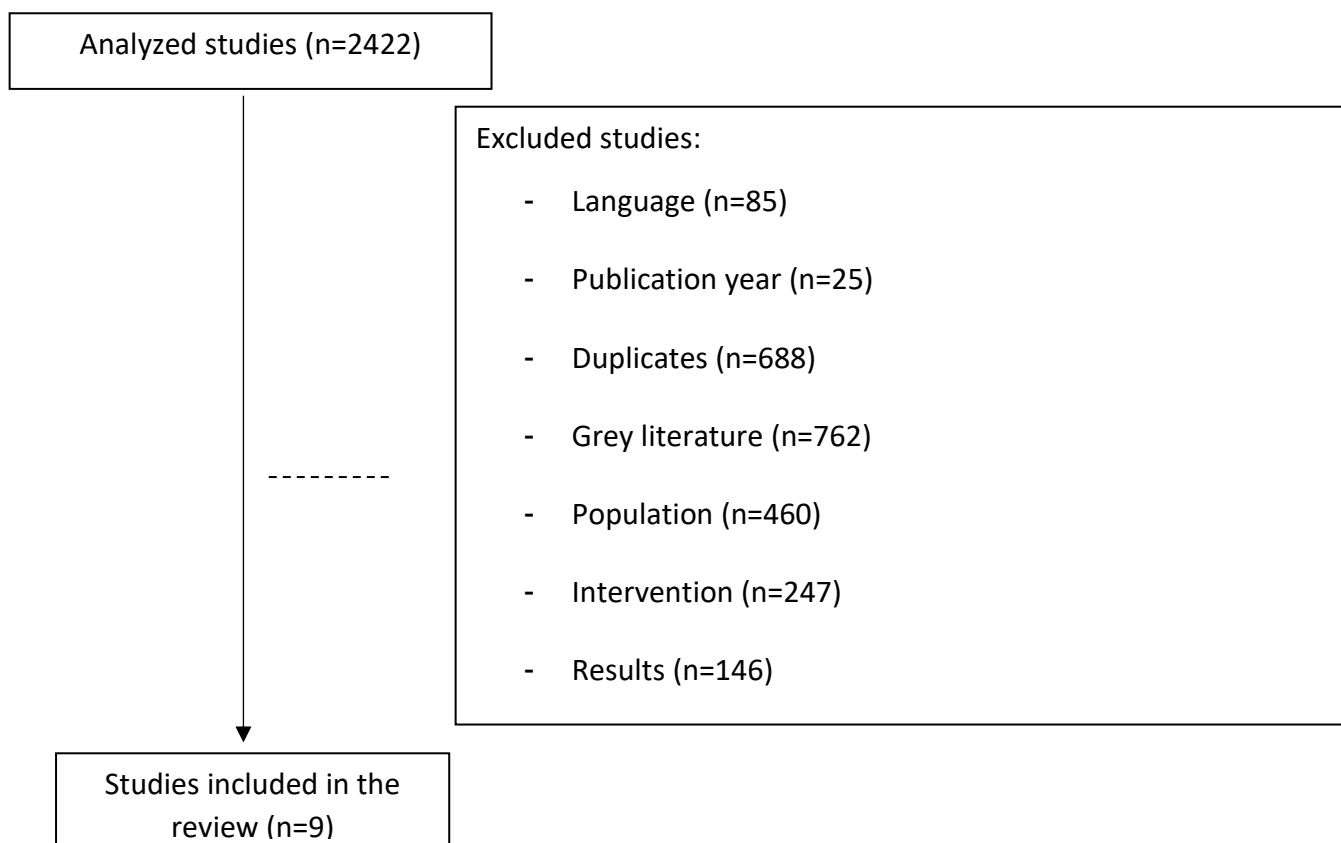


Figure 1

Diagram of the selection process

- Study Characteristics

Among the included studies, six are comparative studies that utilized the CAM (Confusion Assessment Method) (Inouye, 1990) or NEECHAM (Neelon and Champagne Confusion Scale) (Neelon et al., 1996), two are meta-analyses, and one is a systematic review. The distribution of the studies and their main characteristics are described in Table 1 and Table 2. Several non-pharmacological interventions are described:

1) Multicomponent interventions, integrated and complex interventions, mentioned by the majority of studies (n=5), including the systematic review (Matsuura et al., 2022) and the two meta-analyses (Bannon et al., 2019; León-Salas et al., 2020);

2) Different strategies encompassed in Roy's adaptation model, considering the relationship and adaptation between the individual and the surrounding environment (Hamzhepour et al., 2018);

3) Presence or absence of windows in the ICU, considering light exposure and its influence on the circadian rhythm (Lee et al., 2021); and

4) Absence of family visits (Kim et al., 2022), considering the widespread restrictions imposed by the COVID-19 pandemic.

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Table 1

Original studies included in the review and their main characteristics. CAM, Confusion Assessment Method; ICU, Intensive Care Unit; ACS, acute confusional syndrome

First author	Year of publication	Population	Outcome measurement	Intervention	Results
Brennan	2022	2566 patients (3-6 months control [n=1184] vs 4-8 months intervention [n=1434])	CAM	Multicomponent intervention (cognitive, sensory functions, environmental changes, early interventions)	Effectiveness in reducing ACS by 33% (from 30% to 20%), measured by CAM
Jin Lee	2021	150 patients admitted to the ICU (67 ICUs without windows vs 83 ICUs with windows)	CAM-ICU	Comparison between ICUs with windows vs ICUs without windows	ICU with windows associated with a lower incidence of ACS (21.7% vs. 43.3%)
Ju Hee	2021	73 patients (intervention n=35 vs control n=38 with standard treatment)	CAM-ICU	Multicomponent intervention (caregiver education, sensory limitations intervention, ACS assessment, maintenance of sleep-wake patterns, reorientation activities, addressing limited or conditioned mobility)	Reduction in the incidence of ACS (OR=0.19)
Hamzehpour	2018	100 patients (intervention n=50 vs control n=50)	NEECHAM Confusion Scale	Roy's adaptation model (strategies focused on self-concept, physiological functions, interdependence, role functions)	Reduction in the incidence of ACS from the fourth day of intervention
Kim	2022	442 patients (289 patients with restricted visits vs 153 patients without visits)	CAM-ICU	Ban on visits during the COVID-19 pandemic	The visitation ban did not alter the incidence of ACS during the COVID-19 pandemic but proved to be a risk factor for hyperactive or mixed subtype ACS and higher levels of anxiety.

Table 2

Systematic reviews and meta-analyses included in the study and their main characteristics. ACS, Acute Confusional Syndrome

First author	Type of study	Year of publication	Time frame of included studies	Number of studies	Results of interest
Matsuura	Systematic review	2022	until October 2021	11 (2549 participants)	Effectiveness of multicomponent interventions, mainly a combination of: sleep promotion, early mobilization, cognitive stimulation, and assessment; and a combination of sleep promotion with cognitive stimulation.
Léon-Salas	Meta-analysis	2020	until February 2019	10 (2850 participants)	Multicomponent interventions are effective in reducing the incidence, duration, and severity of ACS.
Bannon	Meta-analysis	2018	until March 2018	15 (2812 participants)	Fototerapia e intervenções multicomponente não demonstraram evidência de eficácia na redução da incidência e duração do SCA.

DISCUSSION

Regarding multicomponent interventions, the systematic review and one of the meta-analyses (León-Salas et al., 2020; Matsuura et al., 2022) show promising results, emphasizing the effectiveness of these interventions. Many studies have been exploring multicomponent interventions to prevent and treat delirium in critically ill patients. An example of a multicomponent intervention is the ABCDEF Bundle program, which consists of six elements: regular delirium assessment, proper pain assessment, agitation and anxiety assessment, sleep hygiene promotion, early mobilization, and reduction of sedative medication use. This intervention has been associated with better outcomes in ICU patients, including reduced mechanical ventilation time and lower mortality rates (Pun et al., 2019). The meta-analysis by León-Salas and colleagues highlights the benefit in terms of the incidence, duration, and severity of ACS. However, the evidence specifically related to the ICU (Guo et al., 2016), although statistically significant, does not report the duration of the multicomponent intervention. According to Matsuura et al. (2022), there seems to be a benefit from these interventions when there is a combination of the following: 1) sleep promotion, early mobilization, cognitive stimulation, and delirium assessment; and 2) sleep promotion and cognitive stimulation. However, of the 11 included studies, only the study by Guo and colleagues (Guo et al., 2016) - with the aforementioned limitation - presented both a high quality of outcome assessment and a low risk of bias. Indeed, in the 2018 meta-analysis (Bannon et al., 2019), the results indicate the ineffectiveness of these interventions in terms of delirium incidence and

duration, although the authors acknowledge that this conclusion may stem from the need for more personalized care, considering the characteristics of each patient, the interventions, and the characteristics of the ICU itself.

Roy's Adaptation Model, which focuses on an approach that aims to recognize internal and external changes in a holistic view of the individual, seems to bring benefits (Jennings, 2017), reinforcing Bannon and colleagues' argument on the relevance of personalized care. Despite Bannon's conclusions, the interventions in question involve the nurse as a key element, which obviously leads to inevitable heterogeneity, even when standardized protocols are considered. Like various types of psychotherapy, a personalized non-pharmacological intervention is imbued with great subjectivity and variability, both by the patient and the nurse, making it difficult to validate and draw specific results that are generalizable to anyone.

Delirium is a condition in which, especially in the presence of low cognitive reserves (with age being the main risk factor), changes in thought organization, attention, and temporal-spatial orientation (but also self and allopsychically) are observed. In these neuropsychiatric conditions, various hypotheses have been put forward regarding their etiopathogenesis, including: 1) differences in permeability in the blood-brain barrier (BBB), affecting the passage of toxic and inflammatory substances into the cerebrospinal fluid and consequent neurochemical and neurological dysfunction (Wilson et al., 2002); 2) intoxication or withdrawal from drugs or medications that cross the BBB, such as benzodiazepines or alcohol (Schuckit, 2014); and 3) stress and inflammation resulting from

dysfunction of the BBB itself (Barichello et al., 2021). Neurological dysfunction may include changes in the functioning of the suprachiasmatic nucleus - a central structure in circadian regulation (Poole & Ray, 2022). The causes of delirium are also vast, and their enumeration is beyond the scope of this article; however, besides practically any medical condition (including pain or any physical discomfort), environmental changes, light exposure (or lack thereof), or changes in interpersonal relationships are risk factors for ACS (Poole & Ray, 2022). Therefore, it is understandable that multicomponent interventions that include both a biological and psychosocial perspective, adapted to each particular situation, represent an ideal approach, including: pain assessment and treatment, early mobilization, hydration, monitoring of vital signs, temporal and spatial orientation, prevention of sleep deprivation, involvement of family and caregivers in patient care (Inouye et al., 2014), and valuing zeitgebers (synchronizers), especially light, but also social contacts (including family members), in order to promote proper regulation of the circadian rhythm (Poole & Ray, 2022).

Nevertheless, regarding the efficacy of light exposure, the analysis revealed contradictory results. Bannon and colleagues' meta-analysis concludes that studies on the efficacy of phototherapy are heterogeneous, highlighting a high degree of imprecision, a high risk of bias, and low quality of evidence, according to the GRADE tool (Grading of Recommendations Assessment, Development and Evaluation) (Bannon et al., 2019; Guyatt et al., 2011). A more recent study reveals that the cumulative incidence and risk of developing delirium in the ICU tends to be lower when

the unit has windows with natural light compared to units without this feature (Lee et al., 2021); however, this is a study with a relatively small sample (150 patients admitted to the ICU [67 ICUs without windows vs. 83 ICUs with windows]), and the same study did not show differences in terms of mechanical ventilation time, length of hospital stay, and 28-day mortality.

Regarding the influence of family visits in the ICU and their impact on delirium, Kim and colleagues' study on the restrictions imposed by the COVID-19 pandemic revealed that this factor does not seem to influence the incidence of ACS, although it is associated with a higher risk of non-hypoactive ACS and higher levels of anxiety (Kim et al., 2022). The absence of comforting elements for the patient may trigger greater anxiety and restlessness, leading to more agitated states of confusion.

These findings reinforce the idea that, although the neurobiological mechanisms explaining ACS are becoming clearer: 1) interventions must take into account more than one etiological factor in their approach and 2) there is a need for further investment in clarifying the pathways that explain ACS in order to find appropriate treatments (including non-pharmacological ones).

Regarding limitations, this review used a methodology that involved the conception, selection, inclusion/exclusion of articles, analysis, and interpretation by a small number of researchers. Another limitation is that, although it was an approximation to the PRISMA guidelines for a systematic review and although the methodological quality of the included studies was assessed by two independent reviewers, specific bias assessment tools or others were not used.

Nevertheless, this study's strength lies in covering the last four years of publication and analyzing a large number of articles. It was also intended that the rigor applied in the PRISMA methodology allows the conclusions of this article to be transportable as useful recommendations for clinical practice.

CONCLUSION

Our study shows that personalized nursing care, especially within a multicomponent approach (integrated and considering various factors: cognitive, sensory functions, environmental changes, caregiver education, addressing limited or conditioned mobility, maintaining sleep-wake patterns, reorientation activities), seems to represent the most effective (non-pharmacological) delirium approach.

However, the available, more consistent and current evidence on the non-pharmacological approach to delirium in the ICU by the nursing team does not allow for specific intervention recommendations to be established. Some limitations are related to the fact that the study of non-pharmacological approaches is not easily measurable, there is no standardization of the techniques used, which prevents objective measurement and hinders the standardization of their study, as well as comparison between different studies. It may also present funding bias, as the lack of adequate funding for non-pharmacological research can result in a limited number of studies, affecting the quality and quantity of available evidence.

In the future, the creation of guidelines for standardizing non-pharmacological approaches to delirium could contribute to improving the quality of studies and, consequently, the scientific evidence.

REFERENCES

- Álvarez, E. A., Garrido, M. A., Tobar, E. A., Prieto, S. A., Vergara, S. O., Briceño, C. D., & González, F. J. (2017). Occupational therapy for delirium management in elderly patients without mechanical ventilation in an intensive care unit: A pilot randomized clinical trial. *Journal of critical care*, 37, 85–90. <https://doi.org/10.1016/j.jcrc.2016.09.002>
- Bannon, L., McGaughey, J., Verghis, R., Clarke, M., McAuley, D. F., & Blackwood, B. (2019). The effectiveness of non-pharmacological interventions in reducing the incidence and duration of delirium in critically ill patients: a systematic review and meta-analysis. *Intensive Care Medicine*, 45(1), 1–12. <https://doi.org/10.1007/s00134-018-5452-x>
- Barichello, T., Generoso, J. S., Collodel, A., Petronilho, F., & Dal-Pizzol, F. (2021). The blood-brain barrier dysfunction in sepsis. *Tissue Barriers*, 9(1), 1840912. <https://doi.org/10.1080/21688370.2020.1840912>
- Barr, J., Fraser, G. L., Puntillo, K., Ely, E. W., Gélinas, C., Dasta, J. F., Davidson, J., ... & Jaeschke, R. (2013). Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit. *Critical Care Medicine*, 41(1), 263–306. <https://doi.org/10.1097/CCM.0b013e3182783b72>
- Bento, A. F. G., & Sousa, P. P. (2021). Delirium in adult patients in intensive care: Nursing interventions. *British Journal of Nursing*, 30(9), 534–538. <https://doi.org/10.12968/bjon.2021.30.9.534>
- Blevins, C. S., & DeGennaro, R. (2018). Educational Intervention to Improve Delirium Recognition by Nurses. *American Journal of Critical Care*, 27(4), 270–278. <https://doi.org/10.4037/ajcc2018851>
- Guo, Y., Sun, L., Li, L., Jia, P., Zhang, J., Jiang, H., & Jiang, W. (2016). Impact of multicomponent, nonpharmacologic interventions on perioperative cortisol and melatonin levels and postoperative delirium in elderly oral cancer patients. *Archives of Gerontology and Geriatrics*, 62, 112–117. <https://doi.org/10.1016/j.archger.2015.10.009>
- Guyatt, G., Oxman, A. D., Akl, E. A., Kunz, R., Vist, G., Brozek, J., Norris, S., ... & DeBeer, H. (2011). GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*, 64(4), 383–394. <https://doi.org/10.1016/j.jclinepi.2010.04.026>

- Hamzeshpour, H., Valiee, S., Majedi, M. A., Roshani, D., & Seidi, J. (2018). The effect of care plan based on roy adaptation model on the incidence and severity of delirium in intensive care unit patients: A randomised controlled trial. *Journal of Clinical and Diagnostic Research*, 12(11). <https://doi.org/10.7860/JCDR/2018/36366.12256>
- Inouye, S. K. (1990). Clarifying Confusion: The Confusion Assessment Method. *Annals of Internal Medicine*, 113(12), 941. <https://doi.org/10.7326/0003-4819-113-12-941>
- Inouye, S. K., Westendorp, R. G., & Saczynski, J. S. (2014). Delirium in elderly people. *The Lancet*, 383(9920), 911–922. [https://doi.org/10.1016/S0140-6736\(13\)60688-1](https://doi.org/10.1016/S0140-6736(13)60688-1)
- Jennings, K. M. (2017). The Roy Adaptation Model. *Advances in Nursing Science*, 40(4), 370–383. <https://doi.org/10.1097/ANS.000000000000175>
- Khan, S. H., Xu, C., Purpura, R., Durrani, S., Lindroth, H., Wang, S., ... & Khan, B. A. (2020). Decreasing Delirium Through Music: A Randomized Pilot Trial. *American journal of critical care : an official publication. American Association of Critical-Care Nurses*, 29(2), e31–e38. <https://doi.org/10.4037/ajcc2020175>
- Keating, G. M. (2015). Dexmedetomidine: A Review of Its Use for Sedation in the Intensive Care Setting. *Drugs*, 75(10), 1119–1130. <https://doi.org/10.1007/s40265-015-0419-5>
- Kim, B., Cho, J., Park, J. Y., Kim, H. E., & Oh, J. (2022). Delirium and Anxiety Outcomes Related to Visiting Policy Changes in the Intensive Care Unit During the COVID-19 Pandemic. *Frontiers in Aging Neuroscience*, 14, 1–9. <https://doi.org/10.3389/fnagi.2022.845105>
- Lee, H. J., Bae, E., Lee, H. Y., Lee, S. M., & Lee, J. (2021). Association of natural light exposure and delirium according to the presence or absence of windows in the intensive care unit. *Acute and Critical Care*, 36(4), 332–341. <https://doi.org/10.4266/acc.2021.00556>
- León-Salas, B., Trujillo-Martín, M. M., Martínez del Castillo, L. P., García-García, J., Pérez-Ros, P., Rivas-Ruiz, F., & Serrano-Aguilar, P. (2020). Multicomponent Interventions for the Prevention of Delirium in Hospitalized Older People: A Meta-Analysis. *Journal of the American Geriatrics Society*, 68(12), 2947–2954. <https://doi.org/10.1111/jgs.16768>
- Matsuura, Y., Ohno, Y., Toyoshima, M., & Ueno, T. (2022). Effects of non-pharmacologic prevention on delirium in critically ill patients: A network meta-analysis. *Nursing in Critical Care*, 1–11. <https://doi.org/10.1111/nicc.12780>
- Neelon, V. J., Champagne, M. T., Carlson, J. R., & Funk, S. G. (1996). The NEECHAM Confusion Scale: Construction, Validation, And Clinical Testing. *Nursing Research*, 45(6), 324–330. <https://doi.org/10.1097/00006199-199611000-00002>
- Olmos, M., Varela, D., & Klein, F. (2019). ENFOQUE ACTUAL DE LA ANALGESIA, SEDACIÓN Y EL DELIRIUM EN CUIDADOS CRÍTICOS. *Revista Médica Clínica Las Condes*, 30(2), 126–139. <https://doi.org/10.1016/j.rmclc.2019.03.002>
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372, n71. <https://doi.org/10.1136/bmj.n71>
- Poole, J., & Ray, D. (2022). The Role of Circadian Clock Genes in Critical Illness: The Potential Role of Translational Clock Gene Therapies for Targeting Inflammation, Mitochondrial Function, and Muscle Mass in Intensive Care. *Journal of Biological Rhythms*, 37(4), 385–402. <https://doi.org/10.1177/07487304221092727>
- Pun, B. T., Balas, M. C., Barnes-Daly, M. A., Thompson, J. L., Aldrich, J. M., Barr, J., ... & Ely, E. W. (2019). Caring for Critically Ill Patients with the ABCDEF Bundle. *Critical Care Medicine*, 47(1), 3–14. <https://doi.org/10.1097/CCM.0000000000003482>
- Trogrlić Z, van der Jagt M, Bakker J, Balas MC, Ely EW, van der Voort PH, Ista E. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. *Crit Care*, 19(1)-157. 10.1186/s13054-015-0886-9
- Rains, J., & Chee, N. (2017). The role of occupational and physiotherapy in multi-modal approach to tackling delirium in the intensive care. *Journal of the Intensive Care Society*, 18(4), 318–322. <https://doi.org/10.1177/1751143717720589>
- Schuckit, M. A. (2014). Recognition and Management of Withdrawal Delirium (Delirium Tremens). *New England Journal of Medicine*, 371(22), 2109–2113. <https://doi.org/10.1056/NEJMr1407298>
- Wilson, C. J., Finch, C. E., & Cohen, H. J. (2002). Cytokines and Cognition-The Case for A Head-to-Toe Inflammatory Paradigm. *Journal of the American*

Geriatrics Society, 50(12).
<https://doi.org/10.1046/j.1532-5415.2002.50619>