ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2023 June 9; 12(3): 92-187

Published by Baishideng Publishing Group Inc

WJCCM World Journal of Critical Care Medicine

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The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

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NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Hua-Dong Wang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
June 9, 2023

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 June 9; 12(3): 92-115

DOI: 10.5492/wjccm.v12.i3.92

ISSN 2220-3141 (online)

REVIEW

Sleep during and following critical illness: A narrative review

Laurie Showler, Yasmine Ali Abdelhamid, Jeremy Goldin, Adam M Deane

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Arunachala Murthy T, Australia; Jha P, United States; Sánchez JIA, Colombia

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: January 31, 2023
Revised: February 13, 2023
Accepted: March 22, 2023
Article in press: March 22, 2023
Published online: June 9, 2023

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Abstract

Sleep is a complex process influenced by biological and environmental factors. Disturbances of sleep quantity and quality occur frequently in the critically ill and remain prevalent in survivors for at least 12 mo. Sleep disturbances are associated with adverse outcomes across multiple organ systems but are most strongly linked to delirium and cognitive impairment. This review will outline the predisposing and precipitating factors for sleep disturbance, categorised into patient, environmental and treatment-related factors. The objective and subjective methodologies used to quantify sleep during critical illness will be reviewed. While polysomnography remains the gold-standard, its use in the critical care setting still presents many barriers. Other methodologies are needed to better understand the pathophysiology, epidemiology and treatment of sleep disturbance in this population. Subjective outcome measures, including the Richards-Campbell Sleep Questionnaire, are still required for trials involving a greater number of patients and provide valuable insight into patients' experiences of disturbed sleep. Finally, sleep optimisation strategies are reviewed, including intervention bundles, ambient noise and light reduction, quiet time, and the use of ear plugs and eye masks. While drugs to improve sleep are frequently prescribed to patients in the ICU, evidence supporting their effectiveness is lacking.

Key Words: Critical illness; Critical care; Sleep; Sleep deprivation; Polysomnography; Melatonin

Core Tip: Disturbed sleep is common among the critically ill and contributes to adverse physiological and psychological outcomes. Multiple contributory factors have been identified, including environmental, care-related and patient elements. Assessing sleep in the ICU is challenging, and objective and subjective methods are required to evaluate the disruption to sleep architecture and the patient's experience of this. Both pharmacological and non-pharmacological interventions to improve sleep quality and quantity have been studied with mixed results, however, a multimodal approach to sleep optimisation is likely necessary to improve outcomes.

Citation: Showler L, Ali Abdelhamid Y, Goldin J, Deane AM. Sleep during and following critical illness: A narrative review. *World J Crit Care Med* 2023; 12(3): 92-115
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/92.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.92

INTRODUCTION

Sleep is an essential biological process that is frequently disturbed in patients with critical illness[1,2]. Sleep deprivation in healthy adults is associated with adverse effects on neuropsychiatric, cognitive, cardiovascular, respiratory and endocrine systems and with acute and long-term detrimental effects[3].

There are concerns that an inadequate quantity and quality of sleep during critical illness contributes to increased delirium, depression, and a lesser quality of life in survivors and, potentially, increased mortality, with the detrimental effects of sleep deprivation compounded among those with prolonged admission to the intensive care unit (ICU)[4]. In addition, sleep disturbance is frequently reported as a source of patient distress and has been proposed to have financial implications related to longer ICU admission and increased risk of delirium[5].

Sleep disturbance in the ICU is multifactorial, with pre-morbid diagnoses, acute pathology, treatment and environment all contributing[6,7]. Given the complex pathophysiology, it should be expected that the studied interventions, including pharmacological and non-pharmacological strategies, have had mixed results on sleep[7,8].

This review aims to describe the current understanding of sleep disruption during and after critical illness, current strategies to measure sleep in the ICU, and provide an overview of interventions to improve the quality and quantity of sleep in this population.

LITERATURE SEARCH

A narrative review of the literature was performed. Relevant articles were identified by searching Medline, Embase and the Cochrane database. Search terms included "intensive care unit", "high dependency unit", "critical illness", "sleep", "sleep disturbance", "sleep deprivation", "sleep-wake disorder", and "sleep fragmentation". Searches were limited to human adult subjects and English language articles. No restrictions on the date of publication were imposed. Abstracts were reviewed for relevance, and the reference list of these articles was searched for related articles. The full text of relevant articles was reviewed for inclusion.

OVERVIEW OF NORMAL SLEEP

Sleep is a complex and active process, recognized by reversible perceptual disengagement from, and unresponsiveness to, the environment[9]. The initiation and maintenance of the sleep state are controlled by the coordinated interplay of circadian and homeostatic mechanisms[10-13]. On the basis of polygraphic recordings of brain, muscle and eye activity, normal sleep can be divided into distinct periods, which are recognized as non-rapid eye movement (NREM) and rapid eye movement (REM) sleep[11]. Characteristic features of each sleep stage are described in Table 1[14,15]. NREM sleep is further subdivided into three stages, N1, N2 and N3, reflecting an increasing depth of sleep[16,17]. The N2 phase has characteristic K-complexes and sleep spindles, electrical features which are believed to represent important functions, including the promotion of deeper sleep and memory consolidation[11,18,19]. The N3 phase is synonymous with slow wave sleep, during which many of the physiologically restorative processes of sleep occur[11,20]. REM sleep is when dreaming occurs and is important for memory consolidation and learning[11,21,22]. The brain normally cycles through each phase of sleep over 90-120 min, with 4-5 cycles occurring over the course of the night[11,23]. While the total amount of time spent asleep varies significantly, observational studies indicate that adverse outcomes are

Table 1 Simplified polysomnographic features of the American Academy of Sleep Medicine's phases of sleep

Sleep stage	Electroencephalogram	Electrooculogram	Chin electromyogram
Wake	Alpha activity (sinusoidal 8-13 Hz)	Rapid eye movements; Reading eye movements; Slow eye movements; Blinks	Normal or high tone
N1	< 50% alpha activity; > 50% low amplitude mixed frequency activity (4-7 Hz)	Slow eye movements	Variable, usually lower than wake
N2	Sleep spindles; K-complexes	None	Variable tone
N3	Slow (delta) wave (0.5-2 Hz) ≥ 20%; Sleep spindles may occur	None	Variable tone
REM	Low amplitude mixed frequency activity; No sleep spindles or K-complexes	Rapid eye movements	Low tone

REM: Rapid eye movement.

associated with sleeping less than seven hours or greater than nine hours per day over the long term[24-26]. In summary, both the architecture, or quality, and duration of sleep are important to mediate its beneficial effects.

EPIDEMIOLOGY OF SLEEP DISTURBANCE DURING AND AFTER CRITICAL ILLNESS

Disturbed sleep in the ICU is a near-universal phenomenon. Subjective perception of poor sleep determined using a variety of questionnaires has been reported by 47%-59% of patients[27-30]. Studies using objective measures, including polysomnography and actigraphy, estimate that 67%-100% of patients experience abnormal sleep quality[29,31,32].

Following discharge from the ICU, sleep disturbances persist in 10%-61%[33]. Both objective and subjective measures indicate that sleep disruption improves over time but is still present in up to 61% of ICU survivors 6-12 mo after discharge[34]. In a single-centre, prospective cohort study of 347 patients, Combes *et al*[35] identified sleep disturbance as far as three years after ICU discharge. Women appear to be more affected by persistent sleep disturbances than men[36]. Sleep disruption was associated with other adverse features, including persistent post-traumatic stress disorder, depression, weakness, fatigue, pain and reduced quality of life, although these associations are likely bidirectional[37-42].

Studies that assess sleep using objective methodologies report improvements in sleep architecture between one week and six months post-discharge. Sleep fragmentation, with a high number of arousals, was prominent up to three months, and sleep efficiency remained impaired out to six months[39,43,44]. Objective sleep disturbances correlated with subjectively measured patient perception.

There is a high prevalence of sleep disturbances among ICU patients and survivors that persists for at least 12 mo following discharge and appear to be associated with other long-term, adverse patient outcomes and reduced quality of life.

CAUSES OF SLEEP DISTURBANCE IN THE CRITICALLY ILL

The cause of sleep disruption in the critically ill is multi-factorial and can be divided into environmental, therapy-related and patient factors.

Patient factors

Patient factors, including increasing age, male sex, and poor sleep quality at home, have been associated with worse ICU sleep parameters[36,45]. The relationship between acute illness severity and sleep disruption is biologically plausible but has been inconsistently demonstrated. Two small studies, including a total of 35 patients, found a correlation between greater illness severity, determined by Acute Physiology and Chronic Health Evaluation (APACHE III) score and Simplified Acute Physiology Score (SAPS II) respectively, and greater sleep disruption[46,47]. In contrast, illness severity, as measured by the patient's Acute Physiology and Chronic Health Evaluation (APACHE III) score, was not found to be correlated with total sleep time, sleep fragmentation or subjective perception of sleep quality from four studies involving 264 patients[31,36,45,48].

Patients report that distress, anxiety, and pain are factors that impair their ability to sleep[49-53]. Sleep deprivation has, in turn, been identified as a stressor contributing to patient anxiety and distress and creating a positive feedback loop[51,54-56].

Environmental factors

Loss of diurnal variation and circadian entrainment: Critically ill patients have been shown to have temporally recognized circadian rhythmicity, likely due to the absence or disruption of normal external entraining cues, such as light exposure, changes in ambient temperature and eating patterns[13,42,57,58]. In health, circadian rhythms are crucial for sleep regulation, and disrupted sleep during critical illness is likely to be part of the circadian dysfunction that occurs in these patients[13,58,59].

Ambient light: Diurnal variation in light is an important entrainer of the circadian rhythm. Light intensity, wavelength and spectral distribution all affect the physiological response to light exposure [60]. ICU patients rate ambient light as a common contributing factor to poor sleep[30,61-63]. Both low levels of daytime light and peak light levels in the early evening have been reported, which pose a risk to circadian rhythms and maintenance of normal sleep-wake patterns[6]. Prolonged light exposures have been documented to occur frequently during the nocturnal sleep period[64].

Noise: Patients perceive noise as a significant factor leading to poor sleep in the ICU, with talking, equipment alarms, the television, and use of the bedside phone by staff being common causes[36,46,65]. The World Health Organisation recommends that noise levels within hospital environments should not exceed 35 decibels (dB) during the day and 30 dB at night[66]. Multiple studies report noise levels are frequently greater than this, with equivalent continuous sound levels of 50-75 dB and peaks up to 96 dB [67-69]. This noise level is associated with sleep disruption[45,70]. Polysomnography detected sleep disturbances were observed when sound thresholds exceeded 63 and 59 dB during daytime and nighttime, respectively. Estimates of noise-related sleep disturbance in the ICU vary from 11% to 58% [31,46,62,63,71-74].

Patient-care related

Critically ill patients require intensive monitoring and care 24 h a day. Nursing and medical interventions, including mouth and eye care, decubitus ulcer care, change of dressings, medication administration, blood sampling, endotracheal tube suctioning, clinical examination, and procedures may interfere with patient sleep[46,75]. Patients perceive these care activities as a substantial contributor to sleep disruption[30,62,74]. It has been reported that over the course of a night, patients were subjected to an average of 42.6 to 51 care interactions, with approximately 20% of these resulting in a clinically evident sleep disruption[46,75,76]. One study even identified increased care activities occurring between 02:00 and 05:00[75].

A proportion of nocturnal care activities are essential in the ICU. Whether the frequency and intrusiveness of nocturnal care activities are excessive and lead to harm due to sleep fragmentation and sleep deprivation, such as neurological observations performed and recorded at one-hourly intervals, remains uncertain[77,78].

Treatment-related

Mode of mechanical ventilation: Critically ill patients frequently require respiratory support, and mechanical ventilation contributes to sleep disruption. Patient-ventilator dyssynchrony, abnormal gas exchange, and mechanical ventilation-related central apnoeas are all considered contributory[6,79,80]. Mechanically ventilated patients experience disturbed sleep architecture with frequent arousals and decreased amounts of slow wave and REM sleep[48,57,81]. The effect of the mode of ventilation on sleep has been studied, but due to the limited number of patients observed and methodological limitations, the impact of ventilator mode remains to be determined.

Studies comparing pressure support ventilation (PSV) to assist-control ventilation report point estimates suggesting assist-control decreases fragmentation, increases total sleep time, slow wave sleep and REM sleep, and reduces central apneas, but the wide confidence intervals are indicative of considerable uncertainty about this effect[79,81,82].

A single study comparing pressure control ventilation to pressure support ventilation reported statistically significant improvements in sleep efficiency and proportion of time in N2, N3 and REM sleep with a pressure control mode[83]. Notably, all 26 patients included in the study had chronic respiratory disease, which limits the application of these findings to a broader patient population, and whether nocturnal pressure control ventilation delays liberation from ventilation is also unknown.

Several proportional assist ventilatory modes have been compared to pressure support ventilation with mixed results[84-86]. Details of these studies have been recognized in Table 2.

The association between non-invasive ventilation use and sleep quality has also been evaluated. Using an ICU ventilator, rather than a dedicated non-invasive ventilator, to provide non-invasive respiratory support is associated with reduced patient-ventilator dyssynchrony and number of arousals [87]. In addition, detection of early abnormal sleep architecture in patients with hypercapnoeic respiratory failure was associated with late NIV failure[88].

In the immediate period following discharge from ICU and at both 6 and 12 mo following discharge, exposure to mechanical ventilation during a patient's ICU stay does not seem to be associated with subsequent sleep disturbance[34,47].

Table 2 Comparison of studies assessing the effects of ventilator mode on sleep quantity and quality

Ref.	Study Design	*n*	Treatment arms		Sedation	Outcomes	
Studies comparing pressure support ventilation against assist control ventilation							
Parthasarathy *et al*[79], 2002	Single centre, randomised, cross over study	11	2 h each of: **PSV**; PS to achieve Vt 8 ml/kg	**ACV**; Vt: 8 mL/kg; f: Set as patient RR minus 4/min	Yes	Sleep efficiency: Arousal index, *mean (SD)*	Not reported; ACV 39 (6); PSV 35 (7); No statistically significant difference between ventilation modes
Toublanc *et al* [81], 2007	Single centre, randomised, cross over study	20	4 h each of: **PSV**; PS = 6 cmH2O; Trigger sens = 0.5 cmH2O	**ACV**; Vt: 10 ml/kg; f: 12/min; Increased until no spontaneous inspiratory effort	Free from sedation for 48 h	Sleep efficiency: Arousal index, *mean (SD)*	No difference, values not reported; ACV 7 (SD 5); PSV 7 (SD 5); No statistically significant difference between ventilation modes
Cabello *et al* [82], 2008	Single centre, randomised, cross over study	15	6 h each of: **cPSV**; PS to achieve Vt 6-8 ml/kg (PBW); RR < 35/min; **aPSV**	**ACV**; Vt: 8 mL/kg; f: 10/min (back up)	Free from sedation for 24 h	Sleep efficiency, *median [IQR]*: Arousal index, *median [IQR]*	ACV 58 [48-82], cPSV 44 [29-30], aPSV 63 [29-80]; ACV 30 [17-41], PSV 28 [17-53], aPSV 23 [21-45]; No statistically significant difference between ventilation modes
Studies comparing pressure support ventilation against pressure control ventilation							
Andréjak *et al* [83], 2013	Single centre, randomised,cross over study	26	4 h each of: **PSV**; PS = 6 cmH2O; Trigger sens = 0.5 cmH2O	**PCV**; PS = 20 cmH2O; f: Greater than patient RR I/E ratio: 1/1.2 to 1/1.5	Not reported	Sleep efficiency, *median [IQR]*: Arousal index	PCV 63 [9-100]; PSV 37 [0-96] Not reported; Significantly improved sleep efficiency with PCV
Studies comparing pressure support ventilation against proportional assist ventilation							
Bosma *et al* [84], 2007	Single centre, randomised, cross over study	13	1 night each of: **PSV**	**PAV**	Propofol, midazolam or lorazepam	Sleep efficiency, *mean (SD)*: Arousal index, *median [IQR]:* Patient-ventilator asynchrony per hour, *mean (SD)*	PSV 58% (25); PAV 60 (23); PSV 16 (2-74); PAV 9 (1-41); PSV 53 (59); PAV 24 (15); PAV associated with statistically significantly fewer arousals and episodes of asynchrony
Alexopoulou *et al*[85], 2007	Single centre, randomised, cross over study	17	1 night each of: **PSV_{base}**; PS as before study; **PS_{high}**; Pressure assist increased by 40%-50% from PSVbase or until Paw = 30 cmH2O	**$PAV+_{base}$**; Set to achieve mean inspiratory pressure similar to PSV_{base}; **$PAV+_{high}$**; Percentage of unloading increased by 40%-50% from PSVbase or until it reached 85%	Group A; *n* = 11; Propofol; Group B; *n* = 9; Non-sedated	Group A; Sleep efficiency, *mean (SD)*: Arousal index, *mean (SD)*: Group B; Sleep efficiency, *mean (SD)*: Arousal index, *mean (SD)*	$PAV+_{base}$ 99 (2); PAV_{high} 98 (5); PSV_{base} 93 (11); PSV_{high} 88 (16) (P < 0.05); $PAV+_{base}$ 4.6 (4.9); PAV_{high} 7.4 (11); PSV_{base} 5.4 (3.6); PSV_{high} 6.5 (6.7); $PAV+_{base}$ 76 (11); PAV_{high} 71 (21); PSV_{base} 68 (19); PSV_{high} 72 (15); $PAV+_{base}$ 12 (8.0); PAV_{high} 11 (7.6); PSV_{base} 8.4 (4.8); PSV_{high} 10.5 (9.9); In sedated patients (Group A), PAV+ is associated with a modest, albeit statistically significant at the 0.05 level, improvement in sleep efficiency; No statistically significant differences found between ventilation modes in non-sedated group
Alexopoulou *et al*[86], 2013	Single centre, randomised,cross over study	14	Alternating 4-h blocks over 24 h of: **PSV**; PS maintained at pre-study level	**PAV+**; % of unloading set to achieve a mean inspiratory pressure similar to PSV	Free from sedation and opioids for 24 h	Sleep efficiency, *median [IQR]*: Arousal index, *median [IQR]*	PAV+ 51 [13-66]; PSV 27 [6-22]; PAV+ 11 [4-25]; PSV 12 [3-16]; No statistically significant improvement found with PAV+
Studies comparing pressure support ventilation against neurally adjusted ventilatory assist							
Delisle *et al* [236], 2011	Single centre, randomised, cross over study	14	2 non-consecutive 4-h blocks (d/night) of: **PSV**; PS to achieve Vt 8 mL/kg; RR < 35/min	**NAVA**	Free from sedation and opioids for 24 h	Sleep efficiency, *median [IQR]*: Fragmentation index, *median [IQR]*	NAVA 74 [52-77]; PSV 44 [29-74]; NAVA 18 [8-22]; PSV 34 [25-54]; NAVA statistically significant improvement in the efficiency and reduced fragmentation of sleep

PSV: Pressure support ventilation; cPSV: Clinician adjusted PSV; aPSV: Automatically adjusted PSV; PCV: Pressure control ventilation; PAV: Proportional assist ventilation; PAV+: Proportional assist ventilation with load adjustable factors; NAVA: Neurally adjusted ventilatory assist; IQR: Interquartile range; SD: Standard deviation; *n*: Number of patients. P=NS: Not statistically significant result; Vt: Tidal volume; RR: Spontaneous respiratory rate; f: Mechanical

ventilatory cycle frequency; PS: Pressure support; I/E ratio: Inspiratory-expiratory ratio.

In summary, there appears to be some effect of ventilatory mode on sleep quality and quantity, however, a consistent physiological rationale remains elusive. In addition, the included studies are hindered by small sample sizes, and further larger-scale studies are required to elaborate on the relationship between ventilation mode and sleep.

Feeding and nutrition: Nutritional support is an essential ICU treatment and would commonly be administered as a continuous infusion over 24 h in those that cannot eat[89]. The timing of meals and the associated release of nutritional hormones is an important entraining cue for circadian rhythms. Continuous delivery of nutrition may contribute to circadian rhythm and sleep disruption, and intermittent feeding may reduce this effect[90]. However, intermittent feeding regimens have not been shown to improve patient outcomes, possibly because of delayed gastric emptying[91,92]. Hitherto, there have been no trials evaluating intermittent enteral nutrition on circadian rhythm and sleep parameters, but a randomised clinical trial will soon be completed (ClinicalTrials.gov Identifier: NCT04737200).

Pharmacological: Critically ill patients are exposed to multiple drug classes that may affect sleep quantity and quality. However, very little published research directly quantifies this, and much of the information below is extrapolated from drug effects in other patient populations.

Sedatives and analgesics

Several studies have demonstrated that mechanically ventilated patients receiving sedation have longer total sleep time and higher sleep efficiency but more atypical sleep than patients who are not intubated and sedated[57,93,94]. Propofol is one of the most frequently used sedative agents in the ICU, but there is conflicting evidence of its effect on sleep. Propofol is reported to disrupt REM sleep and delay sleep onset latency, however, in animal models there is evidence that propofol-induced sedation may confer some of sleep's restorative effects[95,96]. A single-centre, prospective cohort study of 50 intubated patients found that sedation with propofol as a single agent was associated with increased sleep duration and decreased fragmentation when compared to fentanyl, propofol and fentanyl, or no sedation[97]. In contrast, a small crossover study of 12 mechanically ventilated patients reported that propofol, compared to no sedation, did not significantly affect total sleep duration or fragmentation, but adversely impacted the duration of REM sleep[98].

Benzodiazepine use is associated with increased total sleep time, resulting from decreased sleep latency and prolongation of the N2 sleep phase, at the cost of reduced slow wave and REM sleep[99]. Opioids, even as a single dose, have been shown to reduce the duration of slow wave and REM sleep [100-102]. The central alpha-2 adrenoreceptor agonist, dexmedetomidine, is associated with increased sleep efficiency and proportions of N3 sleep but decreased REM sleep[96,103,104].

Cardiovascular medications

Adrenergic catecholamines can cause suppression of REM and slow wave sleep[105,106]. Both amiodarone and lipid soluble beta-blockers may theoretically have adverse effects on sleep that include decreased REM sleep and nightmares[99]; however, whether these drugs have any effect during critical illness has not been evaluated.

Antidepressants and antipsychotics

In other patient groups, sedating tricyclic antidepressants such as amitriptyline decrease sleep latency, increase the proportion of slow wave sleep and decrease the proportion of REM[99,107]. Venlafaxine is recognised to suppress REM sleep and cause nightmares, while selective serotonin inhibitors can cause increased wakefulness, reduced total sleep time and decreased REM sleep[99,107,108]. Antipsychotic medications are of particular interest due to their use in the management of delirium and have been observed to have variable effects on sleep architecture. Haloperidol has been shown to increase sleep efficiency, whereas the atypical agents, olanzapine and risperidone, have the additional effect of promoting slow wave sleep[99,109-111].

Miscellaneous

Corticosteroid use is associated with multiple neurocognitive, behavioural and circadian changes that may contribute to poor sleep[99,112]. Exogenous steroid use may cause misalignment of the hypopituitary adrenal axis with adverse effects on the circadian rhythm, which may be further exacerbated by steroid-induced suppression of melatonin secretion[112].

Multiple pharmacological agents may diminish sleep in the ICU. Sedation is frequently necessary to facilitate treatment and reduce patient distress. The true impact of current sedative regimes on sleep quantity and quality remains incompletely defined. Multiple pharmacological agents suppress slow wave and REM sleep, which may contribute to sleep deficit-related morbidity.

SLEEP DISTURBANCE IN THE CRITICALLY ILL

Sleep disturbance may be characterised by abnormalities, including difficulties falling asleep (sleep initiation), staying asleep (sleep maintenance), frequent awakenings or arousals (fragmentation), and atypical sleep architecture. Patients with critical illness largely preserve their total time asleep, or total sleep time, however, this sleep is highly fragmented and spread over 24-h[63,113-118]. Instead of being consolidated in a single nocturnal sleep period, approximately 50% of sleep in critically ill patients occurs during daytime hours[63,114,115].

Sleep architecture during critical illness is frequently abnormal[31,32]. Polysomnographic studies demonstrate a lack of variability in the electroencephalogram (EEG), with a predominance of the 'lighter' N1 and N2 phases, paucity or absence of N3 and REM sleep, and frequent arousals[119,120]. Additional features of atypical sleep include the relative absence of K-complexes and sleep spindles, as well as dissociation of the EEG from behavioural findings. Such dissociations manifest as either pathologic wakefulness, characterised by an EEG frequency consistent with sleep in awake patients or unresponsive patients with EEG frequencies associated with being awake[119]. These EEG abnormalities mean that 16-85% of polysomnographic data in observational studies were not able to be qualified using standard scoring systems[113-115,117,121]. Amended criteria have been proposed that recognise this atypical sleep pattern[113,115]. Watson *et al*[115] proposed an additional seven criteria for sleep scoring in the critically ill with robust reported interrater reliability (weighted kappa 0.80; bootstrapped 95% confidence interval 0.48, 0.89) but this has not been externally validated. Notably, the development of an atypical sleep pattern was strongly associated with the subsequent development of delirium, a longer ICU length of stay, and higher odds of death[116].

In summary, critically ill patients display multiple and severe perturbations in their sleep that are not well described by current sleep scoring classifications. Several of these abnormalities are associated with a worse prognosis, yet it remains unclear if these are modifiable endpoints or markers of disease severity.

MEASURING SLEEP IN THE CRITICALLY ILL

Measuring sleep in the critically ill poses many challenges and is frequently confounded by sedation, encephalopathy, primary neurological insults, and prioritisation of more imminently life-threatening issues[6]. Both objective and subjective measurement tools have been used independently or in combination[59].

OBJECTIVE MEASUREMENT OF SLEEP IN THE CRITICALLY ILL

Polysomnography

Polysomnography uses polygraphic recording of electroencephalographic, electromyographic, and electro-oculographic data to measure sleep and is considered the gold-standard technique. There are two predominant systems for scoring polysomnographic sleep data. The Rechtschaffen and Kales (R&K) criteria, first published in 1968, describe five phases of sleep in healthy individuals but were superseded in 2007 by the American Academy of Sleep Medicine's (AASM) sleep scoring rules[16]. The AASM and R&K scoring rules share many similarities (Table 3) but show relatively low concordance when scoring NREM phases[15-17,122,123]. Moreover, both lack accuracy in quantifying the atypical sleep seen in the critically ill[124]. Logistical, technical, and financial barriers to the use of polysomnography in ICU have been described, including access to specialist equipment and the support of a sleep service for set-up and analysis[119,125,126]. The device itself is reported to interfere with the delivery of patient care, is tolerated poorly by up to 25% of patients, and patient discomfort from the device may worsen sleep[119, 127]. Accordingly, while polysomnography remains the gold-standard technique for ambulant patients, there is a need for other methodologies to quantify sleep during critical illness.

EEG spectral analysis

The electroencephalogram used in polysomnography provides invaluable information about sleep stages. Multiple attempts to simplify this element of sleep analysis have been described, using a reduced number of EEG leads, spectral analysis of the EEG frequencies, and automated scoring algorithms. Several studies have attempted to analyse limited EEG leads using different techniques. Bispectral Index (BIS) was developed as a depth of anaesthesia monitor for use in the operating theatre. A limited channel EEG signal is acquired using a single strip of electrodes applied to the forehead. Bispectral and power spectral analysis of the EEG is used to generate a numerical score to indicate depth of sedation [128]. While BIS has been used to investigate sleep in the critically ill, studies of BIS for sleep monitoring in both healthy volunteers and critically ill adults have reported that BIS is inaccurate for the detection of various sleep stages, particularly in differentiating REM from N1/N2 sleep phases, and correlates

Table 3 Comparison of American Academy of Sleep Medicine's and Rechtschaffen and Kales criteria sleep stage nomenclature

	AASM	R&K
Wake	Stage W	Stage W
NREM sleep	Stage N1	Stage 1
	Stage N2	Stage 2
	Stage N3	Stage 3
		Stage 4
REM sleep	Stage R	Stage REM

AASM: American Academy of Sleep Medicine; R&K: Rechtschaffen and Kales criteria; REM: Rapid eye movement.

weakly with multiple domains on the Richards-Campbell Sleep Questionnaire[129,130].

Alternative attempts to use spectral EEG analysis to monitor sleep in the critically ill, including the odds-ratio product index and ICU depth of sleep index, offer potentially useful alternatives[131]. Spectral EEG analysis using fast Fourier transformation showed perfect inter-observer and intra-observer agreement, however, the sample size of only 14 patients limits the generalizability of this finding[124]. These techniques do not rely on traditional scoring parameters, such as the presence of sleep spindles, and consequently are not affected by the absence or atypia of these features as reported by other authors[113]. The use of spectral analysis has the potential to simplify sleep assessment in the ICU, however, correlation with standard polysomnography parameters, as well as standardization and external validation, will be necessary before it can be more widely applied.

Limited lead EEG

To reduce the complexity associated with the use of polysomnography, several 'simplified' proprietary devices have been trialled. The Sedline™ is a portable monitor that is able to acquire limited lead EEG using bifrontal electrodes to derive a Patient State Index, which represents varying levels of consciousness. Vacas *et al*[132] assessed the feasibility of using the Sedline to monitor sleep in three volunteers and 23 ICU patients and reported that the device was well tolerated but had poor agreement with polysomnography for stages N1 and N3. The Sleep Profiler™ is a wireless device that is applied to the forehead to acquire frontopolar EEG and uses auto-staging software to interpret the data. The Sleep Profiler™ has been evaluated by Jean *et al*[97] and Romagnoli *et al*[133] to assess the effects of sedation on sleep architecture in ICU patients. While reported accuracy is comparable to polysomnography in healthy volunteers, this comparison has not been reported in the ICU population[93].

Actigraphy

Actigraphy devices, commonly worn on the wrist or ankle, use omnidirectional accelerometers to detect limb movement; these limb movements are interpreted using automated algorithms to estimate sleep-wake state[125,134]. These devices are minimally invasive, relatively straightforward to use, and have been used to assess sleep in outpatient settings[135]. Given the frequency and magnitude of critical illness weakness, studies of actigraphy in the critical care setting have identified poor overall accuracy, with over-estimation of total sleep time and sleep efficiency, when compared to polysomnography, nurse observation, or BIS[136]. Actigraphy has been used to evaluate sleep-promoting interventions in ICU, however, the poor correlation with other validated measures of sleep limits inferences from these studies[136,137].

Novel devices: The Nemuri SCAN™, an under-bed mattress sensor, has been evaluated to measure sleep in a total of 29 ICU patients in two prospective observational studies[138,139]. When compared to polysomnography, moderate agreement but poor specificity was reported. In addition, there was no correlation with subjective sleep, quantified using the Richards-Campbell Sleep Questionnaire.

The most frequently used research methods to objectively measure sleep in the critically ill have been summarised in Table 4. There is no methodology available that provides clinicians with real-time objective information each morning regarding the quantity and quality of a patient's sleep the night before. Such information has the capacity to transform clinical care.

SUBJECTIVE MEASUREMENT OF SLEEP IN THE CRITICALLY ILL

Understanding the subjective quality of patients' sleep is an important component of a holistic assessment. Direct patient self-report is of greatest interest, however, due to factors such as delirium and

Table 4 Summary of objective methods of sleep measurement in the critically ill

Method	Benefits	Limitations
Full polysomnography (PSG)	Gold standard technique; Provides polygraphic data on EEG, eye movements and chin tone; Established guidelines for interpreting data for normal sleep	Complex set up; Relatively expensive; Poorly tolerated in 25% of patients; Interferes with nursing care; May interfere with patient sleep; Interpretation requires sleep specialist; No validated criteria for atypical EEG found commonly in critically ill
Bispectral index (BIS) monitor	Small anatomic footprint; Simplified set up compared to PSG; Does not require sleep specialist for interpretation; Less affected by atypical EEG common in critically ill	Inaccurate differentiation of REM from N1/N2 sleep; Correlates weakly with RCSQ; No validated criteria for interpretation of results; Primarily designed to monitor depth of sedation
Limited lead EEG	Small anatomic footprint; Simplified set up compared to PSG; May not require sleep specialist for interpretation	Accuracy dependent on device and auto-staging software; Interpretation dependent on sleep specialist if not using auto-staging
Actigraphy	Minimally invasive; Simple set up; Easy to perform serial measures; Established use in outpatient setting	Poor accuracy compared to PSG and nurse observation, including overestimation of total sleep time and sleep efficiency; Confounded by immobility, weakness, sedation, and neurological injury
Under mattress sensor	Non-invasive modality; Simple set up	Moderate agreement, but poor specificity compared to PSG; No correlation with RCSQ

EEG: Electroencephalogram; N1: Non-REM sleep stage 1; N2: Non-REM sleep stage 2; PSG: Polysomnography; REM: Rapid eye movement sleep; RCSQ: Richards-Campbell Sleep Questionnaire.

administration of sedation and analgesic drugs, it is estimated that only around 50% of the ICU population can participate in such efforts[73].

Thirteen different questionnaires have been used to quantify sleep in the ICU, of which 10 were reported by patients and three reported by ICU nurses[119,140]. Several tools allow for either the patient or nurse to complete them, although accuracy is inconsistent[140].

Of the 13 sleep questionnaires used, the most rigorously studied is the Richards-Campbell Sleep Questionnaire (RCSQ). The RCSQ was specifically designed for use in the ICU population and uses five visual analogue scales to assess the domains of sleep latency, sleep efficiency, sleep depth, number of awakenings and overall sleep quality (Figure 1)[141]. Individual domain scores can be interpreted respectively or combined into a global score, with a score of ≥ 63 out of 100 reported as the optimal cut-off for self-reported 'good sleep'[142]. Both content and criterion validity have been established against polysomnography[143]. While the RCSQ was designed as a patient self-assessment tool, it may also be completed by clinical staff. The accuracy of clinician-completed RCSQ remains unclear with a reported strength of agreement including slight to moderate, moderate, and strong[73,144]. The use of the RCSQ in the outpatient setting has also been established, allowing serial assessments to be continued following ICU discharge[145]. The RCSQ has been translated and validated in multiple languages[146].

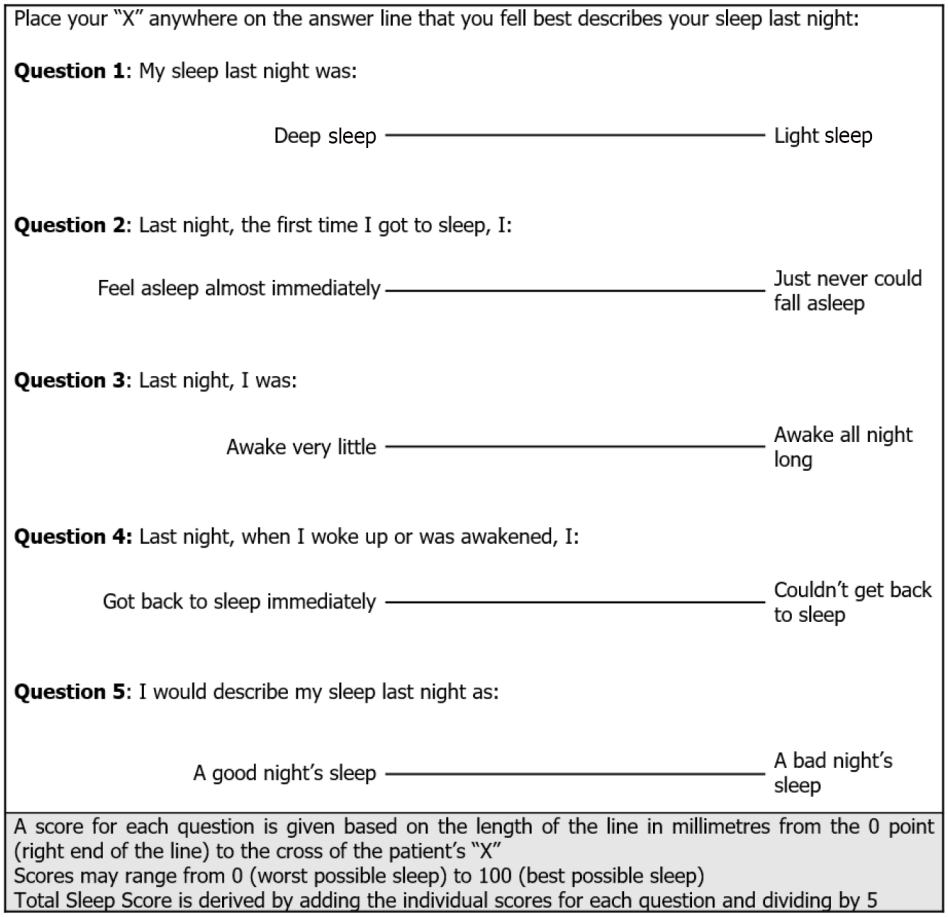
The Verran Snyder-Halpern (VSH) sleep scale is an 8-15 visual analogue scale, self-reported sleep questionnaire that assesses similar domains to the RCSQ but, due to its higher number of questions, is considered more labour intensive[125]. The VSH sleep scale was designed to assess sleep in hospitalised patients without known sleep disorder[125,147,148]. The VSH has been validated for use in the ICU in several studies, but the association between patient and clinician-reported sleep was low[120,149-152].

The Pittsburgh sleep quality index (PSQI) is a nine-item, self-reported sleep questionnaire initially developed for use in the psychiatric population[153]. However, the use of the PSQI in critical care has mainly been to assess sleep following ICU discharge and has no association with objective sleep parameters[154].

Integrating sleep assessment into a daily patient assessment is hindered by the complexity of current tools. The Numeric Rating Scale for sleep (NRS-Sleep) is a single-item assessment tool that requires patients to rank their sleep on a scale of 0 to 10. It was developed in a prospective, multicentre study of 456 ICU patients and using receiver operator curves, a score greater than five was determined as the threshold for good sleep. The NRS-sleep is significantly correlated with mean RCSQ score (Pearson's correlation coefficient 0.88, $P < 0.01$)[155].

The sleep observation tool (SOT) requires an observer to assess and document the patient's sleep or wake status every 15 min and has been found to correctly identify sleep 81.9% of the time compared to polysomnography. It has been used in its standard format to assess the effect of therapeutic interventions and in an amended format that uses 30-min intervals[156-158].

The use of subjective measurement tools alongside objective measures is vital to ensure that future research maintains a patient-focused outcome. The RCSQ is promising as a tool for the measurement of sleep both during and after ICU admission. It may be beneficial for researchers to use a core subjective methodology to facilitate comparisons between studies.



DOI: 10.5492/wjccm.v12.i3.92

Figure 1 Patient completed Richards-Campbell sleep questionnaire.

EFFECTS OF SLEEP DISTURBANCE DURING CRITICAL ILLNESS

The effects of disrupted sleep in the critically ill remain poorly understood. In healthy adults, short-term sleep deprivation is associated with multi-system physiologic disturbances, and longer term is associated with increased risks of obesity, type 2 diabetes, malignancy and death[3].

Neurological

Delirium occurs in up to 80% of mechanically ventilated patients and is independently associated with increased mortality[159]. There are suggestions of a bidirectional relationship with sleep deprivation contributing to the development of delirium, and delirium worsening sleep disturbances[160]. A causal link between sleep deprivation and delirium has not been established, but several studies support an association. The detection of atypical sleep on EEG, commonly seen in critically ill patients, was associated with a significantly increased risk of developing delirium in the following 48 h[113]. A prospective observational before and after study of the introduction of a quality improvement intervention to promote sleep in 300 ICU patients reported a marked reduction in the incidence of delirium (odds ratio 0.46; 95% confidence intervals, 0.23-0.89), however, improvements in RCSQ measured sleep did not reach statistical significance[161]. A similar study on the introduction of a multicomponent, multidisciplinary bundle of interventions in 338 ICU patients reported improved sleep efficiency, decreased daytime sleepiness, and reduced incidence and duration of delirium[162]. The results of a meta-regression conducted by Kakar *et al*[94] reported a somewhat unexpected relationship between total sleep time and delirium, where each hour increase in total sleep time per night was associated with a 5.8% increase in the risk of delirium. This counterintuitive result may be due to confounders, such as duration of mechanical ventilation, depth of sedation or disease severity.

Seizures are exacerbated by sleep deprivation and in focal epilepsy, the risk of seizure has been shown to correlate with day-to-day variations in daily sleep[163,164]. In animal models, REM sleep seems to play an important role in enhancing the seizure threshold[165]. However, the impact of sleep deprivation on seizures during critical illness is yet to be described or quantified.

Sleep deprivation in healthy adults is associated with cognitive dysfunction, including impaired attention, memory and situational awareness[166]. Critical illness survivors frequently report

troublesome short- and long-term impairments of cognitive function[167]. For example, a multicentre observational study of 102 ICU survivors reported that sleep fragmentation was associated with cognitive impairment at seven days post discharge from ICU in patients who had been mechanically ventilated[168]. No measured sleep parameters were associated with cognitive outcomes at 6 or 12 mo.

Endocrine function

Sleep and circadian disruption during critical illness have been proposed to result in endocrine abnormalities, including decreased secretion of anabolic hormones, including testosterone, growth hormone and insulin-like growth factor, as well as increased secretion of catabolic hormones that results in reduced protein synthesis and increased protein breakdown[169]. This net loss of protein contributes to muscle atrophy and critical illness weakness, which may be more marked in older populations and contribute to adverse outcomes, including increased frailty and functional decline in ICU survivors[169, 170].

A single night of sleep deprivation in healthy adults causes impaired glucagon secretion, elevated evening cortisol, and insulin resistance[171,172]. In the critically ill, these endocrine disturbances may conceivably contribute to the development of impaired glucose tolerance and hyperglycaemia[173].

Melatonin is a circadian regulating hormone produced by the pineal gland[174]. Critically ill patients may experience reduced plasma melatonin concentrations due to loss of light-related physiological regulation of melatonin secretion and lack of normal diurnal variation[175-177]. These abnormalities likely contribute to sleep disturbances in the ICU population and have been associated with increased morbidity and mortality in animal models[178].

Immune function

Immune upregulation, including immune cell proliferation and production of pro-inflammatory cytokines, is typical during the early phases of sleep[179]. Natural killer cell activity is reduced by 28% after one night of sleep deprivation, and a significant increase in total white blood cell count is seen after 3-5 d of sleep restriction[180,181]. A reduced response to influenza and hepatitis A vaccination is seen with sleep deprivation, which does not improve with catch-up sleep[182,183]. A retrospective cohort study of 135 patients with coronavirus disease 2019 (COVID-19) reported that poor sleep was linked to more severe lymphopaenia and a more frequent need for ICU admission[184].

Respiratory function

Sleep deprivation is associated with an impaired ventilatory response to hypercapnia and hypoxaemia, reduced cortical respiratory motor output, and decreased inspiratory muscle endurance[185]. In addition, sleep fragmentation, but not sleep deprivation, has been found to increase the risk of upper airway collapsibility, which may predispose to extubation failure[186].

A prospective observational study of 45 patients evaluating sleep alterations and duration of mechanical ventilation, reported that the detection of atypical sleep on polysomnography was associated with a longer period of invasive respiratory support[187]. This relationship remained after multivariate logistic regression. Furthermore, a separate study reported that each percentage increase in slow wave sleep was associated with 0.58 d increase in the duration of mechanical ventilation[94]. Slow wave sleep is usually considered a deeper, restorative sleep phase and is typically reduced or absent during critical illness. Consequently, confounding variables, such as sedation, are influencing these associations.

Psychological

The relationship between sleep deprivation and psychiatric disorders may be bidirectional[188]. Total sleep deprivation in healthy adults disrupts affective functioning[189]. In contrast, one night of total sleep deprivation has been shown to improve depressive symptoms in up to 60% of depressed patients. However, this improvement is not evident in the majority after recovery sleep[190]. Anxiety and depression frequently occur in ICU survivors, occurring in up to 43% and 48% respectively[191]. ICU survivors with depressive symptoms three months after discharge were observed to have a higher likelihood of sleep disturbance, yet the direction of causality is unclear[161].

SLEEP OPTIMISATION STRATEGIES

Given the prevalence, persistence and impact of sleep disturbance during critical illness, there is considerable interest in improving patients' sleep duration and quality. In 2018, the Society of Critical Care Medicine published its clinical practice guidelines for the prevention and management of pain, agitation, delirium, immobility and sleep disruption to summarise the contemporary evidence on this subject[192]. Sleep optimisation strategies can be categorised into non-pharmacological and pharmacological interventions.

NON-PHARMACOLOGICAL MANAGEMENT OF SLEEP DISTURBANCES

Intervention bundles

Several authors have reported on implementing nurse-led or multi-disciplinary, multi-component, intervention bundles to improve patient sleep. Eight domains that could be included in an intervention bundle were described by Beck Edvardsen *et al*[193] including noise reduction; use of earplugs and eye masks; use of music; promotion of natural circadian rhythms; managing pain; use of "quiet time"; clustering of nursing activities, and optimising mechanical ventilation. However, evidence regarding such sleep-promoting intervention bundles is mixed. Improved objective and subjective measures of sleep have been reported in two studies[162,194]. Bundles from each study were implemented by a multi-disciplinary team and contained over 10 interventions, including the offer of eye masks and ear plugs. In contrast, no significant benefit of a sleep promotion bundle was reported in two further studies that had fewer interventions and did not include the provision of ear plugs and eye masks[195,196]. Studies of bundled care assess the net effect of multiple interventions, obscuring the magnitude and direction of effect from the individual components. Consequently, it is unclear which interventions contained in the reported studies are mediating the benefit[197].

Noise reduction

Several strategies have been described to reduce the effect of noise disturbance on sleep. For example, Walder *et al*[198] reported the implementation of five policy steps, including the closure of doors, reducing monitor alarm volumes and, between 23:00 and 05:00, limiting nursing care, conversational noise and direct light in patients' rooms. These interventions successfully reduced nocturnal noise and light. The implementation of a behavioural modification program for nursing staff reported similar results that such measures could reduce ambient noise and light in the ICU to provide a better sleeping environment[199]. However, neither study measured patients' sleep, making it impossible to assess the impact of these environmental interventions on sleep outcomes.

Quiet time

'Quiet time' protocols designate a 1–2-h period during the day during which ambient noise and light are reduced to facilitate patient sleep. Three prospective studies of quiet time, involving 361 patients and using once or twice daily two hour sessions, report that patients are more likely to be reported as asleep during quiet time than during the control period[156,157,200]. Sleep was determined using a novel subjective nurse assessment or the Sleep Observation Tool[201]. Given the short available sleep period, the highly subjective nature of the assessments, and the inability to interpret reported sleep in the context of total sleep time, the inferences are limited. A quasi-experimental, non-randomised, post-test-only study of a once-daily session of quiet time in 129 patients did not detect a significant improvement in sleep measured by RCSQ with increasing numbers of quiet time sessions[202].

While quiet time is a simple, safe and low-cost intervention, methodological issues in the few available studies mean the impact of quiet time on sleep in the ICU remains uncertain.

Ear plugs and eye masks

Earplugs and eye masks offer an inexpensive and potentially low-risk intervention to reduce or diminish the impact of nocturnal ambient noise and light. Despite the intuitive appeal, the available literature reports mixed results (Supplementary Table 1).

Studies evaluating earplugs as a single intervention include a total of 276 patients but are methodologically heterogeneous with respect to duration of the intervention, inclusion of intubated patients, use of sedation, and choice of sleep measurement tool[152,203,204]. One study reported a statistically significant improvement in sleep satisfaction with earplugs but had a 12% dropout rate[152]. Van Rompaey *et al*[204] reported that earplugs were associated with improved sleep on the first study night, but this improvement lessened on the second night and reported sleep was worse than the intervention group by the third night. Litton *et al*[203] proved that using earplugs for noise abatement in the ICU setting was feasible but did not demonstrate a statistically significant benefit to sleep quality.

The combination of ear plugs and eye masks has been assessed together. Several single-centre studies report an improved subjective perception of sleep compared to usual care[195,205-214]. Earplugs and eye masks have also been reported to significantly improve sleep compared to relaxing ocean sounds played for 30 min around the onset of the sleep period[215].

Within the methodological limitations (single centre and lack of blinding), there is increasing evidence that combined eye masks and ear plugs improve self-reported sleep. In contrast, the available literature does not support using earplugs alone.

Music

The use of non-commercial music as a sleep-promoting therapy has been evaluated. In a prospective, quasi-experimental, randomised study, 96 patients who were post-op following coronary artery bypass grafting were exposed to either a daily 30 minute session of music or a rest period[216]. Patients receiving the music intervention were reported to have significantly improved sleep, as measured by

RCSQ, on postoperative day three. Further studies on music to improve sleep in the ICU were unable to identify clear evidence of benefit. A small, randomised, controlled trial of 28 ICU patients receiving either 45 min of music prior to sleep or usual care did not identify a difference in total sleep time or subjective sleep assessment[120]. An increased duration of N3 sleep was reported in the first two hours, however, the polysomnogram was not assessed beyond this window and the significance of this finding is obscured by this methodological choice. A cross-over, randomised, experimental study evaluated the effect of 20 min of music therapy against uninterrupted rest on the BIS[217]. The bispectral index was reduced during the music session; however, no assessment of nocturnal sleep quantity or quality was made, obfuscating any association with improved sleep.

The use of music therapy to improve sleep is not well supported by the published literature. Factors including the type, volume, duration and timing of the intervention are likely all important but have not been well explored to date.

Massage

Studies of massage or therapeutic touch to aid sleep in the ICU have conflicting results. A case series of 53 patients receiving therapeutic touch from a trained nurse could not identify any statistically significant change in physiologic variables[218]. Patients were reported to fall asleep frequently during treatments, but no effect on nocturnal sleep was reported. A quasi-experimental study in 60 patients compared the efficacy of a 10-minute back massage on three consecutive days against usual care and reported improvements in self-reported sleep and actigraphy-determined total sleep on the second and third days of the intervention.

Acupressure

A randomised controlled trial of acupressure for three hours on two consecutive nights was compared to usual care and reported a statistically significant difference in actigraphy-derived total sleep time and sleep quality, as per the Stanford Sleepiness Scale[137]. However, the use of actigraphy, which overestimates total sleep time and is not accurate in the ICU setting, and the Stanford Sleepiness Scale, which has not been validated for use in the ICU, raises questions about the internal validity of this result.

PHARMACOLOGICAL MANAGEMENT OF SLEEP DISTURBANCES

About half of the ICU survivors asked about their sleep believe a sleeping pill would have improved their sleep, but there is scant evidence to support the use of pharmacological sleep aids in this setting [30]. Cohort studies indicate that pharmacological sleep aids are frequently administered to ICU patients[219,220].

Melatonin

Because of the disturbed secretion of melatonin (described above), there is a biologically plausible rationale to support the use of exogenous melatonin. However, a meta-analysis of four studies reported that melatonin, at doses of between 3 and 10 mg per day, had uncertain effects on objective and subjective measures of sleep quantity and quality (Table 5)[136,158,221-223].

More recently, a blinded, parallel-group, placebo-controlled, randomised clinical trial compared 10 mg melatonin to placebo in 203 ICU patients reported a statistically significant improvement in sleep with melatonin represented by an increase in RCSQ by nine points, but no difference in nurse-observed total sleep time[224]. Finally, the Pro-MEDIC study was a multicenter, parallel-group, placebo-controlled randomised clinical trial that included 841 patients and assessed a 4 mg dose of melatonin [225]. While the primary outcome was the incidence of delirium, sleep was recorded using RSCQ. The investigators identified no effect of melatonin on sleep and, as the largest trial to date, provides the greatest certainty as to the effect of melatonin on sleep in the ICU.

Accordingly, while there is a physiological rationale that melatonin should be an effective pharmacological sleep aid in the critically ill, there is a lack of clinical trial data to support its use.

Melatonin receptor agonists

The melatonin receptor agonist, Ramelteon, has been assessed in a single centre, blinded, randomised, placebo-controlled trial using 8 mg ramelteon per day in 88 ICU patients[226]. While the primary outcome was delirium, the use of ramelteon was associated with fewer awakenings and a higher proportion of nights without awakenings but no difference in mean hours of sleep. Determination of sleep status was performed by non-validated, retrospective means, creating uncertainty regarding this tertiary outcome.

Temazepam

There is no clinical trial data to guide the use of temazepam in the critically ill. A single-centre, placebo-controlled, blinded, randomised trial evaluating temazepam is currently recruiting (ANZCTR

Table 5 Summary of randomised clinical trials assessing nocturnal melatonin as a pharmacological sleep aid

Ref.	Design	Patients	Intervention & control	Sedation	Outcome
Ibrahim *et al* [158], 2006	Single centre, double-blind, randomised trial	32 pts	I: Melatonin 4 mg; C: placebo; For ≥ 48 h	Infusions ceased for ≥ 12 h	No significant difference in total sleep time by modified SOT
Bourne *et al* [136], 2008	Single centre, double-blind, randomised trial	24 pts	I: Melatonin 10 mg; C: Placebo; For 4 nights	Ceased for ≥ 30 h	No significant difference in total RCSQ or sleep efficiency by BIS
Foreman *et al* [222], 2015	Single centre, pilot, randomised trial	12 pts	I: Melatonin 3 mg plus eye masks and headphonesC: Standard care; For 1-7 d	Propofol allowed. Opiates ceased > 24 h	Primary outcome not determined in 65% due to uninterpretable PSG
Mistraletti *et al*[221], 2015	Single centre, double-blind, randomised trial	82 pts	I: Melatonin 3+3 mg; C: Placebo; From day 3 of ICU until ICU discharge	Enteral hydroxyzine and lorazepam allowed	No significant difference in total sleep time by nurse observation
Gandolfi *et al* [224], 2020	Double centre, double-blind, randomised trial	203 pts	I: Melatonin 10 mg; C: Placebo For 7 d or until hospital discharge	As per treating clinician	Statistically improved total RCSQ, *mean (SD):* I: 61 (26) C: 70 (21) (P = 0.03); No significant difference in total sleep time by nurse observation
Wibrow *et al* [225], 2021	Multicentre (12), double blind, randomised, trial	841 pts	I: Melatonin 4 mg; C: Placebo; For 14 d or until ICU discharge	As per treating clinician	No significant difference in total RCSQ

BIS: Bispectral index; ICU: Intensive care unit; PSG: Polysomnography; RCSQ: Richards-Campbell Sleep Questionnaire; SOT: Sleep observation tool.

registration number: ACTRN12621000742875).

Nocturnal propofol

Propofol is an intravenous anaesthetic agent that enhances GABA-ergic inhibition in the brain and is frequently administered in the ICU for patient sedation[227]. Engelmann *et al*[228] conducted a single-centre, blinded trial comparing an intravenous infusion of 2 mg/kg/h propofol against a single bolus of intravenous 0.015 mg/kg flunitrazepam for a single night. Sleep quantity was measured using BIS, and the investigators reported a statistically significant improvement in the propofol group. However, the comparison of a continuously infused agent against a single bolus, and the use of BIS to monitor sleep undermine the validity of this result. A randomised cross-over trial of nocturnal propofol infusion in 12 mechanically ventilated ICU patients reported no difference in total sleep time or NREM sleep distribution using polysomnography[98]. A prospective clinical study of 30 mechanically ventilated patients sedated with propofol and morphine evaluated additional doses of propofol to achieve a diurnal sedation pattern[229]. The authors report that 60% of patients receiving additional nocturnal propofol developed a diurnal rhythmicity, which they attributed to natural sleep, rather than deeper anaesthesia, despite using increased sedation in this group. An open-label, randomised, comparative study of 0.3-3 mg/h propofol infusion compared to 0.03-0.2 mg/hr midazolam infusion was performed in 40 conscious ICU patients overnight to assess sleep quality, anxiety and depression[230]. Using the Hospital Anxiety and Depression Scale, no significant difference in sleep quality could be detected. Notably, the Hospital Anxiety and Depression scale is not validated for sleep assessment and is likely to be insufficiently sensitive or specific to measure this outcome accurately.

Overall, there is no convincing published evidence that propofol is able to improve sleep quality or quantity in critically ill patients.

Dexmedetomidine

Two, small pilot experimental studies have assessed the effect of dexmedetomidine on sleep quality and polysomnographic appearances in critically ill patients[85,231]. Subsequent randomised trials have shown that when compared to placebo, dexmedetomidine increases sleep efficiency, total sleep time and percentage of N2 sleep phase in intubated and non-intubated patients[103,133,232]. Subjective measures of sleep have infrequently been assessed but have not reached statistical significance when reported[103]. A single, non-randomised clinical trial of non-intubated, post-abdominal surgery ICU patients compared dexmedetomidine and sufentanil infusion against sufentanil infusion alone[104]. BIS monitoring showed increased total sleep time in the dexmedetomidine group. Although this result is consistent with prior data, the outcome must be interpreted in the context of the significant limitations created by non-random allocation, small sample size and use of BIS monitoring. A blinded, parallel-group, placebo-controlled clinical trial evaluated the effect of nocturnal dexmedetomidine in 100 delirium-free, critically ill patients[233]. The secondary outcome of sleep quality, measured by the Leeds Sleep Evaluation Questionnaire, reported no significant difference in sleep quality with dexmedetomidine.

Studies of dexmedetomidine report objective improvements in sleep duration and architecture. However, many of the studies of dexmedetomidine do not have sleep as a primary outcome; therefore, interpreting these findings should be undertaken with cautious curiosity.

Orexin receptor antagonists

Suvorexant is an orexin receptor antagonist used as a novel hypnotic agent[234]. A single randomised, placebo-controlled trial of 15 mg/d of suvorexant for the prevention of delirium reported a significantly decreased incidence of delirium in the suvorexant group[235]. No other measured parameters, including time to sleep onset, number of awakenings, subjective quality of sleep, or total sleep time, were statistically different.

There are no currently available pharmacological sleep aids that have a robust evidence base to support their use in the ICU population.

CONCLUSION

Sleep is an important issue for the critically ill. Observational studies report that sleep disturbance is common during critical illness, and a growing body of evidence reports that this is subjectively distressing for the patient, causes physiological derangements and is associated with adverse outcomes. The causes for disrupted sleep in this population are multifactorial and, while not unique to the ICU, may be exacerbated by the treatment modalities, the intensity of care delivery, and the severity of illness that is synonymous with the management of critical illness in this setting.

Measuring sleep in the ICU for clinical and research purposes poses many issues. Polysomnography remains the gold-standard technique but is hindered by logistical issues and the frequent occurrence of atypical electroencephalographic findings. Other objective modalities, including actigraphy and BIS, have not proven sufficiently accurate and do not have a clear role in the ICU setting. Validated, subjective measures of sleep provide an important, patient-centred perspective. However, future research may benefit from adopting a core subjective methodology that would facilitate comparisons between studies.

Many interventions have been assessed to improve sleep during critical illness. When used together, earplugs and eye masks seem to improve sleep. However, a clear and reproducible benefit from other non-pharmacologic strategies has been hard to demonstrate. The use of pharmacological sleep aids to improve sleep is common, yet the currently available evidence does not demonstrate consistent, patient-oriented benefits from any agent. Sleep is a complex physiological process, and successful management of sleep disturbance will likely require a multimodal approach to benefit this vulnerable patient group.

ACKNOWLEDGEMENTS

The primary author, Laurie Showler, was supported through an Australian Government Research Training Program Scholarship.

FOOTNOTES

Author contributions: All authors contribute equally to the design and structure of this review; Showler L was the primary reviewer of the included literature and wrote the manuscript; Deane AM was the second reviewer of the included articles and edited the manuscript; Ali Abdelhamid Y and Goldin J wrote and edited the manuscript.

Conflict-of-interest statement: There are no conflicts of interest to disclose.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **Elliott R**, Chawla A, Wormleaton N, Harrington Z. Short-term physical health effects of sleep disruptions attributed to the acute hospital environment: a systematic review. *Sleep Health* 2021; **7**: 508-518 [PMID: 33875386 DOI: 10.1016/j.sleh.2021.03.001]

2 **Honkus VL**. Sleep deprivation in critical care units. *Crit Care Nurs Q* 2003; **26**: 179-89; quiz 190 [PMID: 12930033 DOI: 10.1097/00002727-200307000-00003]

3 **Medic G**, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. *Nat Sci Sleep* 2017; **9**: 151-161 [PMID: 28579842 DOI: 10.2147/NSS.S134864]

4 **Miranda-Ackerman RC**, Lira-Trujillo M, Gollaz-Cervantez AC, Cortés-Flores AO, Zuloaga-Fernández Del Valle CJ, García-González LA, Morgan-Villela G, Barbosa-Camacho FJ, Pintor-Belmontes KJ, Guzmán-Ramírez BG, Bernal-Hernández A, Fuentes-Orozco C, González-Ojeda A. Associations between stressors and difficulty sleeping in critically ill patients admitted to the intensive care unit: a cohort study. *BMC Health Serv Res* 2020; **20**: 631 [PMID: 32646516 DOI: 10.1186/s12913-020-05497-8]

5 **Simini B**. Patients' perceptions of intensive care. *Lancet* 1999; **354**: 571-572 [PMID: 10470711 DOI: 10.1016/s0140-6736(99)02728-2]

6 **Pisani MA**, Friese RS, Gehlbach BK, Schwab RJ, Weinhouse GL, Jones SF. Sleep in the intensive care unit. *Am J Respir Crit Care Med* 2015; **191**: 731-738 [PMID: 25594808 DOI: 10.1164/rccm.201411-2099CI]

7 **Pulak LM**, Jensen L. Sleep in the Intensive Care Unit: A Review. *J Intensive Care Med* 2016; **31**: 14-23 [PMID: 24916753 DOI: 10.1177/0885066614538749]

8 **Chang VA**, Owens RL, LaBuzetta JN. Impact of Sleep Deprivation in the Neurological Intensive Care Unit: A Narrative Review. *Neurocrit Care* 2020; **32**: 596-608 [PMID: 31410770 DOI: 10.1007/s12028-019-00795-4]

9 **Carskadon MA**, Dement WC. Chapter 2 - Normal Human Sleep: An Overview2005

10 **Oh J**, Petersen C, Walsh CM, Bittencourt JC, Neylan TC, Grinberg LT. The role of co-neurotransmitters in sleep and wake regulation. *Mol Psychiatry* 2019; **24**: 1284-1295 [PMID: 30377299 DOI: 10.1038/s41380-018-0291-2]

11 **Carley DW**, Farabi SS. Physiology of Sleep. *Diabetes Spectr* 2016; **29**: 5-9 [PMID: 26912958 DOI: 10.2337/diaspect.29.1.5]

12 **Siegel JM**. Clues to the functions of mammalian sleep. *Nature* 2005; **437**: 1264-1271 [PMID: 16251951 DOI: 10.1038/nature04285]

13 **Daou M**, Telias I, Younes M, Brochard L, Wilcox ME. Abnormal Sleep, Circadian Rhythm Disruption, and Delirium in the ICU: Are They Related? *Front Neurol* 2020; **11**: 549908 [PMID: 33071941 DOI: 10.3389/fneur.2020.549908]

14 **Berry RB**, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, Vaughan BV. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Version 2.2. In: Medicine AAoS, editor. Darien, Illinois: American Academy of Sleep Medicine; 2015

15 **Berry RB**, Wagner M. Fundamentals 3. Sleep Staging in Adults 1. In: Sleep medicine pearls 3rd ed [Internet]. United States of America: Elsevier Saunders. 2015

16 **Moser D**, Anderer P, Gruber G, Parapatics S, Loretz E, Boeck M, Kloesch G, Heller E, Schmidt A, Danker-Hopfe H, Saletu B, Zeitlhofer J, Dorffner G. Sleep classification according to AASM and Rechtschaffen & Kales: effects on sleep scoring parameters. *Sleep* 2009; **32**: 139-149 [PMID: 19238800 DOI: 10.1093/sleep/32.2.139]

17 **Novelli L**, Ferri R, Bruni O. Sleep classification according to AASM and Rechtschaffen and Kales: effects on sleep scoring parameters of children and adolescents. *J Sleep Res* 2010; **19**: 238-247 [PMID: 19912509 DOI: 10.1111/j.1365-2869.2009.00785.x]

18 **Forget D**, Morin CM, Bastien CH. The role of the spontaneous and evoked k-complex in good-sleeper controls and in individuals with insomnia. *Sleep* 2011; **34**: 1251-1260 [PMID: 21886363 DOI: 10.5665/SLEEP.1250]

19 **Fernandez LMJ**, Lüthi A. Sleep Spindles: Mechanisms and Functions. *Physiol Rev* 2020; **100**: 805-868 [PMID: 31804897 DOI: 10.1152/physrev.00042.2018]

20 **Roth T**. Slow wave sleep: does it matter? *J Clin Sleep Med* 2009; **5**: S4-S5 [PMID: 19998868 DOI: 10.5664/jcsm.5.2S.S4]

21 **Peever J**, Fuller PM. Neuroscience: A Distributed Neural Network Controls REM Sleep. *Curr Biol* 2016; **26**: R34-R35 [PMID: 26766231 DOI: 10.1016/j.cub.2015.11.011]

22 **Peever J**, Fuller PM. The Biology of REM Sleep. *Curr Biol* 2017; **27**: R1237-R1248 [PMID: 29161567 DOI: 10.1016/j.cub.2017.10.026]

23 **Chokroverty S**. Overview of Normal Sleep. In: Chokroverty S, editor. Sleep Disorders Medicine: Basic Science, Technical Considerations and Clinical Aspects. New York, NY: Springer New York; 2017; 5-27 [DOI: 10.1007/978-1-4939-6578-6_2]

24 **Chaput JP**, Dutil C, Sampasa-Kanyinga H. Sleeping hours: what is the ideal number and how does age impact this? *Nat Sci Sleep* 2018; **10**: 421-430 [PMID: 30568521 DOI: 10.2147/NSS.S163071]

25 **Cappuccio FP**, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep* 2010; **33**: 585-592 [PMID: 20469800 DOI: 10.1093/sleep/33.5.585]

26 **Banks S**, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med* 2007; **3**: 519-528 [PMID: 17803017 DOI: 10.5664/jcsm.26918]

27 **Nelson JE**, Meier DE, Oei EJ, Nierman DM, Senzel RS, Manfredi PL, Davis SM, Morrison RS. Self-reported symptom experience of critically ill cancer patients receiving intensive care. *Crit Care Med* 2001; **29**: 277-282 [PMID: 11246306 DOI: 10.1097/00003246-200102000-00010]

28 **Little A**, Ethier C, Ayas N, Thanachayanont T, Jiang D, Mehta S. A patient survey of sleep quality in the Intensive Care Unit. *Minerva Anestesiol* 2012; **78**: 406-414 [PMID: 22337154]

29 **Naik RD**, Gupta K, Soneja M, Elavarasi A, Sreenivas V, Sinha S. Sleep Quality and Quantity in Intensive Care Unit Patients: A Cross-sectional Study. *Indian J Crit Care Med* 2018; **22**: 408-414 [PMID: 29962740 DOI: 10.4103/ijccm.IJCCM_65_18]

30 **Martinez FE**, Poulter AL, Seneviratne C, Chrimes A, Havill K, Balogh ZJ, Paech GM. ICU Patients' Perception of Sleep

and Modifiable versus Non-Modifiable Factors That Affect It: A Prospective Observational Study. *J Clin Med* 2022; **11** [PMID: 35807010 DOI: 10.3390/jcm11133725]

31 **Freedman NS**, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 2001; **163**: 451-457 [PMID: 11179121 DOI: 10.1164/ajrccm.163.2.9912128]

32 **Elliott R**, McKinley S, Cistulli P, Fien M. Characterisation of sleep in intensive care using 24-hour polysomnography: an observational study. *Crit Care* 2013; **17**: R46 [PMID: 23506782 DOI: 10.1186/cc12565]

33 **Altman MT**, Knauert MP, Pisani MA. Sleep Disturbance after Hospitalization and Critical Illness: A Systematic Review. *Ann Am Thorac Soc* 2017; **14**: 1457-1468 [PMID: 28644698 DOI: 10.1513/AnnalsATS.201702-148SR]

34 **Orwelius L**, Nordlund A, Nordlund P, Edéll-Gustafsson U, Sjöberg F. Prevalence of sleep disturbances and long-term reduced health-related quality of life after critical care: a prospective multicenter cohort study. *Crit Care* 2008; **12**: R97 [PMID: 18673569 DOI: 10.1186/cc6973]

35 **Combes A**, Costa MA, Trouillet JL, Baudot J, Mokhtari M, Gibert C, Chastre J. Morbidity, mortality, and quality-of-life outcomes of patients requiring >or=14 days of mechanical ventilation. *Crit Care Med* 2003; **31**: 1373-1381 [PMID: 12771605 DOI: 10.1097/01.Ccm.0000065188.87029.C3]

36 **Bihari S**, Doug McEvoy R, Matheson E, Kim S, Woodman RJ, Bersten AD. Factors affecting sleep quality of patients in intensive care unit. *J Clin Sleep Med* 2012; **8**: 301-307 [PMID: 22701388 DOI: 10.5664/jcsm.1920]

37 **McKinley S**, Fien M, Elliott R, Elliott D. Sleep and psychological health during early recovery from critical illness: an observational study. *J Psychosom Res* 2013; **75**: 539-545 [PMID: 24290043 DOI: 10.1016/j.jpsychores.2013.09.007]

38 **McKinley S**, Aitken LM, Alison JA, King M, Leslie G, Burmeister E, Elliott D. Sleep and other factors associated with mental health and psychological distress after intensive care for critical illness. *Intensive Care Med* 2012; **38**: 627-633 [PMID: 22318635 DOI: 10.1007/s00134-012-2477-4]

39 **Solverson KJ**, Easton PA, Doig CJ. Assessment of sleep quality post-hospital discharge in survivors of critical illness. *Respir Med* 2016; **114**: 97-102 [PMID: 27109818 DOI: 10.1016/j.rmed.2016.03.009]

40 **Choi J**, Hoffman LA, Schulz R, Tate JA, Donahoe MP, Ren D, Given BA, Sherwood PR. Self-reported physical symptoms in intensive care unit (ICU) survivors: pilot exploration over four months post-ICU discharge. *J Pain Symptom Manage* 2014; **47**: 257-270 [PMID: 23856099 DOI: 10.1016/j.jpainsymman.2013.03.019]

41 **Parsons EC**, Kross EK, Caldwell ES, Kapur VK, McCurry SM, Vitiello MV, Hough CL. Post-discharge insomnia symptoms are associated with quality of life impairment among survivors of acute lung injury. *Sleep Med* 2012; **13**: 1106-1109 [PMID: 22763017 DOI: 10.1016/j.sleep.2012.05.010]

42 **Benítez ID**, Moncusí-Moix A, Vaca R, Gort-Paniello C, Minguez O, Santisteve S, Carmona P, Torres G, Fagotti J, Labarca G, Torres A, González J, de Gonzalo-Calvo D, Barbé F, Targa ADS. Sleep and Circadian Health of Critical COVID-19 Survivors 3 Months After Hospital Discharge. *Crit Care Med* 2022; **50**: 945-954 [PMID: 35234413 DOI: 10.1097/CCM.0000000000005476]

43 **Lee CM**, Herridge MS, Gabor JY, Tansey CM, Matte A, Hanly PJ. Chronic sleep disorders in survivors of the acute respiratory distress syndrome. *Intensive Care Med* 2009; **35**: 314-320 [PMID: 18802684 DOI: 10.1007/s00134-008-1277-3]

44 **Alvaro PK**, Roberts RM, Harris JK. A Systematic Review Assessing Bidirectionality between Sleep Disturbances, Anxiety, and Depression. *Sleep* 2013; **36**: 1059-1068 [PMID: 23814343 DOI: 10.5665/sleep.2810]

45 **Wang CY**, Shang M, Feng LZ, Zhou CL, Zhou QS, Hu K. Correlation between APACHE III score and sleep quality in ICU patients. *J Int Med Res* 2019; **47**: 3670-3680 [PMID: 31238759 DOI: 10.1177/0300060519856745]

46 **Gabor JY**, Cooper AB, Crombach SA, Lee B, Kadikar N, Bettger HE, Hanly PJ. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med* 2003; **167**: 708-715 [PMID: 12598213 DOI: 10.1164/rccm.2201090]

47 **Fanfulla F**, Ceriana P, D'Artavilla Lupo N, Trentin R, Frigerio F, Nava S. Sleep disturbances in patients admitted to a step-down unit after ICU discharge: the role of mechanical ventilation. *Sleep* 2011; **34**: 355-362 [PMID: 21358853 DOI: 10.1093/sleep/34.3.355]

48 **Hardin KA**, Seyal M, Stewart T, Bonekat HW. Sleep in critically ill chemically paralyzed patients requiring mechanical ventilation. *Chest* 2006; **129**: 1468-1477 [PMID: 16778263 DOI: 10.1378/chest.129.6.1468]

49 **Wong FY**, Arthur DG. Hong Kong patients' experiences of intensive care after surgery: nurses' and patients' views. *Intensive Crit Care Nurs* 2000; **16**: 290-303 [PMID: 11000603 DOI: 10.1054/iccn.2000.1515]

50 **Johansson L**, Bergbom I, Lindahl B. Meanings of being critically ill in a sound-intensive ICU patient room - a phenomenological hermeneutical study. *Open Nurs J* 2012; **6**: 108-116 [PMID: 22977654 DOI: 10.2174/1874434601206010108]

51 **Chahraoui K**, Laurent A, Bioy A, Quenot JP. Psychological experience of patients 3 months after a stay in the intensive care unit: A descriptive and qualitative study. *J Crit Care* 2015; **30**: 599-605 [PMID: 25776895 DOI: 10.1016/j.jcrc.2015.02.016]

52 **Ding Q**, Redeker NS, Pisani MA, Yaggi HK, Knauert MP. Factors Influencing Patients' Sleep in the Intensive Care Unit: Perceptions of Patients and Clinical Staff. *Am J Crit Care* 2017; **26**: 278-286 [PMID: 28668912 DOI: 10.4037/ajcc2017333]

53 **Mattiussi E**, Danielis M, Venuti L, Vidoni M, Palese A. Sleep deprivation determinants as perceived by intensive care unit patients: Findings from a systematic review, meta-summary and meta-synthesis. *Intensive Crit Care Nurs* 2019; **53**: 43-53 [PMID: 30926174 DOI: 10.1016/j.iccn.2019.03.006]

54 **Arain M**, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? *BMC Med Res Methodol* 2010; **10**: 67 [PMID: 20637084 DOI: 10.1186/1471-2288-10-67]

55 **Tembo AC**, Parker V, Higgins I. The experience of sleep deprivation in intensive care patients: findings from a larger hermeneutic phenomenological study. *Intensive Crit Care Nurs* 2013; **29**: 310-316 [PMID: 23806731 DOI: 10.1016/j.iccn.2013.05.003]

56 **Novaes MA**, Knobel E, Bork AM, Pavão OF, Nogueira-Martins LA, Ferraz MB. Stressors in ICU: perception of the

patient, relatives and health care team. *Intensive Care Med* 1999; **25**: 1421-1426 [PMID: 10660851 DOI: 10.1007/s001340051091]

57 **Gehlbach BK**, Chapotot F, Leproult R, Whitmore H, Poston J, Pohlman M, Miller A, Pohlman AS, Nedeltcheva A, Jacobsen JH, Hall JB, Van Cauter E. Temporal disorganization of circadian rhythmicity and sleep-wake regulation in mechanically ventilated patients receiving continuous intravenous sedation. *Sleep* 2012; **35**: 1105-1114 [PMID: 22851806 DOI: 10.5665/sleep.1998]

58 **Telias I**, Wilcox ME. Sleep and Circadian Rhythm in Critical Illness. *Crit Care* 2019; **23**: 82 [PMID: 30850003 DOI: 10.1186/s13054-019-2366-0]

59 **Nilius G**, Richter M, Schroeder M. Updated Perspectives on the Management of Sleep Disorders in the Intensive Care Unit. *Nat Sci Sleep* 2021; **13**: 751-762 [PMID: 34135650 DOI: 10.2147/NSS.S284846]

60 **Blume C**, Garbazza C, Spitschan M. Effects of light on human circadian rhythms, sleep and mood. *Somnologie (Berl)* 2019; **23**: 147-156 [PMID: 31534436 DOI: 10.1007/s11818-019-00215-x]

61 **Elliott R**, Rai T, McKinley S. Factors affecting sleep in the critically ill: an observational study. *J Crit Care* 2014; **29**: 859-863 [PMID: 24973105 DOI: 10.1016/j.jcrc.2014.05.015]

62 **Freedman NS**, Kotzer N, Schwab RJ. Patient perception of sleep quality and etiology of sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 1999; **159**: 1155-1162 [PMID: 10194160 DOI: 10.1164/ajrccm.159.4.9806141]

63 **Hilton BA**. Quantity and quality of patients' sleep and sleep-disturbing factors in a respiratory intensive care unit. *J Adv Nurs* 1976; **1**: 453-468 [PMID: 1050357 DOI: 10.1111/j.1365-2648.1976.tb00932.x]

64 **Dunn H**, Anderson MA, Hill PD. Nighttime lighting in intensive care units. *Crit Care Nurse* 2010; **30**: 31-37 [PMID: 20515882 DOI: 10.4037/ccn2010342]

65 **Darbyshire JL**, Müller-Trapet M, Cheer J, Fazi FM, Young JD. Mapping sources of noise in an intensive care unit. *Anaesthesia* 2019; **74**: 1018-1025 [PMID: 31066046 DOI: 10.1111/anae.14690]

66 **Berglund B**, Lindval T, Schwela DH. Guidelines for community noise. World Health Organisation. Geneva. 1999

67 **Xie H**, Kang J, Mills GH. Clinical review: The impact of noise on patients' sleep and the effectiveness of noise reduction strategies in intensive care units. *Crit Care* 2009; **13**: 208 [PMID: 19344486 DOI: 10.1186/cc7154]

68 **Jaiswal SJ**, Garcia S, Owens RL. Sound and Light Levels Are Similarly Disruptive in ICU and non-ICU Wards. *J Hosp Med* 2017; **12**: 798-804 [PMID: 28991944 DOI: 10.12788/jhm.2826]

69 **Balogh D**, Kittinger E, Benzer A, Hackl JM. Noise in the ICU. *Intensive Care Med* 1993; **19**: 343-346 [PMID: 8227725 DOI: 10.1007/bf01694709]

70 **Elbaz M**, Léger D, Sauvet F, Champigneulle B, Rio S, Strauss M, Chennaoui M, Guilleminault C, Mira JP. Sound level intensity severely disrupts sleep in ventilated ICU patients throughout a 24-h period: a preliminary 24-h study of sleep stages and associated sound levels. *Ann Intensive Care* 2017; **7**: 25 [PMID: 28255956 DOI: 10.1186/s13613-017-0248-7]

71 **Lawson N**, Thompson K, Saunders G, Saiz J, Richardson J, Brown D, Ince N, Caldwell M, Pope D. Sound intensity and noise evaluation in a critical care unit. *Am J Crit Care* 2010; **19**: e88-98; quiz e99 [PMID: 21041190 DOI: 10.4037/ajcc2010180]

72 **Jones J**, Hoggart B, Withey J, Donaghue K, Ellis BW. What the patients say: A study of reactions to an intensive care unit. *Intensive Care Med* 1979; **5**: 89-92 [PMID: 458040 DOI: 10.1007/bf01686054]

73 **Frisk U**, Nordström G. Patients' sleep in an intensive care unit--patients' and nurses' perception. *Intensive Crit Care Nurs* 2003; **19**: 342-349 [PMID: 14637294 DOI: 10.1016/s0964-3397(03)00076-4]

74 **Uğraş GA**, Oztekin SD. Patient perception of environmental and nursing factors contributing to sleep disturbances in a neurosurgical intensive care unit. *Tohoku J Exp Med* 2007; **212**: 299-308 [PMID: 17592217 DOI: 10.1620/tjem.212.299]

75 **Celik S**, Oztekin D, Akyolcu N, Işsever H. Sleep disturbance: the patient care activities applied at the night shift in the intensive care unit. *J Clin Nurs* 2005; **14**: 102-106 [PMID: 15656854 DOI: 10.1111/j.1365-2702.2004.01010.x]

76 **Tamburri LM**, DiBrienza R, Zozula R, Redeker NS. Nocturnal care interactions with patients in critical care units. *Am J Crit Care* 2004; **13**: 102-12; quiz 114 [PMID: 15043238 DOI: 10.4037/ajcc2004.13.2.102]

77 **McLaughlin DC**, Hartjes TM, Freeman WD. Sleep Deprivation in Neurointensive Care Unit Patients From Serial Neurological Checks: How Much Is Too Much? *J Neurosci Nurs* 2018; **50**: 205-210 [PMID: 29894442 DOI: 10.1097/JNN.0000000000000378]

78 **Stone JJ**, Childs S, Smith LE, Battin M, Papadakos PJ, Huang JH. Hourly neurologic assessments for traumatic brain injury in the ICU. *Neurol Res* 2014; **36**: 164-169 [PMID: 24410060 DOI: 10.1179/1743132813Y.0000000285]

79 **Parthasarathy S**, Tobin MJ. Effect of ventilator mode on sleep quality in critically ill patients. *Am J Respir Crit Care Med* 2002; **166**: 1423-1429 [PMID: 12406837 DOI: 10.1164/rccm.200209-999OC]

80 **Boyko Y**, Ording H, Jennum P. Sleep disturbances in critically ill patients in ICU: how much do we know? *Acta Anaesthesiol Scand* 2012; **56**: 950-958 [PMID: 22404330 DOI: 10.1111/j.1399-6576.2012.02672.x]

81 **Toublanc B**, Rose D, Glérant JC, Francois G, Mayeux I, Rodenstein D, Jounieaux V. Assist-control ventilation vs. low levels of pressure support ventilation on sleep quality in intubated ICU patients. *Intensive Care Med* 2007; **33**: 1148-1154 [PMID: 17492431 DOI: 10.1007/s00134-007-0659-2]

82 **Cabello B**, Thille AW, Drouot X, Galia F, Mancebo J, d'Ortho MP, Brochard L. Sleep quality in mechanically ventilated patients: comparison of three ventilatory modes. *Crit Care Med* 2008; **36**: 1749-1755 [PMID: 18496373 DOI: 10.1097/CCM.0b013e3181743f41]

83 **Andréjak C**, Monconduit J, Rose D, Toublanc B, Mayeux I, Rodenstein D, Jounieaux V. Does using pressure-controlled ventilation to rest respiratory muscles improve sleep in ICU patients? *Respir Med* 2013; **107**: 534-541 [PMID: 23391488 DOI: 10.1016/j.rmed.2012.12.012]

84 **Bosma K**, Ferreyra G, Ambrogio C, Pasero D, Mirabella L, Braghiroli A, Appendini L, Mascia L, Ranieri VM. Patient-ventilator interaction and sleep in mechanically ventilated patients: pressure support versus proportional assist ventilation. *Crit Care Med* 2007; **35**: 1048-1054 [PMID: 17334259 DOI: 10.1097/01.Ccm.0000260055.64235.7c]

85 **Alexopoulou C**, Kondili E, Vakouti E, Klimathianaki M, Prinianakis G, Georgopoulos D. Sleep during proportional-assist ventilation with load-adjustable gain factors in critically ill patients. *Intensive Care Med* 2007; **33**: 1139-1147 [PMID:

17458541 DOI: 10.1007/s00134-007-0630-2]
86 **Alexopoulou C**, Kondili E, Plataki M, Georgopoulos D. Patient-ventilator synchrony and sleep quality with proportional assist and pressure support ventilation. *Intensive Care Med* 2013; **39**: 1040-1047 [PMID: 23417203 DOI: 10.1007/s00134-013-2850-y]
87 **Córdoba-Izquierdo A**, Drouot X, Thille AW, Galia F, Roche-Campo F, Schortgen F, Prats-Soro E, Brochard L. Sleep in hypercapnic critical care patients under noninvasive ventilation: conventional versus dedicated ventilators. *Crit Care Med* 2013; **41**: 60-68 [PMID: 23222258 DOI: 10.1097/CCM.0b013e31826764e3]
88 **Roche-Campo F**, Thille AW, Drouot X, Galia F, Margarit L, Córdoba-Izquierdo A, Mancebo J, d'Ortho MP, Brochard L. Comparison of sleep quality with mechanical versus spontaneous ventilation during weaning of critically III tracheostomized patients. *Crit Care Med* 2013; **41**: 1637-1644 [PMID: 23507721 DOI: 10.1097/CCM.0b013e318287f569]
89 **Heffernan AJ**, Talekar C, Henain M, Purcell L, Palmer M, White H. Comparison of continuous versus intermittent enteral feeding in critically ill patients: a systematic review and meta-analysis. *Crit Care* 2022; **26**: 325 [PMID: 36284334 DOI: 10.1186/s13054-022-04140-8]
90 **Kouw IWK**, Heilbronn LK, van Zanten ARH. Intermittent feeding and circadian rhythm in critical illness. *Curr Opin Crit Care* 2022; **28**: 381-388 [PMID: 35797531 DOI: 10.1097/MCC.0000000000000960]
91 **McNelly AS**, Bear DE, Connolly BA, Arbane G, Allum L, Tarbhai A, Cooper JA, Hopkins PA, Wise MP, Brealey D, Rooney K, Cupitt J, Carr B, Koelfat K, Damink SO, Atherton PJ, Hart N, Montgomery HE, Puthucheary ZA. Effect of Intermittent or Continuous Feed on Muscle Wasting in Critical Illness: A Phase 2 Clinical Trial. *Chest* 2020; **158**: 183-194 [PMID: 32247714 DOI: 10.1016/j.chest.2020.03.045]
92 **Kar P**, Jones KL, Horowitz M, Chapman MJ, Deane AM. Measurement of gastric emptying in the critically ill. *Clin Nutr* 2015; **34**: 557-564 [PMID: 25491245 DOI: 10.1016/j.clnu.2014.11.003]
93 **Finan PH**, Richards JM, Gamaldo CE, Han D, Leoutsakos JM, Salas R, Irwin MR, Smith MT. Validation of a Wireless, Self-Application, Ambulatory Electroencephalographic Sleep Monitoring Device in Healthy Volunteers. *J Clin Sleep Med* 2016; **12**: 1443-1451 [PMID: 27707438 DOI: 10.5664/jcsm.6262]
94 **Kakar E**, Priester M, Wessels P, Slooter AJC, Louter M, van der Jagt M. Sleep assessment in critically ill adults: A systematic review and meta-analysis. *J Crit Care* 2022; **71**: 154102 [PMID: 35849874 DOI: 10.1016/j.jcrc.2022.154102]
95 **Tung A**, Lynch JP, Mendelson WB. Prolonged sedation with propofol in the rat does not result in sleep deprivation. *Anesth Analg* 2001; **92**: 1232-1236 [PMID: 11323352 DOI: 10.1097/00000539-200105000-00028]
96 **Song J**, Um YH, Kim TW, Kim SM, Kwon SY, Hong S-C. Sleep and Anesthesia. *Sleep Med Res* 2018; **9**: 11-19 [DOI: 10.17241/smr.2018.00164]
97 **Jean R**, Shah P, Yudelevich E, Genese F, Gershner K, Levendowski D, Martillo M, Ventura I, Basu A, Ochieng P, Gibson CD. Effects of deep sedation on sleep in critically ill medical patients on mechanical ventilation. *J Sleep Res* 2020; **29**: e12894 [PMID: 31352685 DOI: 10.1111/jsr.12894]
98 **Kondili E**, Alexopoulou C, Xirouchaki N, Georgopoulos D. Effects of propofol on sleep quality in mechanically ventilated critically ill patients: a physiological study. *Intensive Care Med* 2012; **38**: 1640-1646 [PMID: 22752356 DOI: 10.1007/s00134-012-2623-z]
99 **Bourne RS**, Mills GH. Sleep disruption in critically ill patients--pharmacological considerations. *Anaesthesia* 2004; **59**: 374-384 [PMID: 15023109 DOI: 10.1111/j.1365-2044.2004.03664.x]
100 **Cronin A**, Keifer JC, Baghdoyan HA, Lydic R. Opioid inhibition of rapid eye movement sleep by a specific mu receptor agonist. *Br J Anaesth* 1995; **74**: 188-192 [PMID: 7696070 DOI: 10.1093/bja/74.2.188]
101 **Shaw IR**, Lavigne G, Mayer P, Choinière M. Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: a preliminary study. *Sleep* 2005; **28**: 677-682 [PMID: 16477954 DOI: 10.1093/sleep/28.6.677]
102 **Dimsdale JE**, Norman D, DeJardin D, Wallace MS. The effect of opioids on sleep architecture. *J Clin Sleep Med* 2007; **3**: 33-36 [PMID: 17557450]
103 **Sun YM**, Zhu SN, Zhang C, Li SL, Wang DX. Effect of low-dose dexmedetomidine on sleep quality in postoperative patients with mechanical ventilation in the intensive care unit: A pilot randomized trial. *Front Med (Lausanne)* 2022; **9**: 931084 [PMID: 36117973 DOI: 10.3389/fmed.2022.931084]
104 **Lu W**, Fu Q, Luo X, Fu S, Hu K. Effects of dexmedetomidine on sleep quality of patients after surgery without mechanical ventilation in ICU. *Medicine (Baltimore)* 2017; **96**: e7081 [PMID: 28591048 DOI: 10.1097/MD.0000000000007081]
105 **Litton E**, Elliott R, Thompson K, Watts N, Seppelt I, Webb SAR; ANZICS Clinical Trials Group and The George Institute for Global Health. Using Clinically Accessible Tools to Measure Sound Levels and Sleep Disruption in the ICU: A Prospective Multicenter Observational Study. *Crit Care Med* 2017; **45**: 966-971 [PMID: 28362644 DOI: 10.1097/CCM.0000000000002405]
106 **Monti JM**. Catecholamines and the sleep-wake cycle. I. EEG and behavioral arousal. *Life Sci* 1982; **30**: 1145-1157 [PMID: 7045557 DOI: 10.1016/0024-3205(82)90656-7]
107 **Wichniak A**, Wierzbicka A, Walęcka M, Jernajczyk W. Effects of Antidepressants on Sleep. *Curr Psychiatry Rep* 2017; **19**: 63 [PMID: 28791566 DOI: 10.1007/s11920-017-0816-4]
108 Miljatovic AM. Comparative effects of venlafaxine and mirtazapine on sleep physiology measures in patients with major depresive disorder and insomnia. *European Psychiatry* 2012; **27**: 1 [DOI: 10.1016/S0924-9338(12)75521-9]
109 **Moreno RA**, Hanna MM, Tavares SM, Wang YP. A double-blind comparison of the effect of the antipsychotics haloperidol and olanzapine on sleep in mania. *Braz J Med Biol Res* 2007; **40**: 357-366 [PMID: 17334533 DOI: 10.1590/s0100-879x2007000300011]
110 **Yamashita H**, Morinobu S, Yamawaki S, Horiguchi J, Nagao M. Effect of risperidone on sleep in schizophrenia: a comparison with haloperidol. *Psychiatry Res* 2002; **109**: 137-142 [PMID: 11927138 DOI: 10.1016/s0165-1781(02)00009-4]
111 **Giménez S**, Clos S, Romero S, Grasa E, Morte A, Barbanoj MJ. Effects of olanzapine, risperidone and haloperidol on sleep after a single oral morning dose in healthy volunteers. *Psychopharmacology (Berl)* 2007; **190**: 507-516 [PMID:

17205319 DOI: 10.1007/s00213-006-0633-7]
112 **Cole JL**. Steroid-Induced Sleep Disturbance and Delirium: A Focused Review for Critically Ill Patients. *Fed Pract* 2020; **37**: 260-267 [PMID: 32669778]
113 **Drouot X**, Roche-Campo F, Thille AW, Cabello B, Galia F, Margarit L, d'Ortho MP, Brochard L. A new classification for sleep analysis in critically ill patients. *Sleep Med* 2012; **13**: 7-14 [PMID: 22153778 DOI: 10.1016/j.sleep.2011.07.012]
114 **Knauert MP**, Yaggi HK, Redeker NS, Murphy TE, Araujo KL, Pisani MA. Feasibility study of unattended polysomnography in medical intensive care unit patients. *Heart Lung* 2014; **43**: 445-452 [PMID: 25023504 DOI: 10.1016/j.hrtlng.2014.06.049]
115 **Watson PL**, Pandharipande P, Gehlbach BK, Thompson JL, Shintani AK, Dittus BS, Bernard GR, Malow BA, Ely EW. Atypical sleep in ventilated patients: empirical electroencephalography findings and the path toward revised ICU sleep scoring criteria. *Crit Care Med* 2013; **41**: 1958-1967 [PMID: 23863228 DOI: 10.1097/CCM.0b013e31828a3f75]
116 **Knauert MP**, Gilmore EJ, Murphy TE, Yaggi HK, Van Ness PH, Han L, Hirsch LJ, Pisani MA. Association between death and loss of stage N2 sleep features among critically Ill patients with delirium. *J Crit Care* 2018; **48**: 124-129 [PMID: 30179762 DOI: 10.1016/j.jcrc.2018.08.028]
117 **Cooper AB**, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ. Sleep in critically ill patients requiring mechanical ventilation. *Chest* 2000; **117**: 809-818 [PMID: 10713011 DOI: 10.1378/chest.117.3.809]
118 **Aurell J**, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *Br Med J (Clin Res Ed)* 1985; **290**: 1029-1032 [PMID: 3921096 DOI: 10.1136/bmj.290.6474.1029]
119 **Weinhouse GL**, Kimchi E, Watson P, Devlin JW. Sleep Assessment in Critically Ill Adults: Established Methods and Emerging Strategies. *Crit Care Explor* 2022; **4**: e0628 [PMID: 35156048 DOI: 10.1097/CCE.0000000000000628]
120 **Su CP**, Lai HL, Chang ET, Yiin LM, Perng SJ, Chen PW. A randomized controlled trial of the effects of listening to non-commercial music on quality of nocturnal sleep and relaxation indices in patients in medical intensive care unit. *J Adv Nurs* 2013; **69**: 1377-1389 [PMID: 22931483 DOI: 10.1111/j.1365-2648.2012.06130.x]
121 **Darbyshire JL**, Borthwick M, Edmonds P, Vollam S, Hinton L, Young JD. Measuring sleep in the intensive care unit: Electroencephalogram, actigraphy, or questionnaire? *J Intensive Care Soc* 2020; **21**: 22-27 [PMID: 32284714 DOI: 10.1177/1751143718816910]
122 **Fallmann S**, Chen L. Computational Sleep Behavior Analysis: A Survey. *IEEE Access* 2019; **7**: 142421-142440 [DOI: 10.1109/ACCESS.2019.2944801]
123 **Quereshi S**, Karilla S, Vanichayobon S. Human sleep scoring based on K-nearest neighbors. *Turk J Elec Eng & Comp Sci* 2018; **26**: 2802-2818 [DOI: 10.3906/elk-1805-12]
124 **Ambrogio C**, Koebnick J, Quan SF, Ranieri M, Parthasarathy S. Assessment of sleep in ventilator-supported critically III patients. *Sleep* 2008; **31**: 1559-1568 [PMID: 19014076 DOI: 10.1093/sleep/31.11.1559]
125 **Delaney LJ Van Harren F**, Currie M, Huang H-CC, Lopez V Sleep Monitoring Techniques within Intensive Care. International Journal of Nursing Clinical Practice 2015; 2: 114 [DOI: 10.15344/2394-4978/2015/114]
126 **Bourne RS**, Minelli C, Mills GH, Kandler R. Clinical review: Sleep measurement in critical care patients: research and clinical implications. *Crit Care* 2007; **11**: 226 [PMID: 17764582 DOI: 10.1186/cc5966]
127 **Richards KC**, Wang YY, Jun J, Ye L. A Systematic Review of Sleep Measurement in Critically Ill Patients. *Front Neurol* 2020; **11**: 542529 [PMID: 33240191 DOI: 10.3389/fneur.2020.542529]
128 **Lewis SR**, Pritchard MW, Fawcett LJ, Punjasawadwong Y. Bispectral index for improving intraoperative awareness and early postoperative recovery in adults. *Cochrane Database Syst Rev* 2019; **9**: CD003843 [PMID: 31557307 DOI: 10.1002/14651858.CD003843.pub4]
129 **Nicholson T**, Patel J, Sleigh JW. Sleep patterns in intensive care unit patients: a study using the bispectral index. *Crit Care Resusc* 2001; **3**: 86-91 [PMID: 16610990]
130 **Pedrão RAA**, Riella RJ, Richards K, Valderramas SR. Viability and validity of the bispectral index to measure sleep in patients in the intensive care unit. *Rev Bras Ter Intensiva* 2020; **32**: 535-541 [PMID: 33263704 DOI: 10.5935/0103-507X.20200083]
131 **Reinke L**, van der Hoeven JH, van Putten MJ, Dieperink W, Tulleken JE. Intensive care unit depth of sleep: proof of concept of a simple electroencephalography index in the non-sedated. *Crit Care* 2014; **18**: R66 [PMID: 24716479 DOI: 10.1186/cc13823]
132 **Vacas S**, McInrue E, Gropper MA, Maze M, Zak R, Lim E, Leung JM. The Feasibility and Utility of Continuous Sleep Monitoring in Critically Ill Patients Using a Portable Electroencephalography Monitor. *Anesth Analg* 2016; **123**: 206-212 [PMID: 27159066 DOI: 10.1213/ANE.0000000000001330]
133 **Romagnoli S**, Villa G, Fontanarosa L, Tofani L, Pinelli F, De Gaudio AR, Ricci Z. Sleep duration and architecture in non-intubated intensive care unit patients: an observational study. *Sleep Med* 2020; **70**: 79-87 [PMID: 32229421 DOI: 10.1016/j.sleep.2019.11.1265]
134 **Schwab KE**, Ronish B, Needham DM, To AQ, Martin JL, Kamdar BB. Actigraphy to Evaluate Sleep in the Intensive Care Unit. A Systematic Review. *Ann Am Thorac Soc* 2018; **15**: 1075-1082 [PMID: 29944386 DOI: 10.1513/AnnalsATS.201801-004OC]
135 **Acker JG**, Becker-Carus C, Büttner-Teleaga A, Cassel W, Danker-Hopfe H, Dück A, et al The role of actigraphy in sleep medicine.
Somnologie 2021; 25: 89-98 [DOI: 10.1007/s11818-021-00306-8]
136 **Bourne RS**, Mills GH, Minelli C. Melatonin therapy to improve nocturnal sleep in critically ill patients: encouraging results from a small randomised controlled trial. *Crit Care* 2008; **12**: R52 [PMID: 18423009 DOI: 10.1186/cc6871]
137 **Chen JH**, Chao YH, Lu SF, Shiung TF, Chao YF. The effectiveness of valerian acupressure on the sleep of ICU patients: a randomized clinical trial. *Int J Nurs Stud* 2012; **49**: 913-920 [PMID: 22391336 DOI: 10.1016/j.ijnurstu.2012.02.012]
138 **Nagatomo K**, Masuyama T, Iizuka Y, Makino J, Shiotsuka J, Sanui M. Validity of an under-mattress sensor for objective sleep measurement in critically ill patients: a prospective observational study. *J Intensive Care* 2020; **8**: 16 [PMID: 32071722 DOI: 10.1186/s40560-020-0433-x]

139 **Matsui K**, Sato N, Idei M, Arakida M, Seino Y, Ishikawa JY, Nakagawa M, Akaho R, Nishimura K, Nomura T. An Automated Algorithm for Determining Sleep Using Single-Channel Electroencephalography to Detect Delirium: A Prospective Observational Study in Intensive Care Units. *Healthcare (Basel)* 2022; **10** [PMID: 36141389 DOI: 10.3390/healthcare10091776]

140 **Jeffs EL**, Darbyshire JL. Measuring Sleep in the Intensive Care Unit: A Critical Appraisal of the Use of Subjective Methods. *J Intensive Care Med* 2019; **34**: 751-760 [PMID: 28631532 DOI: 10.1177/0885066617712197]

141 **Richards K**. Techniques for measurement of sleep in critical care. *Focus Crit Care* 1987; **14**: 34-40 [PMID: 3650169]

142 **Elliott R**, Axelin A, Richards KC, Vahlberg T, Ritmala-Castren M. Sensitivity and specificity of proposed Richards-Campbell Sleep Questionnaire cut-off scores for good quality sleep during an ICU stay. *J Clin Nurs* 2022 [PMID: 35570380 DOI: 10.1111/jocn.16348]

143 **Richards KC**, O'Sullivan PS, Phillips RL. Measurement of sleep in critically ill patients. *J Nurs Meas* 2000; **8**: 131-144 [PMID: 11227580]

144 **Louis M**, Treger K, Ashby T, Smotherman C, Gautum S, Seeram V, Cury J, Jones L. Patient-related factors may influence nursing perception of sleep in the Intensive Care Unit. *PLoS One* 2020; **15**: e0226323 [PMID: 31905204 DOI: 10.1371/journal.pone.0226323]

145 **Ritmala-Castren M**, Axelin A, Richards KC, Mitchell ML, Vahlberg T, Leino-Kilpi H. Investigating the construct and concurrent validity of the Richards-Campbell Sleep Questionnaire with intensive care unit patients and home sleepers. *Aust Crit Care* 2022; **35**: 130-135 [PMID: 34049774 DOI: 10.1016/j.aucc.2021.04.001]

146 **Murata H**, Oono Y, Sanui M, Saito K, Yamaguchi Y, Takinami M, Richards KC, Henker R. The Japanese version of the Richards-Campbell Sleep Questionnaire: Reliability and validity assessment. *Nurs Open* 2019; **6**: 808-814 [PMID: 31367403 DOI: 10.1002/nop2.252]

147 **Snyder-Halpern R**, Verran JA. Instrumentation to describe subjective sleep characteristics in healthy subjects. *Res Nurs Health* 1987; **10**: 155-163 [PMID: 3647537 DOI: 10.1002/nur.4770100307]

148 **Reishtein JL**. Sleep in mechanically ventilated patients. *Crit Care Nurs Clin North Am* 2005; **17**: 251-255 [PMID: 16115533 DOI: 10.1016/j.ccell.2005.04.004]

149 **Richardson S**. Effects of relaxation and imagery on the sleep of critically ill adults. *Dimens Crit Care Nurs* 2003; **22**: 182-190 [PMID: 12893996 DOI: 10.1097/00003465-200307000-00009]

150 **Richardson A**, Crow W, Coghill E, Turnock C. A comparison of sleep assessment tools by nurses and patients in critical care. *J Clin Nurs* 2007; **16**: 1660-1668 [PMID: 17459137 DOI: 10.1111/j.1365-2702.2005.01546.x]

151 **Hsu WC**, Guo SE, Chang CH. Back massage intervention for improving health and sleep quality among intensive care unit patients. *Nurs Crit Care* 2019; **24**: 313-319 [PMID: 30942526 DOI: 10.1111/nicc.12428]

152 **Scotto CJ**, McClusky C, Spillan S, Kimmel J. Earplugs improve patients' subjective experience of sleep in critical care. *Nurs Crit Care* 2009; **14**: 180-184 [PMID: 19531035 DOI: 10.1111/j.1478-5153.2009.00344.x]

153 **Buysse DJ**, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28**: 193-213 [PMID: 2748771 DOI: 10.1016/0165-1781(89)90047-4]

154 **Zitser J**, Allen IE, Falgàs N, Le MM, Neylan TC, Kramer JH, Walsh CM. Pittsburgh Sleep Quality Index (PSQI) responses are modulated by total sleep time and wake after sleep onset in healthy older adults. *PLoS One* 2022; **17**: e0270095 [PMID: 35749529 DOI: 10.1371/journal.pone.0270095]

155 **Rood P**, Frenzel T, Verhage R, Bonn M, van der Hoeven H, Pickkers P, van den Boogaard M. Development and daily use of a numeric rating score to assess sleep quality in ICU patients. *J Crit Care* 2019; **52**: 68-74 [PMID: 30981928 DOI: 10.1016/j.jcrc.2019.04.009]

156 **Dennis CM**, Lee R, Woodard EK, Szalaj JJ, Walker CA. Benefits of quiet time for neuro-intensive care patients. *J Neurosci Nurs* 2010; **42**: 217-224 [PMID: 20804117 DOI: 10.1097/jnn.0b013e3181e26c20]

157 **Olson DM**, Borel CO, Laskowitz DT, Moore DT, McConnell ES. Quiet time: a nursing intervention to promote sleep in neurocritical care units. *Am J Crit Care* 2001; **10**: 74-78 [PMID: 11244674]

158 **Ibrahim MG**, Bellomo R, Hart GK, Norman TR, Goldsmith D, Bates S, Egi M. A double-blind placebo-controlled randomised pilot study of nocturnal melatonin in tracheostomised patients. *Crit Care Resusc* 2006; **8**: 187-191 [PMID: 16930101]

159 **Aitken LM**, Elliott R, Mitchell M, Davis C, Macfarlane B, Ullman A, Wetzig K, Datt A, McKinley S. Sleep assessment by patients and nurses in the intensive care: An exploratory descriptive study. *Aust Crit Care* 2017; **30**: 59-66 [PMID: 27094380 DOI: 10.1016/j.aucc.2016.04.001]

160 **Figueroa-Ramos MI**, Arroyo-Novoa CM, Lee KA, Padilla G, Puntillo KA. Sleep and delirium in ICU patients: a review of mechanisms and manifestations. *Intensive Care Med* 2009; **35**: 781-795 [PMID: 19165463 DOI: 10.1007/s00134-009-1397-4]

161 **Kamdar BB**, Needham DM, Collop NA. Sleep deprivation in critical illness: its role in physical and psychological recovery. *J Intensive Care Med* 2012; **27**: 97-111 [PMID: 21220271 DOI: 10.1177/0885066610394322]

162 **Patel J**, Baldwin J, Bunting P, Laha S. The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. *Anaesthesia* 2014; **69**: 540-549 [PMID: 24813132 DOI: 10.1111/anae.12638]

163 **Dell KL**, Payne DE, Kremen V, Maturana MI, Gerla V, Nejedly P, Worrell GA, Lenka L, Mivalt F, Boston RC, Brinkmann BH, D'Souza W, Burkitt AN, Grayden DB, Kuhlmann L, Freestone DR, Cook MJ. Seizure likelihood varies with day-to-day variations in sleep duration in patients with refractory focal epilepsy: A longitudinal electroencephalography investigation. *EClinicalMedicine* 2021; **37**: 100934 [PMID: 34386736 DOI: 10.1016/j.eclinm.2021.100934]

164 **Razavi B**, Fisher RS. Chapter 7 - Sleep and Epilepsy. In: Miglis MG, editor. Sleep and Neurologic Disease. San Diego: Academic Press; 2017; 129-140 [DOI: 10.1016/B978-0-12-804074-4.00007-8]

165 **Kumar P**, Raju TR. Seizure susceptibility decreases with enhancement of rapid eye movement sleep. *Brain Res* 2001; **922**: 299-304 [PMID: 11743963 DOI: 10.1016/s0006-8993(01)03174-2]

166 **Pilcher JJ**, Huffcutt AI. Effects of sleep deprivation on performance: a meta-analysis. *Sleep* 1996; **19**: 318-326 [PMID: 8776790 DOI: 10.1093/sleep/19.4.318]

167 **Wilcox ME**, Brummel NE, Archer K, Ely EW, Jackson JC, Hopkins RO. Cognitive dysfunction in ICU patients: risk factors, predictors, and rehabilitation interventions. *Crit Care Med* 2013; **41**: S81-S98 [PMID: 23989098 DOI: 10.1097/CCM.0b013e3182a16946]

168 **Wilcox ME**, McAndrews MP, Van J, Jackson JC, Pinto R, Black SE, Lim AS, Friedrich JO, Rubenfeld GD. Sleep Fragmentation and Cognitive Trajectories After Critical Illness. *Chest* 2021; **159**: 366-381 [PMID: 32717265 DOI: 10.1016/j.chest.2020.07.036]

169 **Elías MN**, Munro CL, Liang Z, Calero K, Ji M. Sleep and Intensive Care Unit-Acquired Weakness in Critically Ill Older Adults. *Dimens Crit Care Nurs* 2019; **38**: 20-28 [PMID: 30499789 DOI: 10.1097/DCC.0000000000000335]

170 **Vanhorebeek I**, Latronico N, Van den Berghe G. ICU-acquired weakness. *Intensive Care Med* 2020; **46**: 637-653 [PMID: 32076765 DOI: 10.1007/s00134-020-05944-4]

171 **Aldabal L**, Bahammam AS. Metabolic, endocrine, and immune consequences of sleep deprivation. *Open Respir Med J* 2011; **5**: 31-43 [PMID: 21754974 DOI: 10.2174/1874306401105010031]

172 **Donga E**, van Dijk M, van Dijk JG, Biermasz NR, Lammers GJ, van Kralingen KW, Corssmit EP, Romijn JA. A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. *J Clin Endocrinol Metab* 2010; **95**: 2963-2968 [PMID: 20371664 DOI: 10.1210/jc.2009-2430]

173 **Deane AM**, Horowitz M. Dysglycaemia in the critically ill - significance and management. *Diabetes Obes Metab* 2013; **15**: 792-801 [PMID: 23368662 DOI: 10.1111/dom.12078]

174 **Tordjman S**, Chokron S, Delorme R, Charrier A, Bellissant E, Jaafari N, Fougerou C. Melatonin: Pharmacology, Functions and Therapeutic Benefits. *Curr Neuropharmacol* 2017; **15**: 434-443 [PMID: 28503116 DOI: 10.2174/1570159X14666161228122115]

175 **Shilo L**, Dagan Y, Smorjik Y, Weinberg U, Dolev S, Komptel B, Balaum H, Shenkman L. Patients in the intensive care unit suffer from severe lack of sleep associated with loss of normal melatonin secretion pattern. *Am J Med Sci* 1999; **317**: 278-281 [PMID: 10334113 DOI: 10.1097/00000441-199905000-00002]

176 **Perras B**, Meier M, Dodt C. Light and darkness fail to regulate melatonin release in critically ill humans. *Intensive Care Med* 2007; **33**: 1954-1958 [PMID: 17609927 DOI: 10.1007/s00134-007-0769-x]

177 **Olofsson K**, Alling C, Lundberg D, Malmros C. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. *Acta Anaesthesiol Scand* 2004; **48**: 679-684 [PMID: 15196098 DOI: 10.1111/j.0001-5172.2004.00401.x]

178 **Reynolds FD**, Dauchy R, Blask D, Dietz PA, Lynch D, Zuckerman R. The pineal gland hormone melatonin improves survival in a rat model of sepsis/shock induced by zymosan A. *Surgery* 2003; **134**: 474-479 [PMID: 14555936 DOI: 10.1067/s0039-6060(03)00253-8]

179 **Besedovsky L**, Lange T, Born J. Sleep and immune function. *Pflugers Arch* 2012; **463**: 121-137 [PMID: 22071480 DOI: 10.1007/s00424-011-1044-0]

180 **Lasselin J**, Rehman JU, Åkerstedt T, Lekander M, Axelsson J. Effect of long-term sleep restriction and subsequent recovery sleep on the diurnal rhythms of white blood cell subpopulations. *Brain Behav Immun* 2015; **47**: 93-99 [PMID: 25451611 DOI: 10.1016/j.bbi.2014.10.004]

181 **Boudjeltia KZ**, Faraut B, Stenuit P, Esposito MJ, Dyzma M, Brohée D, Ducobu J, Vanhaeverbeek M, Kerkhofs M. Sleep restriction increases white blood cells, mainly neutrophil count, in young healthy men: a pilot study. *Vasc Health Risk Manag* 2008; **4**: 1467-1470 [PMID: 19337560 DOI: 10.2147/vhrm.s3934]

182 **Spiegel K**, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; **354**: 1435-1439 [PMID: 10543671 DOI: 10.1016/s0140-6736(99)01376-8]

183 **Lange T**, Perras B, Fehm HL, Born J. Sleep enhances the human antibody response to hepatitis A vaccination. *Psychosom Med* 2003; **65**: 831-835 [PMID: 14508028 DOI: 10.1097/01.psy.0000091382.61178.f1]

184 **Zhang J**, Xu D, Xie B, Zhang Y, Huang H, Liu H, Chen H, Sun Y, Shang Y, Hashimoto K, Yuan S. Poor-sleep is associated with slow recovery from lymphopenia and an increased need for ICU care in hospitalized patients with COVID-19: A retrospective cohort study. *Brain Behav Immun* 2020; **88**: 50-58 [PMID: 32512133 DOI: 10.1016/j.bbi.2020.05.075]

185 **Chen HI**, Tang YR. Sleep loss impairs inspiratory muscle endurance. *Am Rev Respir Dis* 1989; **140**: 907-909 [PMID: 2802378 DOI: 10.1164/ajrccm/140.4.907]

186 **Sériès F**, Roy N, Marc I. Effects of sleep deprivation and sleep fragmentation on upper airway collapsibility in normal subjects. *Am J Respir Crit Care Med* 1994; **150**: 481-485 [PMID: 8049833 DOI: 10.1164/ajrccm.150.2.8049833]

187 **Thille AW**, Reynaud F, Marie D, Barrau S, Rousseau L, Rault C, Diaz V, Meurice JC, Coudroy R, Frat JP, Robert R, Drouot X. Impact of sleep alterations on weaning duration in mechanically ventilated patients: a prospective study. *Eur Respir J* 2018; **51** [PMID: 29519925 DOI: 10.1183/13993003.02465-2017]

188 **Krystal AD**. Psychiatric disorders and sleep. *Neurol Clin* 2012; **30**: 1389-1413 [PMID: 23099143 DOI: 10.1016/j.ncl.2012.08.018]

189 **Grèzes J**, Erblang M, Vilarem E, Quiquempoix M, Van Beers P, Guillard M, Sauvet F, Mennella R, Rabat A. Impact of total sleep deprivation and related mood changes on approach-avoidance decisions to threat-related facial displays. *Sleep* 2021; **44** [PMID: 34313789 DOI: 10.1093/sleep/zsab186]

190 **Giedke H**, Schwärzler F. Therapeutic use of sleep deprivation in depression. *Sleep Med Rev* 2002; **6**: 361-377 [PMID: 12531127]

191 **Davydow DS**, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. *Psychosom Med* 2008; **70**: 512-519 [PMID: 18434495 DOI: 10.1097/PSY.0b013e31816aa0dd]

192 **Devlin JW**, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochwerg B, Balas MC, van den Boogaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak

CJ, Flood PD, Kiedrowski K, Alhazzani W. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018; **46**: e825-e873 [PMID: 30113379 DOI: 10.1097/CCM.0000000000003299]

193 **Beck Edvardsen J**, Hetmann F. Promoting Sleep in the Intensive Care Unit. *SAGE Open Nurs* 2020; **6**: 2377960820930209 [PMID: 33415285 DOI: 10.1177/2377960820930209]

194 **Andrews JL**, Louzon PR, Torres X, Pyles E, Ali MH, Du Y, Devlin JW. Impact of a Pharmacist-Led Intensive Care Unit Sleep Improvement Protocol on Sleep Duration and Quality. *Ann Pharmacother* 2021; **55**: 863-869 [PMID: 33166192 DOI: 10.1177/1060028020973198]

195 **Kamdar BB**, King LM, Collop NA, Sakamuri S, Colantuoni E, Neufeld KJ, Bienvenu OJ, Rowden AM, Touradji P, Brower RG, Needham DM. The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. *Crit Care Med* 2013; **41**: 800-809 [PMID: 23314584 DOI: 10.1097/CCM.0b013e3182746442]

196 **Faraklas I**, Holt B, Tran S, Lin H, Saffle J, Cochran A. Impact of a nursing-driven sleep hygiene protocol on sleep quality. *J Burn Care Res* 2013; **34**: 249-254 [PMID: 23412331 DOI: 10.1097/BCR.0b013e318283d175]

197 **Lavallée JF**, Gray TA, Dumville J, Russell W, Cullum N. The effects of care bundles on patient outcomes: a systematic review and meta-analysis. *Implement Sci* 2017; **12**: 142 [PMID: 29187217 DOI: 10.1186/s13012-017-0670-0]

198 **Walder B**, Francioli D, Meyer JJ, Lançon M, Romand JA. Effects of guidelines implementation in a surgical intensive care unit to control nighttime light and noise levels. *Crit Care Med* 2000; **28**: 2242-2247 [PMID: 10921547 DOI: 10.1097/00003246-200007000-00010]

199 **Monsén MG**, Edéll-Gustafsson UM. Noise and sleep disturbance factors before and after implementation of a behavioural modification programme. *Intensive Crit Care Nurs* 2005; **21**: 208-219 [PMID: 16039958 DOI: 10.1016/j.iccn.2004.12.002]

200 **McAndrew NS**, Leske J, Guttormson J, Kelber ST, Moore K, Dabrowski S. Quiet time for mechanically ventilated patients in the medical intensive care unit. *Intensive Crit Care Nurs* 2016; **35**: 22-27 [PMID: 26916664 DOI: 10.1016/j.iccn.2016.01.003]

201 **Edwards GB**, Schuring LM. Pilot study: validating staff nurses' observations of sleep and wake states among critically ill patients, using polysomnography. *Am J Crit Care* 1993; **2**: 125-131 [PMID: 8358460]

202 **Maidl CA**, Leske JS, Garcia AE. The influence of "quiet time" for patients in critical care. *Clin Nurs Res* 2014; **23**: 544-559 [PMID: 23847172 DOI: 10.1177/1054773813493000]

203 **Litton E**, Elliott R, Ferrier J, Webb SAR. Quality sleep using earplugs in the intensive care unit: the QUIET pilot randomised controlled trial. *Crit Care Resusc* 2017; **19**: 128-133 [PMID: 28651508]

204 **Van Rompaey B**, Elseviers MM, Van Drom W, Fromont V, Jorens PG. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. *Crit Care* 2012; **16**: R73 [PMID: 22559080 DOI: 10.1186/cc11330]

205 **Yazdannik AR**, Zareie A, Hasanpour M, Kashefi P. The effect of earplugs and eye mask on patients' perceived sleep quality in intensive care unit. *Iran J Nurs Midwifery Res* 2014; **19**: 673-678 [PMID: 25558268]

206 **Dave K**, Qureshi A, Gopichandran L. Effects of Earplugs and Eye Masks on Perceived Quality of Sleep during Night among Patients in Intensive Care Units. *AJNER* 2015; **5**: 319-322 [DOI: 10.5958/2349-2996.2015.00065.8]

207 **Bajwa N Saini P**, Kaur H, Kalra S, Kaur J. Effect of ear plugs and eye mask on sleep among ICU patients: a randomized control trial. *Int J Curr Res* 2015; **7**: 23741-23745

208 **Akpinar RB**, Aksoy M, Kant E. Effect of earplug/eye mask on sleep and delirium in intensive care patients. *Nurs Crit Care* 2022; **27**: 537-545 [PMID: 35021263 DOI: 10.1111/nicc.12741]

209 **Obanor OO**, McBroom MM, Elia JM, Ahmed F, Sasaki JD, Murphy KM, Chalk S, Menard GA, Pratt NV, Venkatachalam AM, Romito BT. The Impact of Earplugs and Eye Masks on Sleep Quality in Surgical ICU Patients at Risk for Frequent Awakenings. *Crit Care Med* 2021; **49**: e822-e832 [PMID: 33870919 DOI: 10.1097/CCM.0000000000005031]

210 **Demoule A**, Carreira S, Lavault S, Pallanca O, Morawiec E, Mayaux J, Arnulf I, Similowski T. Impact of earplugs and eye mask on sleep in critically ill patients: a prospective randomized study. *Crit Care* 2017; **21**: 284 [PMID: 29157258 DOI: 10.1186/s13054-017-1865-0]

211 **Richardson A**, Allsop M, Coghill E, Turnock C. Earplugs and eye masks: do they improve critical care patients' sleep? *Nurs Crit Care* 2007; **12**: 278-286 [PMID: 17983362 DOI: 10.1111/j.1478-5153.2007.00243.x]

212 **Jones C**, Dawson D. Eye masks and earplugs improve patient's perception of sleep. *Nurs Crit Care* 2012; **17**: 247-254 [PMID: 22897811 DOI: 10.1111/j.1478-5153.2012.00501.x]

213 **Hu RF**, Jiang XY, Hegadoren KM, Zhang YH. Effects of earplugs and eye masks combined with relaxing music on sleep, melatonin and cortisol levels in ICU patients: a randomized controlled trial. *Crit Care* 2015; **19**: 115 [PMID: 25881268 DOI: 10.1186/s13054-015-0855-3]

214 **Arttawejkul P**, Reutrakul S, Muntham D, Chirakalwasan N. Effect of Nighttime Earplugs and Eye Masks on Sleep Quality in Intensive Care Unit Patients. *Indian J Crit Care Med* 2020; **24**: 6-10 [PMID: 32148342 DOI: 10.5005/jp-journals-10071-23321]

215 **Chaudhary A**, Kumari V, Neetu N. Sleep Promotion among Critically Ill Patients: Earplugs/Eye Mask versus Ocean Sound-A Randomized Controlled Trial Study. *Crit Care Res Pract* 2020; **2020**: 8898172 [PMID: 33425385 DOI: 10.1155/2020/8898172]

216 **Zimmerman L**, Nieveen J, Barnason S, Schmaderer M. The effects of music interventions on postoperative pain and sleep in coronary artery bypass graft (CABG) patients. *Sch Inq Nurs Pract* 1996; **10**: 153-170; discussion 171 [PMID: 8826769]

217 **Jaber S**, Bahloul H, Guétin S, Chanques G, Sebbane M, Eledjam JJ. [Effects of music therapy in intensive care unit without sedation in weaning patients versus non-ventilated patients]. *Ann Fr Anesth Reanim* 2007; **26**: 30-38 [PMID: 17085009 DOI: 10.1016/j.annfar.2006.09.002]

218 **Cox C**, Hayes J. Physiologic and psychodynamic responses to the administration of therapeutic touch in critical care. *Complement Ther Nurs Midwifery* 1999; **5**: 87-92 [PMID: 10754826 DOI: 10.1016/s1353-6117(99)80026-2]

219 **Wong C**, Ho J, Ankravs MJ, Sharrock L, Kee K, Goldin J, MacIsaac C, Presneill JJ, Ali Abdelhamid Y, Deane AM.

Administration of pharmacological sleep aids prior to, during and following critical illness. *Intern Med J* 2022; **52**: 1962-1970 [PMID: 34392601 DOI: 10.1111/imj.15492]

220 **Hamidi A**, Roberts RJ, Weinhouse GL, Szumita PM, Degrado JR, Dube KM, Kovacevic MP, Choi M, Sevinsky R, Duprey MS, Devlin JW. Characterization of Nocturnal Neuroactive Medication Use and Related Sleep Documentation in Critically Ill Adults. *Crit Care Explor* 2021; **3**: e0367 [PMID: 33786443 DOI: 10.1097/CCE.0000000000000367]

221 **Mistraletti G**, Umbrello M, Sabbatini G, Miori S, Taverna M, Cerri B, Mantovani ES, Formenti P, Spanu P, D'Agostino A, Salini S, Morabito A, Fraschini F, Reiter RJ, Iapichino G. Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial. *Minerva Anestesiol* 2015; **81**: 1298-1310 [PMID: 25969139]

222 **Foreman B**, Westwood AJ, Claassen J, Bazil CW. Sleep in the neurological intensive care unit: feasibility of quantifying sleep after melatonin supplementation with environmental light and noise reduction. *J Clin Neurophysiol* 2015; **32**: 66-74 [PMID: 25647773 DOI: 10.1097/WNP.0000000000000110]

223 **Lewis SR**, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF. Melatonin for the promotion of sleep in adults in the intensive care unit. *Cochrane Database Syst Rev* 2018; **5**: CD012455 [PMID: 29746721 DOI: 10.1002/14651858.CD012455.pub2]

224 **Gandolfi JV**, Di Bernardo APA, Chanes DAV, Martin DF, Joles VB, Amendola CP, Sanches LC, Ciorlia GL, Lobo SM. The Effects of Melatonin Supplementation on Sleep Quality and Assessment of the Serum Melatonin in ICU Patients: A Randomized Controlled Trial. *Crit Care Med* 2020; **48**: e1286-e1293 [PMID: 33048904 DOI: 10.1097/CCM.0000000000004690]

225 **Wibrow B**, Martinez FE, Myers E, Chapman A, Litton E, Ho KM, Regli A, Hawkins D, Ford A, van Haren FMP, Wyer S, McCaffrey J, Rashid A, Kelty E, Murray K, Anstey M. Prophylactic melatonin for delirium in intensive care (Pro-MEDIC): a randomized controlled trial. *Intensive Care Med* 2022; **48**: 414-425 [PMID: 35220473 DOI: 10.1007/s00134-022-06638-9]

226 **Nishikimi M**, Numaguchi A, Takahashi K, Miyagawa Y, Matsui K, Higashi M, Makishi G, Matsui S, Matsuda N. Effect of Administration of Ramelteon, a Melatonin Receptor Agonist, on the Duration of Stay in the ICU: A Single-Center Randomized Placebo-Controlled Trial. *Crit Care Med* 2018; **46**: 1099-1105 [PMID: 29595562 DOI: 10.1097/CCM.0000000000003132]

227 **Williams DB**, Akabas MH. Structural evidence that propofol stabilizes different GABA(A) receptor states at potentiating and activating concentrations. *J Neurosci* 2002; **22**: 7417-7424 [PMID: 12196563 DOI: 10.1523/jneurosci.22-17-07417.2002]

228 **Engelmann C**, Wallenborn J, Olthoff D, Kaisers UX, Rüffert H. Propofol versus flunitrazepam for inducing and maintaining sleep in postoperative ICU patients. *Indian J Crit Care Med* 2014; **18**: 212-219 [PMID: 24872650 DOI: 10.4103/0972-5229.130572]

229 **McLeod G**, Wallis C, Dick J, Cox C, Patterson A, Colvin J. Use of 2% propofol to produce diurnal sedation in critically ill patients. *Intensive Care Med* 1997; **23**: 428-434 [PMID: 9142583 DOI: 10.1007/s001340050352]

230 **Treggiari-Venzi M**, Borgeat A, Fuchs-Buder T, Gachoud JP, Suter PM. Overnight sedation with midazolam or propofol in the ICU: effects on sleep quality, anxiety and depression. *Intensive Care Med* 1996; **22**: 1186-1190 [PMID: 9120111 DOI: 10.1007/bf01709334]

231 **Oto J**, Yamamoto K, Koike S, Onodera M, Imanaka H, Nishimura M. Sleep quality of mechanically ventilated patients sedated with dexmedetomidine. *Intensive Care Med* 2012; **38**: 1982-1989 [PMID: 22961436 DOI: 10.1007/s00134-012-2685-y]

232 **Wu XH**, Cui F, Zhang C, Meng ZT, Wang DX, Ma J, Wang GF, Zhu SN, Ma D. Low-dose Dexmedetomidine Improves Sleep Quality Pattern in Elderly Patients after Noncardiac Surgery in the Intensive Care Unit: A Pilot Randomized Controlled Trial. *Anesthesiology* 2016; **125**: 979-991 [PMID: 27571256 DOI: 10.1097/aln.0000000000001325]

233 **Skrobik Y**, Duprey MS, Hill NS, Devlin JW. Low-Dose Nocturnal Dexmedetomidine Prevents ICU Delirium. A Randomized, Placebo-controlled Trial. *Am J Respir Crit Care Med* 2018; **197**: 1147-1156 [PMID: 29498534 DOI: 10.1164/rccm.201710-1995OC]

234 **Rhyne DN**, Anderson SL. Suvorexant in insomnia: efficacy, safety and place in therapy. *Ther Adv Drug Saf* 2015; **6**: 189-195 [PMID: 26478806 DOI: 10.1177/2042098615595359]

235 **Hatta K**, Kishi Y, Wada K, Takeuchi T, Ito S, Kurata A, Murakami K, Sugita M, Usui C, Nakamura H; DELIRIA-J Group. Preventive Effects of Suvorexant on Delirium: A Randomized Placebo-Controlled Trial. *J Clin Psychiatry* 2017; **78**: e970-e979 [PMID: 28767209 DOI: 10.4088/JCP.16m11194]

236 **Delisle S**, Ouellet P, Bellemare P, Tétrault JP, Arsenault P. Sleep quality in mechanically ventilated patients: comparison between NAVA and PSV modes. *Ann Intensive Care* 2011; **1**: 42 [PMID: 21955588 DOI: 10.1186/2110-5820-1-42]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 June 9; 12(3): 116-129

DOI: 10.5492/wjccm.v12.i3.116

ISSN 2220-3141 (online)

MINIREVIEWS

Approaches to neuroprotection in pediatric neurocritical care

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Aydin S, Turkey; Govindarajan KK, India

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: March 1, 2023
Revised: March 30, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: June 9, 2023

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Abstract

Acute neurologic injuries represent a common cause of morbidity and mortality in children presenting to the pediatric intensive care unit. After primary neurologic insults, there may be cerebral brain tissue that remains at risk of secondary insults, which can lead to worsening neurologic injury and unfavorable outcomes. A fundamental goal of pediatric neurocritical care is to mitigate the impact of secondary neurologic injury and improve neurologic outcomes for critically ill children. This review describes the physiologic framework by which strategies in pediatric neurocritical care are designed to reduce the impact of secondary brain injury and improve functional outcomes. Here, we present current and emerging strategies for optimizing neuroprotective strategies in critically ill children.

Key Words: Neuroprotection; Pediatric neurocritical care; Cerebral perfusion; Cerebrovascular pressure reactivity

Core Tip: Acute neurologic injuries are a common cause of morbidity and mortality in critically ill children. A fundamental goal of pediatric neurocritical care is to mitigate the impact of secondary neurologic injury in critically ill children. Here, we discuss strategies for optimizing neuroprotective strategies in critically ill children.

Citation: Kochar A, Hildebrandt K, Silverstein R, Appavu B. Approaches to neuroprotection in pediatric neurocritical care. *World J Crit Care Med* 2023; 12(3): 116-129
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/116.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.116

INTRODUCTION

Neurologic injuries represent a substantial component of pediatric intensive care unit (PICU) utilization in the United States. Analyses of admissions to a large tertiary PICU have demonstrated that neurologic diagnoses are present in approximately one quarter of PICU admissions (25.4%)[1] and acute brain injury is the most common proximate cause of death in children admitted to a PICU accounting for up to 65% of PICU mortality[2]. Additionally, children admitted to the PICU are estimated to acquire new long-term functional disability at a rate of 4.8%[3] by hospital discharge with evidence of further decline in functional status after discharge[4]. The significant contribution of neurologic injury to PICU morbidity and mortality has resulted in an increasing emphasis to develop evidence-based practices to prevent acute brain injury in systemically ill patients and to mitigate the impact of such injuries once they occur. Here, we review current approaches to neuroprotective care in commonly seen pediatric critical care conditions as well as ongoing and future research targets that promise individualized, precision-based care.

MECHANISMS OF SECONDARY NEUROLOGIC INJURY

The evolution of neurologic dysfunction after an acute insult is multiphasic. The primary neurologic injury represents an initial inciting event which results in neuronal cell death, for example acute energy failure in the setting of arterial ischemic stroke or direct mechanical shearing of axons in traumatic brain injury (TBI). Some of the damage caused by the primary injury is typically complete at the time of recognition or presentation to care. However, in many situations there remains at-risk brain tissue that can be acutely rescued if brain homeostasis is optimized with appropriate cerebral blood flow (CBF) to meet metabolic demand. A classic example of such an intervention in adult neurocritical care is thrombolytic and other reperfusion therapy that salvages the ischemic penumbra after acute arterial ischemic stroke. Minimizing ongoing or recurrent mismatch between cerebral perfusion and brain metabolic demand during critical care management represents one of the primary goals of neurocritical care.

Following the primary injury, multiple parallel physiologic pathways emerge that result in further cellular injury if not prevented (Figure 1). A fundamental goal in pediatric neurocritical care is to limit secondary brain injury by optimizing cerebral oxygen delivery and its use[5]. Secondary brain injury is the additive cerebral injury which is created by an imbalance of supply and demand in cerebral metabolism.

TARGETS FOR NEUROPROTECTION IN THE PICU

Neuroprotection generally refers to the preservation of cerebral function by mitigating the above sources of secondary injury[6]. In the PICU, this approach can be broken down into a variety of directives including optimization of cerebral perfusion, limitation of cerebral metabolic demand, and mitigation against cerebral edema.

Optimize cerebral perfusion

The process of optimizing cerebral perfusion for a given patient or pathology requires attention to several physiologic and hemodynamic targets for neuroprotection with consideration of both CBF as well as blood content.

CBF is primarily determined by cerebral perfusion pressure (CPP) and cerebral vascular resistance. CPP is calculated as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). Importantly, however, measurements of MAP vary significantly by site and methodology[7]. Additionally, adult data has demonstrated that invasive arterial blood pressure measurements levelled at the heart underestimates the MAP at the level of the circle of Willis by approximately 15% when a patients head of bed is elevated to 30° or 45° suggesting head of bed positioning is an important consideration in critically ill patients[8]. Hypotension in pediatric ICU patients has been associated with increased mortality after cardiac arrest and worse outcomes after stroke and TBI[9-13]. Consensus-based pediatric guidelines have focused on maintaining MAPs above minimum thresholds and CPP thresholds when invasive ICP monitoring is available (Table 1)[14-16]. While specific thresholds have been proposed for both MAPs and ICPs, some evidence suggests optimal values varies by age and are on average higher than current guidelines-based recommendations[17]. Further research is needed to identify appropriate minimum thresholds in pediatric neurocritical care populations.

Cerebral vascular resistance is the other major determinant of CBF. Arterial carbon dioxide tension ($PaCO_2$) is the primary modifiable physiologic parameter that impacts cerebral vascular resistance in patients with intact cerebrovascular reactivity, though significant hypoxemia can also play a role in cerebrovascular vasodilation[18]. Increased $PaCO_2$ results in cerebrovascular vasodilation which is often

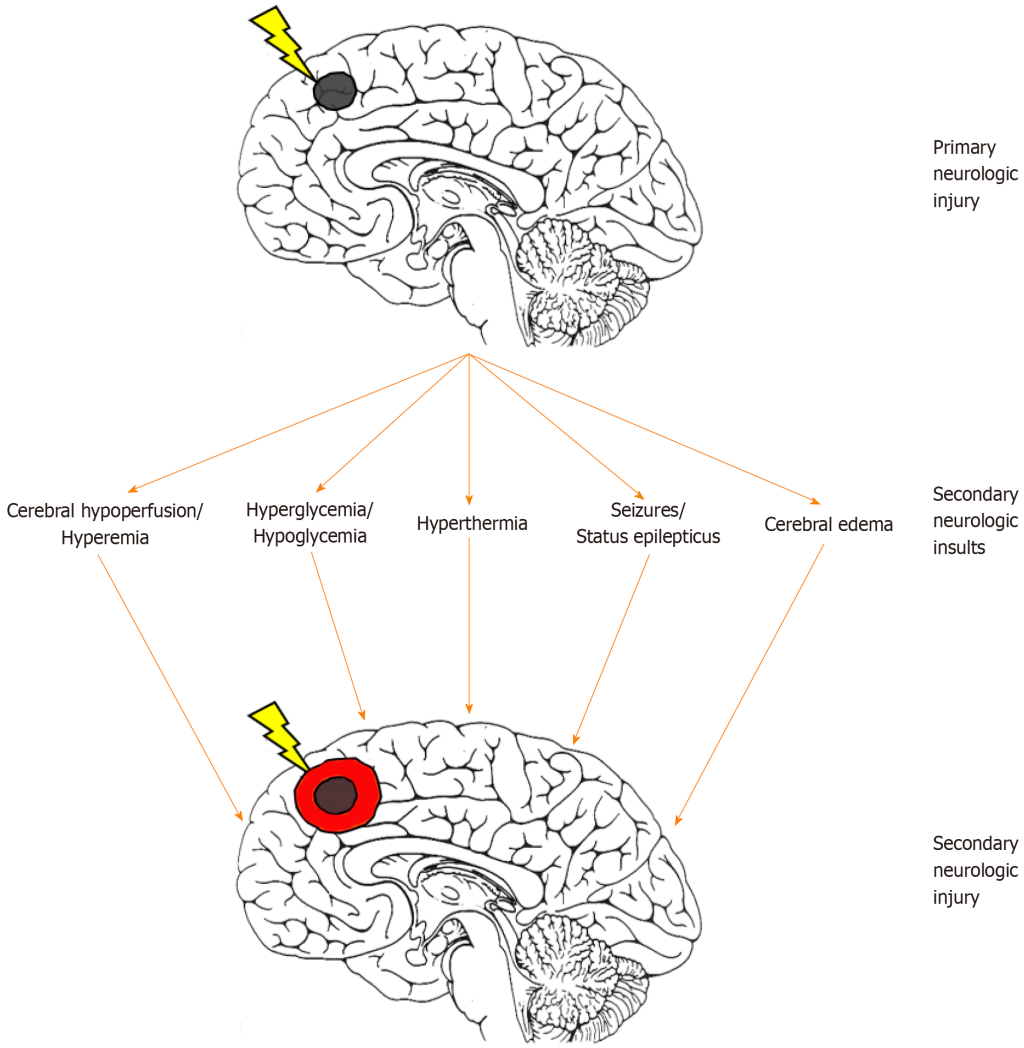
Table 1 Summary of consensus-based guideline recommendations for pediatric neuroprotection

Pathology	Optimize cerebral perfusion	Limit cerebral metabolic demand	Mitigate cerebral edema
Severe traumatic brain injury[15]	Maintain age appropriate CPP (Minimum ≥ 40 mmHg)	Targeted normothermias: 35 °C−38 °C	Maintain sodium: ≥ 140 mEq/L
	If PbtO2 available: ≥ 10 mmHg	Maintain adequate sedation and analgesia	Maintain HOB = 30 °C
	Maintain ICP < 20 mmHg	Benzodiazepine + Opiate as initial therapy	Second tier therapies
	Targeted normoxemia: SpO2 92%−99%	Consider continuous EEG	Surgical intervention
	Maintain PaCo2: 35-40 mmHg	Phenytoin or levetiracetam for seizures	Barbiturate infusion
	Target euglycemia: 100–180 mg/dL		Moderate hypothermia (32 °C−34 °C)
	Target euvolemia: CVP 4−10 mmHg		Hyperventilation (PaCO2 28-34 mmHg)
	Maintain hemoglobin: > 7 g/dL		Increased hyperosmolar therapy
Post-Cardiac arrest[14]	Maintain MAP ≥ 5th percentile for age	Targeted normothermia: 36 °C−37.5 °C	
	Targeted normoxemia: SpO2 94%−99%	Consider 48 h of T 32 °C− 34 °C for OHCA	
	Maintain PaCo2: 35-45 mmHg	Maintain adequate sedation and analgesia	
	Target euglycemia: 80−180 mg/dL	Continuous EEG	
		Treat seizures if identified	
Acute arterial ischemic stroke[80]	Treat hypertension with caution in patients with intracranial vascular stenosis	Maintain temperature < 38 °C	Consider decompressive surgery for malignant edema
	Aggressively treat hypotension		For large volume infarcts (> 1/2 MCA territory)
	Treat hyperglycemia to target 140-180 mg/dL		Consider early decompressive hemicraniectomy (< 24 h)
	Treat hypoglycemia: < 60 mg/dL		Serial imaging and frequent assessments for 72 h

CPP: Cerebral perfusion pressure; PbtO2: Partial pressure of brain tissue oxygenation; ICP: Intracranial Pressure; SpO2: Peripheral oxygen saturation; PaCo2: Arterial carbon dioxide tension; CVP: Central venous pressure; EEG: Electroencephalography; HOB: Head of bed; MAP: Mean arterial pressure; OHCA: Out-of-hospital cardiac arrest; MCA: Middle cerebral artery.

desirable when hypoperfusion is the primary insult as seen with permissive hypercapnia in acute stroke care, though is less desirable in cases where cerebral edema and intracranial hypertension are predominant as it results in a net increase in the intracranial blood volume compartment further contributing to increased ICP. Current pediatric literature supports maintaining normocapnia in most pathologies. Impaired carbon dioxide reactivity to brain tissue oxygenation ($PbtO_2$) can be observed after injuries such as TBI, and recognition of such situations may influence targeting of $PaCO_2$ levels.

Partial pressure of blood oxygenation (PaO_2), glucose and hemoglobin content are also important in ensuring adequate cerebral perfusion after acute brain injury. Both hyperoxia and hypoxia are common in pediatric patients after cardiac arrest and TBI, however the impact of oxygen exposure on outcomes remains unclear[19-21]. Arterial hypoxemia in the injured brain results in reduced cerebral oxygen delivery, potentiating injury in ischemic tissue and further contributing to neuronal excitotoxicity. Conversely, hyperoxia is thought to increase oxidative stress through increased production of free radical species and has been associated with increased mortality after cardiac arrest in adult populations [22]. Available data from pediatric investigations has been equivocal on the effect of arterial hypoxia or hyperoxia on morbidity or mortality after cardiac arrest or TBI. One large retrospective review demonstrated increased mortality in pediatric post arrest patients with a $PaO_2 \geq 300$ mmHg or $PaO_2 \leq 60$ mmHg on the first arterial blood gas after PICU admission[23]. Other retrospective cohort studies as well as one prospective multicenter observational study of pediatric post-arrest patients have not redemonstrated this association[19,21,24]. Retrospective analysis of pediatric TBI patients has not demonstrated an association between hypoxia and outcome, though extrapolation of this data is limited as hypoxia is often identified and treated rapidly during resuscitation[20,25,26]. A recently published



DOI: 10.5492/wjccm.v12.i3.116

Figure 1 Development of secondary neurologic injury after pediatric acute brain injury. After primary brain injury (black circle), a host of secondary neurologic insults can contribute to worsening of the initial injury, resulting in secondary neurologic injury (red circle). Neuromonitoring for secondary brain insults and optimization of neuroprotection may help mitigate against secondary neurologic injury in children with acute brain injuries.

systematic review and meta-analysis did demonstrate an association between arterial hyperoxia (as defined by PaO_2 > 250 mmHg) and increased mortality pediatric study populations that included post-cardiac arrest, TBI, extracorporeal membrane oxygenation and general pediatric critical care[27]. Neuroprotective strategies in pediatric critical care generally support maintaining normoxemia while avoiding hyperoxia, though specific thresholds vary. Emerging data in pediatric TBI patients where invasive $PbtO_2$ monitoring is available suggests that episodes of cerebral hypoxia (as measured by $PbtO_2$ < 10 mmHg or 15 mmHg) is associated with unfavorable clinical outcomes as well as reduced performance on neuropsychiatric testing > 1 year post injury[28-30].

Hyperglycemia (serum glucose > 200 mg/dL) on admission after pediatric TBI has been demonstrated to be a predictor of mortality and ICU length of stay suggesting high serum glucose may be a marker of brain injury severity[31-34]. Similarly, persistent hyperglycemia 12-72 h after admission has also been independently associated with mortality and poor clinical outcomes, though prospective data assessing the impact of narrow glycemic control on outcomes is limited[35-37].

Retrospective evaluations of anemia in pediatric TBI patients have not demonstrated a significant association between anemia or need for packed red blood cell transfusion with outcomes to support transfusion thresholds that differ from standard pediatric ICU practices[38,39].

Limit cerebral metabolic demand

Decreasing the mismatch between cerebral perfusion and metabolic demand is a critical component to neuroprotection after acute brain injury by reducing the amount of tissue experiencing relative ischemia. Mechanisms that limit cerebral metabolism may also slow the pathological processes that contribute to secondary injury such as the enzymatic pathways that result in cell death and the neuro-inflammatory cascade that potentiates vasogenic edema. Physiologically, there are three primary targets

for intervention that affect cerebral metabolic activity: Temperature, sedation, and antiseizure medications to combat acute symptomatic seizures.

Optimal temperature management for patients with acute brain injuries has been the subject of extensive research in both adult and pediatric populations. Early animal data demonstrated a linear relationship between temperature and CBF and oxygen consumption suggesting a 6% decrease in cerebral metabolic demand for each decrease of 1 °C compared to normothermia[40]. Conversely, animal studies conducted in the 1980-1990s concluded that mild hypothermia of up 2 °C conferred significant neuroprotective benefits in rat models of focal and global cerebral ischemia[41-43]. Conversely, even brief periods of hyperthermia of 3 h in similar models were associated with increased infarct volume[44-46]. The deleterious effect of fever in neurological injuries has since been redemonstrated in both adult and pediatric populations across multiple neurologic pathologies including stroke, TBI and post cardiac arrest[46-48]. In light of this data, targeted temperature management with the goal of aggressive avoidance of fever has been adopted as standard of care in patients with acute brain injury.

Of greater debate is whether the practice of induced hypothermia (typically within the range of 32-35 °C) improves neurologic outcomes in selected pediatric populations. A recent meta-analysis of eight randomized controlled trials assessing therapeutic hypothermia in pediatric severe TBI found a non-statistically significant trend towards increased mortality in patients who were treated with therapeutic hypothermia compared to normothermic controls[49]. In post-arrest care, two large, multicenter, randomized controlled trials have been conducted to assess the benefit of therapeutic hypothermia after cardiac arrest in children separately evaluating comatose children after in-hospital (THAPCA-IH) and out-of-hospital (THAPCA-OH) arrests. These trials investigated the impact of 48 h of targeted hypothermia (target 33 °C) followed by gradual rewarming and continued targeted temperature management (target 36.8 °C) for a total of 120 h after protocol initiation compared with 120 h of targeted normothermia (target 36.8 °C) on 1-year survival with a good functional outcome (defined as an age corrected standard score of 70 or higher on the Vineland Adaptive Behavior Scales, second edition). The THAPCA-IH trial was terminated during interim analysis for futility as the primary outcome did not differ between groups, though notably the safety analysis did not demonstrate any significant differences in adverse events or 28-d mortality across groups[50]. THAPCA-OH found slightly higher rates of 1-year survival with good functional outcomes in the hypothermia group compared to (20% *vs* 12%) though this difference was not statistically significant. Secondary analysis found significantly increased survival time in the therapeutic hypothermia group when compared to normothermia (149 d *vs* 119 d)[51]. Given these findings, investigation into the potential benefit of therapeutic hypothermia in pediatric out-of-hospital cardiac arrest remains ongoing and there remains provider and center dependent variability in practice. The Pediatric Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients trial (NCT05376267) aims to assess the efficacy of cooling and optimal duration of hypothermia in pediatric survivors of out-of-hospital cardiac arrests and is currently enrolling with estimated completion in 2028.

Effective sedation and analgesia play an important role in limiting cerebral metabolic demand and have also been shown to have independent agent-specific effects on CBF, autoregulation and vasomotor reactivity[52]. As such, the optimal selection of anesthetic agents for pathology dependent neuroprotection is a target for ongoing research. In general, for critically ill children in the ICU the most frequently reported anesthetic agents used are benzodiazepines and opiates with frequently used secondary agents including dexmedetomidine, propofol, barbiturates, ketamine and clonidine[53]. Of these, benzodiazepines, dexmedetomidine, propofol and barbiturates have the effect of decreasing both cerebral oxygen consumption and CBF and are often used in patients where there is concern for increased ICP or significant risk for cerebral edema. Ketamine has historically been avoided in patients with acute brain injury as early data suggested its use resulted in direct cerebrovascular vasodilation leading to increased CBF and potentially increased ICP[54]. A more recent prospective pediatric trial suggested that ketamine administration in ventilated patients with intracranial hypertension refractory to initial therapies may in fact reduce ICP by an average of 30% while increasing CPPs and may therefore be safe and effective in patients with acute brain injury[55]. Neuromuscular blockade has also been shown to decrease global oxygen consumption and energy expenditure in mechanically ventilated children. This is an important consideration in children who are shivering when undergoing targeted temperature management and is used extensively in patients with refractory elevations in ICP[56,57]. The use of barbiturate coma to treat acute, refractory intracranial hypertension for pediatric TBI has been shown to be effective in decreasing ICP and is included as a consideration for second-tier therapies in the most recent consensus-based Brain Trauma Foundation guidelines[15,16,58].

The emergence of continuous electroencephalography (cEEG) has allowed for a greater understanding that seizures and ictal-interictal continuum (IIC) patterns are common after acute brain injury and are associated with physiologic changes that suggest an increase in metabolic demand[59,60]. The IIC represents a pattern on EEG that does not qualify as an electrographic seizure but has a reasonable chance to be contributing toward neuronal injury or pathologic clinical symptoms[61]. Periodic discharges, an IIC pattern, has been observed to be associated with elevated lactate-pyruvate ratios in adult TBI patients undergoing cerebral microdialysis monitoring, indicating metabolic crisis[62]. Higher frequency periodic discharges have been observed to be associated with increases in regional CBF and

CPP, and when reaching frequencies of ≥ 2.0 Hz, are associated with reductions in brain tissue hypoxia [63]. These findings indicate that periodic discharges are associated with increases at metabolic demand which are partially compensated at lower frequencies but are insufficiently compensated at ≥ 2.0 Hz. In a cohort of adult patients with aneurysmal subarachnoid hemorrhage, seizures themselves were associated with tachycardia, tachypnea, hypertension, as well as rise in delayed CBF[64]. Among pediatric TBI patients, specific quantitative electroencephalographic components of seizure activity have been linked to changes in cerebral and systemic physiology, with ictal spectral edge frequency being negatively associated with ICP and peak value frequency being positively associated with heart rate [65]. Seizures and IIC patterns can often be treated effectively with antiseizure medications, indicating that their use may be important as a neuroprotective strategy to mitigate against metabolic crises.

Mitigate against cerebral edema

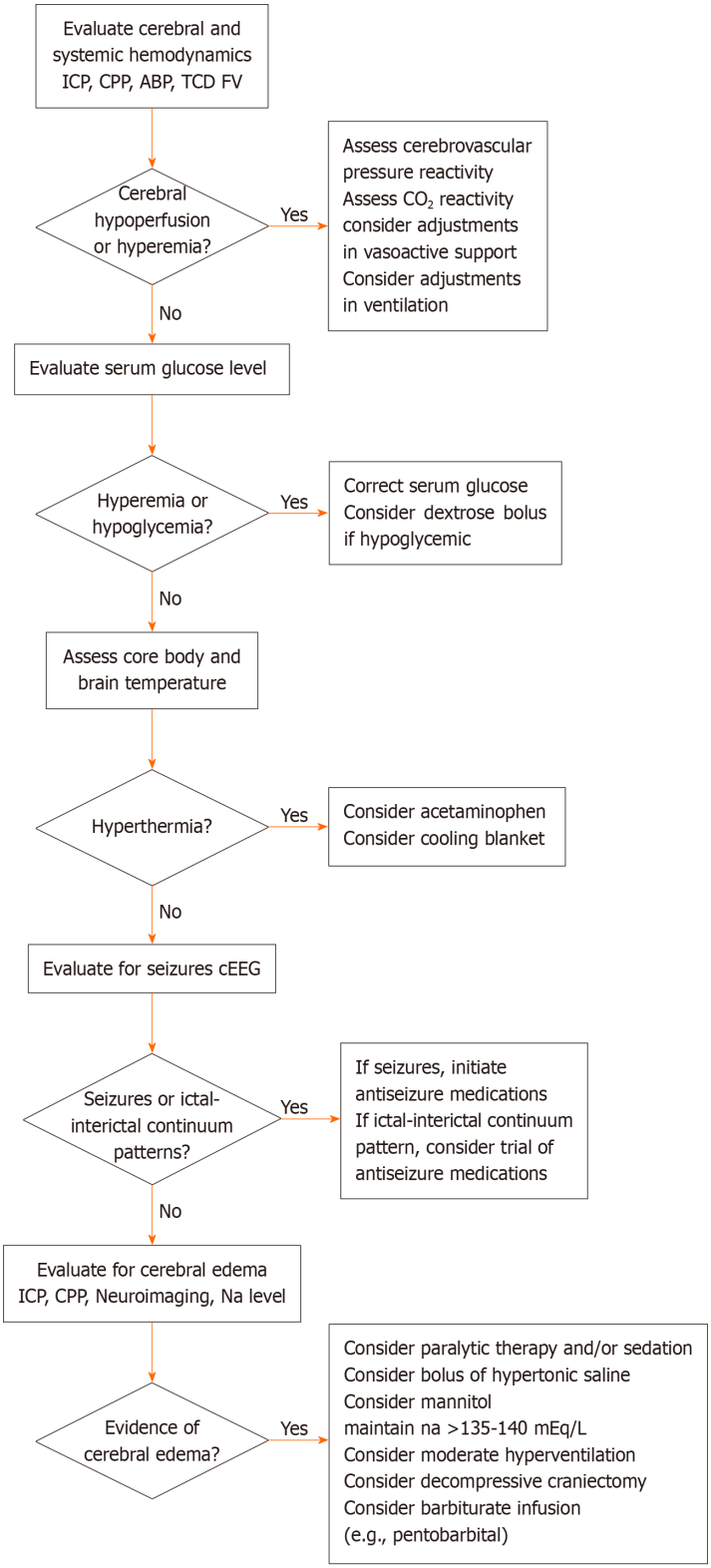
Cerebral edema represents an increase in brain volume that is contained within cerebral interstitial tissue, and can manifest as vasogenic, cytotoxic, hydrostatic, or osmotic edema[66,67]. Vasogenic edema manifests with blood brain barrier breakdown and increased water permeability within brain interstitia. Cytotoxic edema results due to metabolic crisis, cell death, and an influx of water and ions into intracellular space. Hydrostatic edema can occur in the setting of obstructive hydrocephalus and is the result of a net influx of spinal fluid from the ventricular space into brain parenchyma. Osmotic edema is a very particular form of cerebral edema in which there is a specific isolated osmotic gradient between brain parenchyma and the cerebrovascular system. Optimizing temperature management, ventilation, and sedative therapy, as described above, remain important elements in mitigating secondary brain insults arising from cerebral edema. Hyperosmolar therapy exists to aid in mitigation of cerebral edema, with common utilization of hypertonic saline and mannitol. A recent comparative effectiveness study of pediatric TBI patients demonstrated bolus dosing of hypertonic saline to be superior to mannitol in reduction of intracranial hypertension[68]. Some evidence suggests that hyperosmolar therapy is more likely to be effective in reducing intracranial hypertension when there is evidence of efficient cerebrovascular pressure reactivity (CVPR)[69-71]. Emerging research has demonstrated several biomarkers that target the blood-brain barrier or receptors of aquaporin-4 or vasopressin V1a to mitigate cerebral edema, although these are not yet standard treatment targets in clinical care[72]. When medical efforts to mitigate against malignant cerebral edema have failed in the setting of refractory intracranial hypertension, therapeutic decompressive craniectomy can be considered[15].

STANDARDIZED AND INDIVIDUALIZED APPROACHES TO NEUROPROTECTION

The emergence of neurocritical care as a subspecialty has been strengthened by increasing evidence that clinical care implemented with specialized expertise is associated with improved outcomes for critically ill patients with neurologic injuries. A recent large meta-analysis suggested that adult patients who underwent interventions arising from neurocritical care units, neurointensivists or neurocritical care consulting services had improved survival and functional outcomes as compared to adults with similar conditions who experienced general care in intensive care units[73]. A cohort study of pediatric TBI patients demonstrated that implementation of a pediatric neurocritical care program with a standardized evidence-based approach to neurologic monitoring and clinical care was associated with improved outcomes[74]. Such findings have helped the maturation of several specialized pediatric neurocritical care services across the United States and North America, with an array of diverse models including multidisciplinary consultation services as well as dedicated pediatric neurocritical care units that include involvement from neurologists, pediatric intensivists and neurosurgeons[75-79]. These services work toward providing institutional standardized care pathways for common neurocritical care conditions founded upon the latest evidence-based guidelines, often providing standardized or age-based thresholds for intervention (Figure 2).

Whereas the implementation of standardized institutional pathways for neurocritical care carries an association with improved outcomes at an epidemiological level, there is a severe lack of high-level evidence to demonstrate that specific clinical interventions improve outcomes for commonly seen conditions such as TBI, cardiac arrest, and arterial ischemic and hemorrhagic stroke[14-16,80]. Given the lack of high-level evidence, clinical decisions are often made in context of moderate or low-level evidence alongside fundamental and conceptual knowledge regarding pathophysiological mechanisms of critical care diseases. To this end, there are opportunities to evaluate, at the patient-level, whether individualized targeting of care may aid in optimizing neuroprotection.

Critically ill patients in the ICU often have an abundance of continuous physiologic data collected *via* various monitoring techniques including heart rate, invasive arterial blood pressure, end-tidal CO2 and respiratory rate or ventilator settings. Patients with acute brain injuries typically warrant additional neurophysiologic monitoring. This includes ICP monitoring using an external ventricular drain or intraparenchymal monitor, intraparenchymal brain tissue oxygenation, regional oxygen saturation *via* near infrared spectroscopy, cEEG, pupillometry, or information on CBF provided by various imaging techniques including transcranial doppler and thermal diffusion flowmetry[81,82]. Until recently, this



DOI: 10.5492/wjccm.v12.i3.116

Figure 2 Stepwise algorithm for neuroprotection in pediatric neurocritical care. ICP: Intracranial pressure; CPP: Cerebral perfusion pressure; ABP: Arterial blood pressure; TCD: Transcranial Doppler ultrasound; FV: Flow velocities; CO_2: Carbon reactivity; cEEG: Continuous electroencephalography; NA: Sodium; mEq/L: Milliequivalents per liter.

information was typically evaluated in isolation or in small subsets. Recent advances in technology have facilitated the development of integrated platforms that aggregate and time-synchronize this information, allowing for easier visualization by the clinician. This approach, known as multimodality neurologic monitoring, has also allowed for investigation of how changes in one physiologic parameter potentially affect others. This allows for a greater understanding of real-time, patient-specific physiology to inform clinical decision making[83].

The utilization of neurologic monitoring is aimed towards recognition of biosignatures of secondary brain injury and initiation of treatment based upon such features. The most common and non-invasive form of this is the recognition and treatment of seizures and IIC patterns based on cEEG. Invasive methods allow for detection of intracranial hypertension and brain tissue hypoxia, with a variety of neuroprotective strategies available to use depending on the underlying source of such insults. A recent survey of pediatric neurocritical care centers in 2020 demonstrated that 20 hospitals use transcranial Doppler ultrasound as part of clinical care for management of pediatric intracranial hemorrhage, arterial ischemic stroke, or TBI, with utilization aimed toward determining when to obtain neuroimaging, how to manipulate CPP, and whether to perform surgical interventions[84]. A single-center cohort of TBI patients undergoing standardized multimodality neurologic monitoring reporting demonstrated that such reporting influenced timing of neuroimaging, ICP monitoring discontinuation, use of paralytic, hyperosmolar and pentobarbital therapies, neurosurgical interventions, use of provocative cerebral autoregulation testing, ventilator and CPP adjustments and neurologic prognostication discussions[85]. Future multicenter work describing use of integrated multimodality neurologic monitoring as a means for detecting biosignatures of secondary brain injury may aid in better understanding benign and malignant neurophysiologic patterns, methods of determining therapeutic efficacy of specific interventions, and comparative effectiveness strategies to determine whether such interventions may improve functional outcomes.

The integration of multiple streams of time-synchronized physiologic data has allowed for the development of real-time biomarkers of key neurophysiologic processes. CVPR can be assessed when integrating arterial blood pressure with neuromonitoring features that may act as surrogates of CBF [83]. Using transcranial Doppler ultrasound, the mean velocity index or systolic velocity index describes CVPR utilizing transcranial doppler ultrasound flow velocity characteristics with arterial blood pressure [86,87]. With patients undergoing continuous ICP monitoring, the pressure reactivity index (PRx) and other similar indices can be utilized with an assumption that slow wave fluctuations in ICP are directly related to changes in cerebral arterial blood volume[83]. The PRx, as an example, represents a moving Pearson correlation coefficient relating slow wave fluctuations in arterial blood pressure with ICP. Elevated PRx values (approaching +1) are postulated to represent inefficient CVPR, whereas lower values (approaching -1) are postulated to represent efficient CVPR[88].

When PRx is plotted with error bars across a range of CPP, parabolic curves can often be extrapolated, with the lowest PRx value, or nadir of the parabolic curve, representing the 'optimal CPP' at which CVPR is most efficient. From this, theoretical lower and upper limits of CVPR can be estimated based upon specific thresholds of elevated PRx values[89] (Figure 3). Multiple pediatric TBI studies have linked higher PRx values to worsened outcomes, and there is also evidence that increased time below the lower limit of CVPR is associated with unfavorable outcomes[90-93]. A recent feasibility randomized control trial of adult TBI patients evaluated patients who were treated with CPP targets based upon existing Brain Trauma Foundation guidelines and compared them to patients who were individualized to optimal CPP targets based upon PRx. This trial of 60 patients demonstrated that there were no significant differences in safety endpoints between the two groups, supporting the notion that prospective trials powered for clinical outcomes may be safe and feasible[94]. Other model-based indices of CVPR exist using brain tissue oxygenation, cerebral regional oximetry or other neuromonitoring techniques, with evidence from cardiac arrest, extracorporeal membrane oxygenation and other conditions that suggest that inefficient CVPR or deviations from optimal values of CVPR may be associated with unfavorable outcomes[95-98]. Future prospective work with such techniques may help in determining the efficacy for which they can be used to optimize neuroprotection across a wide range of critical care conditions.

EXISTING KNOWLEDGE GAPS AND FUTURE DIRECTIONS

While emerging evidence demonstrates that specific physiologic biomarkers are linked to functional outcomes after pediatric acute brain injuries, there is a severe lack of evidence toward specific neurotherapeutic strategies that improve functional outcomes. Knowledge gaps remain regarding whether biomarkers can be used to better understand whether specific neuroprotective treatments confer potential to benefit for patients stratified toward specific underlying physiologic profiles. Neuroprotective measures optimal toward care in TBI using invasive neuromonitoring may not necessarily translate to other non-traumatic conditions in which invasive monitoring may not be used. It also remains unclear whether implementation of specific strategies, such as vasoactive support for CPP-guided management, may be appropriate for neonates and very young infants where CBF differs from older children[99]. Future comparative effectiveness studies and clinical trials involving different pediatric acute brain injury conditions will be needed to further address these knowledge gaps.

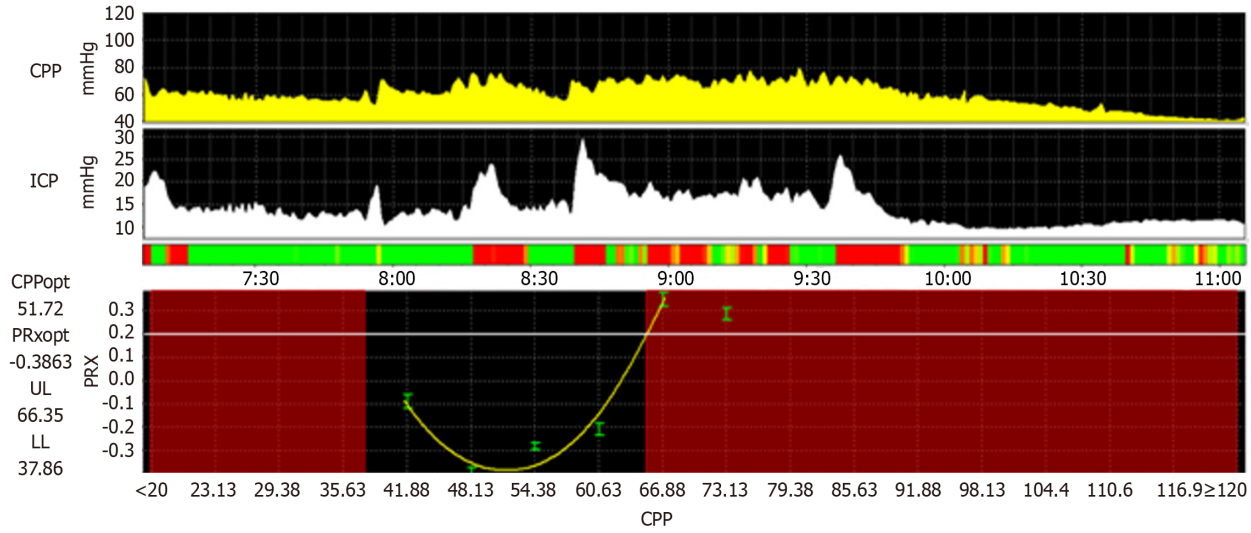


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Figure 3 Example of identification of optimal cerebral perfusion in a 2-year-old male with severe traumatic brain injury. Here, the PRx is plotted across a range of CPP values over a four-hour window, demonstrating a parabolic curve which suggests that the lowest point of the curve (51.72 mmHg; CPPopt) represents the CPP at which cerebrovascular pressure reactivity is most efficient. By using cutoffs of greater than 0.2, the lower limit of cerebrovascular pressure reactivity is estimated at 37.86 mmHg and the upper limit of cerebrovascular pressure reactivity is estimated at 66.35 mmHg. PRx: Pressure reactivity index; CPP: Cerebral perfusion pressure; CPPOpt: Optimal cerebral perfusion pressure; ICP: Intracranial pressure; PRXopt: Optimal pressure reactivity index; UL: Upper limit of cerebrovascular pressure reactivity; LL: Lower limit of cerebrovascular pressure reactivity.

CONCLUSION

Neuroprotection is a foundational component of pediatric neurocritical care. Standardized clinical approaches that integrate evidence-based guidelines with fundamental and conceptual neurophysiologic knowledge have been associated improved outcomes for patients with acute neurologic injuries. Substantial knowledge gaps remain regarding key clinical interventions that may improve patient outcomes. Multimodality neurologic monitoring demonstrates strong promise toward augmenting a patient-centered approach for optimized neuroprotection.

FOOTNOTES

Author contributions: Kochar A, Hildebrandt K, Silverstein R and Appavu B contributed to the conception of this review, analysis of the data, and writing of the manuscript, and all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Liu XF
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Moreau JF**, Fink EL, Hartman ME, Angus DC, Bell MJ, Linde-Zwirble WT, Watson RS. Hospitalizations of children with neurologic disorders in the United States. *Pediatr Crit Care Med* 2013; **14**: 801-810 [PMID: 23842588 DOI:

10.1097/PCC.0b013e31828aa71f]
2 **Au AK**, Carcillo JA, Clark RS, Bell MJ. Brain injuries and neurological system failure are the most common proximate causes of death in children admitted to a pediatric intensive care unit. *Pediatr Crit Care Med* 2011; **12**: 566-571 [PMID: 21037501 DOI: 10.1097/PCC.0b013e3181fe3420]
3 **Pollack MM**, Holubkov R, Funai T, Clark A, Berger JT, Meert K, Newth CJ, Shanley T, Moler F, Carcillo J, Berg RA, Dalton H, Wessel DL, Harrison RE, Doctor A, Dean JM, Jenkins TL; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Pediatric intensive care outcomes: development of new morbidities during pediatric critical care. *Pediatr Crit Care Med* 2014; **15**: 821-827 [PMID: 25226501 DOI: 10.1097/PCC.0000000000000250]
4 **Pinto NP**, Rhinesmith EW, Kim TY, Ladner PH, Pollack MM. Long-Term Function After Pediatric Critical Illness: Results From the Survivor Outcomes Study. *Pediatr Crit Care Med* 2017; **18**: e122-e130 [PMID: 28107265 DOI: 10.1097/PCC.0000000000001070]
5 **Sekhon MS**, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. *Crit Care* 2017; **21**: 90 [PMID: 28403909 DOI: 10.1186/s13054-017-1670-9]
6 **Germans MR**, Boogaarts HD, Macdonald RL. Neuroprotection in Critical Care Neurology. *Semin Neurol* 2016; **36**: 642-648 [PMID: 27907969 DOI: 10.1055/s-0036-1592359]
7 **Siaron KB**, Cortes MX, Stutzman SE, Venkatachalam A, Ahmed KM, Olson DM. Blood Pressure measurements are site dependent in a cohort of patients with neurological illness. *Sci Rep* 2020; **10**: 3382 [PMID: 32099051 DOI: 10.1038/s41598-020-60414-7]
8 **Lele AV**, Wilson D, Chalise P, Nazzaro J, Krishnamoorthy V, Vavilala MS. Differences in blood pressure by measurement technique in neurocritically ill patients: A technological assessment. *J Clin Neurosci* 2018; **47**: 97-102 [PMID: 29113858 DOI: 10.1016/j.jocn.2017.10.079]
9 **Erickson SL**, Killien EY, Wainwright M, Mills B, Vavilala MS. Mean Arterial Pressure and Discharge Outcomes in Severe Pediatric Traumatic Brain Injury. *Neurocrit Care* 2021; **34**: 1017-1025 [PMID: 33108627 DOI: 10.1007/s12028-020-01121-z]
10 **Topjian AA**, Telford R, Holubkov R, Nadkarni VM, Berg RA, Dean JM, Moler FW; Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) Trial Investigators. Association of Early Postresuscitation Hypotension With Survival to Discharge After Targeted Temperature Management for Pediatric Out-of-Hospital Cardiac Arrest: Secondary Analysis of a Randomized Clinical Trial. *JAMA Pediatr* 2018; **172**: 143-153 [PMID: 29228147 DOI: 10.1001/jamapediatrics.2017.4043]
11 **Topjian AA**, French B, Sutton RM, Conlon T, Nadkarni VM, Moler FW, Dean JM, Berg RA. Early postresuscitation hypotension is associated with increased mortality following pediatric cardiac arrest. *Crit Care Med* 2014; **42**: 1518-1523 [PMID: 24561563 DOI: 10.1097/CCM.0000000000000216]
12 **Grelli KN**, Gindville MC, Walker CH, Jordan LC. Association of Blood Pressure, Blood Glucose, and Temperature With Neurological Outcome After Childhood Stroke. *JAMA Neurol* 2016; **73**: 829-835 [PMID: 27214847 DOI: 10.1001/jamaneurol.2016.0992]
13 **Samant UB 4th**, Mack CD, Koepsell T, Rivara FP, Vavilala MS. Time of hypotension and discharge outcome in children with severe traumatic brain injury. *J Neurotrauma* 2008; **25**: 495-502 [PMID: 18419252 DOI: 10.1089/neu.2007.0491]
14 **Topjian AA**, de Caen A, Wainwright MS, Abella BS, Abend NS, Atkins DL, Bembea MM, Fink EL, Guerguerian AM, Haskell SE, Kilgannon JH, Lasa JJ, Hazinski MF. Pediatric Post-Cardiac Arrest Care: A Scientific Statement From the American Heart Association. *Circulation* 2019; **140**: e194-e233 [PMID: 31242751 DOI: 10.1161/CIR.0000000000000697]
15 **Kochanek PM**, Tasker RC, Bell MJ, Adelson PD, Carney N, Vavilala MS, Selden NR, Bratton SL, Grant GA, Kissoon N, Reuter-Rice KE, Wainwright MS. Management of Pediatric Severe Traumatic Brain Injury: 2019 Consensus and Guidelines-Based Algorithm for First and Second Tier Therapies. *Pediatr Crit Care Med* 2019; **20**: 269-279 [PMID: 30830015 DOI: 10.1097/PCC.0000000000001737]
16 **Kochanek PM**, Tasker RC, Carney N, Totten AM, Adelson PD, Selden NR, Davis-O'Reilly C, Hart EL, Bell MJ, Bratton SL, Grant GA, Kissoon N, Reuter-Rice KE, Vavilala MS, Wainwright MS. Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition: Update of the Brain Trauma Foundation Guidelines, Executive Summary. *Pediatr Crit Care Med* 2019; **20**: 280-289 [PMID: 30830016 DOI: 10.1097/PCC.0000000000001736]
17 **Woods KS**, Horvat CM, Kantawala S, Simon DW, Rakkar J, Kochanek PM, Clark RSB, Au AK. Intracranial and Cerebral Perfusion Pressure Thresholds Associated With Inhospital Mortality Across Pediatric Neurocritical Care. *Pediatr Crit Care Med* 2021; **22**: 135-146 [PMID: 33229873 DOI: 10.1097/PCC.0000000000002618]
18 **Kety SS**, Schmidt CF. The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men. *J Clin Invest* 1948; **27**: 484-492 [PMID: 16695569 DOI: 10.1172/JCI101995]
19 **Bennett KS**, Clark AE, Meert KL, Topjian AA, Schleien CL, Shaffner DH, Dean JM, Moler FW; Pediatric Emergency Care Medicine Applied Research Network. Early oxygenation and ventilation measurements after pediatric cardiac arrest: lack of association with outcome. *Crit Care Med* 2013; **41**: 1534-1542 [PMID: 23552509 DOI: 10.1097/CCM.0b013e318287f54c]
20 **Zebrack M**, Dandoy C, Hansen K, Scaife E, Mann NC, Bratton SL. Early resuscitation of children with moderate-to-severe traumatic brain injury. *Pediatrics* 2009; **124**: 56-64 [PMID: 19564283 DOI: 10.1542/peds.2008-1006]
21 **Guerra-Wallace MM**, Casey FL 3rd, Bell MJ, Fink EL, Hickey RW. Hyperoxia and hypoxia in children resuscitated from cardiac arrest. *Pediatr Crit Care Med* 2013; **14**: e143-e148 [PMID: 23392367 DOI: 10.1097/PCC.0b013e3182720440]
22 **Kilgannon JH**, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, Parrillo JE, Trzeciak S; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA* 2010; **303**: 2165-2171 [PMID: 20516417 DOI: 10.1001/jama.2010.707]
23 **Ferguson LP**, Durward A, Tibby SM. Relationship between arterial partial oxygen pressure after resuscitation from

cardiac arrest and mortality in children. *Circulation* 2012; **126**: 335-342 [PMID: 22723307 DOI: 10.1161/CIRCULATIONAHA.111.085100]

24 **Del Castillo J**, López-Herce J, Matamoros M, Cañadas S, Rodriguez-Calvo A, Cechetti C, Rodriguez-Núñez A, Alvarez AC; Iberoamerican Pediatric Cardiac Arrest Study Network RIBEPCI. Hyperoxia, hypocapnia and hypercapnia as outcome factors after cardiac arrest in children. *Resuscitation* 2012; **83**: 1456-1461 [PMID: 22841610 DOI: 10.1016/j.resuscitation.2012.07.019]

25 **Pigula FA**, Wald SL, Shackford SR, Vane DW. The effect of hypotension and hypoxia on children with severe head injuries. *J Pediatr Surg* 1993; **28**: 310-4; discussion 315 [PMID: 8468638 DOI: 10.1016/0022-3468(93)90223-8]

26 **Kannan N**, Wang J, Mink RB, Wainwright MS, Groner JI, Bell MJ, Giza CC, Zatzick DF, Ellenbogen RG, Boyle LN, Mitchell PH, Rivara FP, Rowhani-Rahbar A, Vavilala MS; PEGASUS (Pediatric Guideline Adherence Outcomes) Study. Timely Hemodynamic Resuscitation and Outcomes in Severe Pediatric Traumatic Brain Injury: Preliminary Findings. *Pediatr Emerg Care* 2018; **34**: 325-329 [PMID: 27387972 DOI: 10.1097/PEC.0000000000000803]

27 **Lilien TA**, Groeneveld NS, van Etten-Jamaludin F, Peters MJ, Buysse CMP, Ralston SL, van Woensel JBM, Bos LDJ, Bem RA. Association of Arterial Hyperoxia With Outcomes in Critically Ill Children: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2022; **5**: e2142105 [PMID: 34985516 DOI: 10.1001/jamanetworkopen.2021.42105]

28 **Schrieff-Elson LE**, Thomas KG, Rohlwink UK, Figaji AA. Low brain oxygenation and differences in neuropsychological outcomes following severe pediatric TBI. *Childs Nerv Syst* 2015; **31**: 2257-2268 [PMID: 26337700 DOI: 10.1007/s00381-015-2892-2]

29 **Figaji AA**, Zwane E, Thompson C, Fieggen AG, Argent AC, Le Roux PD, Peter JC. Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury. Part 1: Relationship with outcome. *Childs Nerv Syst* 2009; **25**: 1325-1333 [PMID: 19214532 DOI: 10.1007/s00381-009-0822-x]

30 **Lang SS**, Kumar NK, Zhao C, Zhang DY, Tucker AM, Storm PB, Heuer GG, Gajjar AA, Kim CT, Yuan I, Sotardi S, Kilbaugh TJ, Huh JW. Invasive brain tissue oxygen and intracranial pressure (ICP) monitoring *vs* ICP-only monitoring in pediatric severe traumatic brain injury. *J Neurosurg Pediatr* 2022; 1-11 [PMID: 35623367 DOI: 10.3171/2022.4.PEDS21568]

31 **Chong SL**, Harjanto S, Testoni D, Ng ZM, Low CY, Lee KP, Lee JH. Early Hyperglycemia in Pediatric Traumatic Brain Injury Predicts for Mortality, Prolonged Duration of Mechanical Ventilation, and Intensive Care Stay. *Int J Endocrinol* 2015; **2015**: 719476 [PMID: 26074963 DOI: 10.1155/2015/719476]

32 **Cochran A**, Scaife ER, Hansen KW, Downey EC. Hyperglycemia and outcomes from pediatric traumatic brain injury. *J Trauma* 2003; **55**: 1035-1038 [PMID: 14676647 DOI: 10.1097/01.TA.0000031175.96507.48]

33 **Fu YQ**, Chong SL, Lee JH, Liu CJ, Fu S, Loh TF, Ng KC, Xu F. The impact of early hyperglycaemia on children with traumatic brain injury. *Brain Inj* 2017; **31**: 396-400 [PMID: 28296528 DOI: 10.1080/02699052.2016.1264629]

34 **Aşılıoğlu N**, Turna F, Paksu MS. Admission hyperglycemia is a reliable outcome predictor in children with severe traumatic brain injury. *J Pediatr (Rio J)* 2011; **87**: 325-328 [PMID: 21597650 DOI: 10.2223/JPED.2097]

35 **Elkon B**, Cambrin JR, Hirshberg E, Bratton SL. Hyperglycemia: an independent risk factor for poor outcome in children with traumatic brain injury*. *Pediatr Crit Care Med* 2014; **15**: 623-631 [PMID: 24849146 DOI: 10.1097/PCC.0000000000000170]

36 **Smith RL**, Lin JC, Adelson PD, Kochanek PM, Fink EL, Wisniewski SR, Bayir H, Tyler-Kabara EC, Clark RS, Brown SD, Bell MJ. Relationship between hyperglycemia and outcome in children with severe traumatic brain injury. *Pediatr Crit Care Med* 2012; **13**: 85-91 [PMID: 21499170 DOI: 10.1097/PCC.0b013e3182192c30]

37 **Seyed Saadat SM**, Bidabadi E, Seyed Saadat SN, Mashouf M, Salamat F, Yousefzadeh S. Association of persistent hyperglycemia with outcome of severe traumatic brain injury in pediatric population. *Childs Nerv Syst* 2012; **28**: 1773-1777 [PMID: 22526446 DOI: 10.1007/s00381-012-1753-5]

38 **Luo HC**, Fu YQ, You CY, Liu CJ, Xu F. Comparison of admission serum albumin and hemoglobin as predictors of outcome in children with moderate to severe traumatic brain injury: A retrospective study. *Medicine (Baltimore)* 2019; **98**: e17806 [PMID: 31689863 DOI: 10.1097/MD.0000000000017806]

39 **Yee KF**, Walker AM, Gilfoyle E. The Effect of Hemoglobin Levels on Mortality in Pediatric Patients with Severe Traumatic Brain Injury. *Can Respir J* 2016; **2016**: 6803860 [PMID: 27445560 DOI: 10.1155/2016/6803860]

40 **ROSOMOFF HL**, HOLADAY DA. Cerebral blood flow and cerebral oxygen consumption during hypothermia. *Am J Physiol* 1954; **179**: 85-88 [PMID: 13207391 DOI: 10.1152/ajplegacy.1954.179.1.85]

41 **Busto R**, Dietrich WD, Globus MY, Valdés I, Scheinberg P, Ginsberg MD. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. *J Cereb Blood Flow Metab* 1987; **7**: 729-738 [PMID: 3693428 DOI: 10.1038/jcbfm.1987.127]

42 **Minamisawa H**, Smith ML, Siesjö BK. The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. *Ann Neurol* 1990; **28**: 26-33 [PMID: 2375631 DOI: 10.1002/ana.410280107]

43 **Meden P**, Overgaard K, Pedersen H, Boysen G. The influence of body temperature on infarct volume and thrombolytic therapy in a rat embolic stroke model. *Brain Res* 1994; **647**: 131-138 [PMID: 8069695 DOI: 10.1016/0006-8993(94)91407-9]

44 **Baena RC**, Busto R, Dietrich WD, Globus MY, Ginsberg MD. Hyperthermia delayed by 24 h aggravates neuronal damage in rat hippocampus following global ischemia. *Neurology* 1997; **48**: 768-773 [PMID: 9065563 DOI: 10.1212/wnl.48.3.768]

45 **Shum-Tim D**, Nagashima M, Shinoka T, Bucerius J, Nollert G, Lidov HG, du Plessis A, Laussen PC, Jonas RA. Postischemic hyperthermia exacerbates neurologic injury after deep hypothermic circulatory arrest. *J Thorac Cardiovasc Surg* 1998; **116**: 780-792 [PMID: 9806385 DOI: 10.1016/s0022-5223(98)00449-8]

46 **Castillo J**, Dávalos A, Marrugat J, Noya M. Timing for fever-related brain damage in acute ischemic stroke. *Stroke* 1998; **29**: 2455-2460 [PMID: 9836750 DOI: 10.1161/01.str.29.12.2455]

47 **Suz P**, Vavilala MS, Souter M, Muangman S, Lam AM. Clinical features of fever associated with poor outcome in severe pediatric traumatic brain injury. *J Neurosurg Anesthesiol* 2006; **18**: 5-10 [PMID: 16369134 DOI: 10.1097/01.ana.0000189079.26212.37]

48 **Bembea MM**, Nadkarni VM, Diener-West M, Venugopal V, Carey SM, Berg RA, Hunt EA; American Heart Association National Registry of Cardiopulmonary Resuscitation Investigators. Temperature patterns in the early postresuscitation period after pediatric inhospital cardiac arrest. *Pediatr Crit Care Med* 2010; **11**: 723-730 [PMID: 20431503 DOI: 10.1097/PCC.0b013e3181dde659]

49 **Du Q**, Liu Y, Chen X, Li K. Effect of Hypothermia Therapy on Children with Traumatic Brain Injury: A Meta-Analysis of Randomized Controlled Trials. *Brain Sci* 2022; **12** [PMID: 36009072 DOI: 10.3390/brainsci12081009]

50 **Moler FW**, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, Meert KL, Browning B, Pemberton VL, Page K, Gildea MR, Scholefield BR, Shankaran S, Hutchison JS, Berger JT, Ofori-Amanfo G, Newth CJ, Topjian A, Bennett KS, Koch JD, Pham N, Chanani NK, Pineda JA, Harrison R, Dalton HJ, Alten J, Schleien CL, Goodman DM, Zimmerman JJ, Bhalala US, Schwarz AJ, Porter MB, Shah S, Fink EL, McQuillen P, Wu T, Skellett S, Thomas NJ, Nowak JE, Baines PB, Pappachan J, Mathur M, Lloyd E, van der Jagt EW, Dobyns EL, Meyer MT, Sanders RC Jr, Clark AE, Dean JM; THAPCA Trial Investigators. Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children. *N Engl J Med* 2017; **376**: 318-329 [PMID: 28118559 DOI: 10.1056/NEJMoa1610493]

51 **Moler FW**, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, Meert KL, Clark AE, Browning B, Pemberton VL, Page K, Shankaran S, Hutchison JS, Newth CJ, Bennett KS, Berger JT, Topjian A, Pineda JA, Koch JD, Schleien CL, Dalton HJ, Ofori-Amanfo G, Goodman DM, Fink EL, McQuillen P, Zimmerman JJ, Thomas NJ, van der Jagt EW, Porter MB, Meyer MT, Harrison R, Pham N, Schwarz AJ, Nowak JE, Alten J, Wheeler DS, Bhalala US, Lidsky K, Lloyd E, Mathur M, Shah S, Wu T, Theodorou AA, Sanders RC Jr, Dean JM; THAPCA Trial Investigators. Therapeutic hypothermia after out-of-hospital cardiac arrest in children. *N Engl J Med* 2015; **372**: 1898-1908 [PMID: 25913022 DOI: 10.1056/NEJMoa1411480]

52 **Slupe AM**, Kirsch JR. Effects of anesthesia on cerebral blood flow, metabolism, and neuroprotection. *J Cereb Blood Flow Metab* 2018; **38**: 2192-2208 [PMID: 30009645 DOI: 10.1177/0271678X18789273]

53 **Curley MA**, Wypij D, Watson RS, Grant MJ, Asaro LA, Cheifetz IM, Dodson BL, Franck LS, Gedeit RG, Angus DC, Matthay MA; RESTORE Study Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators Network. Protocolized sedation *vs* usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. *JAMA* 2015; **313**: 379-389 [PMID: 25602358 DOI: 10.1001/jama.2014.18399]

54 **Takeshita H**, Okuda Y, Sari A. The effects of ketamine on cerebral circulation and metabolism in man. *Anesthesiology* 1972; **36**: 69-75 [PMID: 5006989 DOI: 10.1097/00000542-197201000-00013]

55 **Bar-Joseph G**, Guilburd Y, Tamir A, Guilburd JN. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *J Neurosurg Pediatr* 2009; **4**: 40-46 [PMID: 19569909 DOI: 10.3171/2009.1.PEDS08319]

56 **Vernon DD**, Witte MK. Effect of neuromuscular blockade on oxygen consumption and energy expenditure in sedated, mechanically ventilated children. *Crit Care Med* 2000; **28**: 1569-1571 [PMID: 10834713 DOI: 10.1097/00003246-200005000-00051]

57 **Chin KH**, Bell MJ, Wisniewski SR, Balasubramani GK, Kochanek PM, Beers SR, Brown SD, Adelson PD; Pediatric Traumatic Brain Injury Consortium: Hypothermia Investigators. Effect of administration of neuromuscular blocking agents in children with severe traumatic brain injury on acute complication rates and outcomes: a secondary analysis from a randomized, controlled trial of therapeutic hypothermia. *Pediatr Crit Care Med* 2015; **16**: 352-358 [PMID: 25599147 DOI: 10.1097/PCC.0000000000000344]

58 **Velle F**, Lewén A, Howells T, Enblad P, Nilsson P. Intracranial pressure-based barbiturate coma treatment in children with refractory intracranial hypertension due to traumatic brain injury. *J Neurosurg Pediatr* 2019; 1-9 [PMID: 31881539 DOI: 10.3171/2019.10.PEDS19268]

59 **Alkhachroum A**, Appavu B, Egawa S, Foreman B, Gaspard N, Gilmore EJ, Hirsch LJ, Kurtz P, Lambrecq V, Kromm J, Vespa P, Zafar SF, Rohaut B, Claassen J. Electroencephalogram in the intensive care unit: a focused look at acute brain injury. *Intensive Care Med* 2022; **48**: 1443-1462 [PMID: 35997792 DOI: 10.1007/s00134-022-06854-3]

60 **Appavu B**, Riviello JJ. Electroencephalographic Patterns in Neurocritical Care: Pathologic Contributors or Epiphenomena? *Neurocrit Care* 2018; **29**: 9-19 [PMID: 28660340 DOI: 10.1007/s12028-017-0424-5]

61 **Hirsch LJ**, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, Lee JW, Wusthoff CJ, Hahn CD, Westover MB, Gerard EE, Herman ST, Haider HA, Osman G, Rodriguez-Ruiz A, Maciel CB, Gilmore EJ, Fernandez A, Rosenthal ES, Claassen J, Husain AM, Yoo JY, So EL, Kaplan PW, Nuwer MR, van Putten M, Sutter R, Drislane FW, Trinka E, Gaspard N. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. *J Clin Neurophysiol* 2021; **38**: 1-29 [PMID: 33475321 DOI: 10.1097/WNP.0000000000000806]

62 **Vespa P**, Tubi M, Claassen J, Buitrago-Blanco M, McArthur D, Velazquez AG, Tu B, Prins M, Nuwer M. Metabolic crisis occurs with seizures and periodic discharges after brain trauma. *Ann Neurol* 2016; **79**: 579-590 [PMID: 26814699 DOI: 10.1002/ana.24606]

63 **Witsch J**, Frey HP, Schmidt JM, Velazquez A, Falo CM, Reznik M, Roh D, Agarwal S, Park S, Connolly ES, Claassen J. Electroencephalographic Periodic Discharges and Frequency-Dependent Brain Tissue Hypoxia in Acute Brain Injury. *JAMA Neurol* 2017; **74**: 301-309 [PMID: 28097330 DOI: 10.1001/jamaneurol.2016.5325]

64 **Claassen J**, Perotte A, Albers D, Kleinberg S, Schmidt JM, Tu B, Badjatia N, Lantigua H, Hirsch LJ, Mayer SA, Connolly ES, Hripcsak G. Nonconvulsive seizures after subarachnoid hemorrhage: Multimodal detection and outcomes. *Ann Neurol* 2013; **74**: 53-64 [PMID: 23813945 DOI: 10.1002/ana.23859]

65 **Appavu BL**, Fox J, Kuwabara M, Burrows BT, Temkit M', Adelson PD. Association of Cerebral and Systemic Physiology With Quantitative Electroencephalographic Characteristics of Early Posttraumatic Seizures. *J Clin Neurophysiol* 2022 [PMID: 36007060 DOI: 10.1097/WNP.0000000000000965]

66 **Silverstein R**, Appavu B. Cerebral edema in childhood. In: Roos RP, Editor-in-Chief. Medlink Neurology. San Diego: Medlink, LLC. Available at www.medlink.com. Updated: 06.11.2022.

67 **Liotta EM**. Management of Cerebral Edema, Brain Compression, and Intracranial Pressure. *Continuum (Minneap Minn)* 2021; **27**: 1172-1200 [PMID: 34618757 DOI: 10.1212/CON.0000000000000988]

68 **Kochanek PM**, Adelson PD, Rosario BL, Hutchison J, Miller Ferguson N, Ferrazzano P, O'Brien N, Beca J, Sarnaik A,

LaRovere K, Bennett TD, Deep A, Gupta D, Willyerd FA, Gao S, Wisniewski SR, Bell MJ; ADAPT Investigators. Comparison of Intracranial Pressure Measurements Before and After Hypertonic Saline or Mannitol Treatment in Children With Severe Traumatic Brain Injury. *JAMA Netw Open* 2022; **5**: e220891 [PMID: 35267036 DOI: 10.1001/jamanetworkopen.2022.0891]

69 **Froese L**, Dian J, Batson C, Gomez A, Unger B, Zeiler FA. The impact of hypertonic saline on cerebrovascular reactivity and compensatory reserve in traumatic brain injury: an exploratory analysis. *Acta Neurochir (Wien)* 2020; **162**: 2683-2693 [PMID: 32959342 DOI: 10.1007/s00701-020-04579-0]

70 **Wellard J**, Kuwabara M, Adelson PD, Appavu B. Physiologic Characteristics of Hyperosmolar Therapy After Pediatric Traumatic Brain Injury. *Front Neurol* 2021; **12**: 662089 [PMID: 33959090 DOI: 10.3389/fneur.2021.662089]

71 **Zipfel J**, Engel J, Hockel K, Heimberg E, Schuhmann MU, Neunhoeffer F. Effects of hypertonic saline on intracranial pressure and cerebral autoregulation in pediatric traumatic brain injury. *J Neurosurg Pediatr* 2021; 1-7 [PMID: 34560657 DOI: 10.3171/2021.6.PEDS21143]

72 **Jha RM**, Kochanek PM, Simard JM. Pathophysiology and treatment of cerebral edema in traumatic brain injury. *Neuropharmacology* 2019; **145**: 230-246 [PMID: 30086289 DOI: 10.1016/j.neuropharm.2018.08.004]

73 **Pham X**, Ray J, Neto AS, Laing J, Perucca P, Kwan P, O'Brien TJ, Udy AA. Association of Neurocritical Care Services With Mortality and Functional Outcomes for Adults With Brain Injury: A Systematic Review and Meta-analysis. *JAMA Neurol* 2022; **79**: 1049-1058 [PMID: 36036899 DOI: 10.1001/jamaneurol.2022.2456]

74 **Pineda JA**, Leonard JR, Mazotas IG, Noetzel M, Limbrick DD, Keller MS, Gill J, Doctor A. Effect of implementation of a paediatric neurocritical care programme on outcomes after severe traumatic brain injury: a retrospective cohort study. *Lancet Neurol* 2013; **12**: 45-52 [PMID: 23200264 DOI: 10.1016/S1474-4422(12)70269-7]

75 **LaRovere KL**, Murphy SA, Horak R, Vittner P, Kapur K, Proctor M, Tasker RC. Pediatric Neurocritical Care: Evolution of a New Clinical Service in PICUs Across the United States. *Pediatr Crit Care Med* 2018; **19**: 1039-1045 [PMID: 30134362 DOI: 10.1097/PCC.0000000000001708]

76 **Murphy SA**, Bell MJ, Clark ME, Whalen MJ, Noviski N. Pediatric Neurocritical Care: A Short Survey of Current Perceptions and Practices. *Neurocrit Care* 2015; **23**: 149-158 [PMID: 25693892 DOI: 10.1007/s12028-015-0120-2]

77 **Wainwright MS**, Grimason M, Goldstein J, Smith CM, Amlie-Lefond C, Revivo G, Noah ZL, Harris ZL, Epstein LG. Building a pediatric neurocritical care program: a multidisciplinary approach to clinical practice and education from the intensive care unit to the outpatient clinic. *Semin Pediatr Neurol* 2014; **21**: 248-254 [PMID: 25727506 DOI: 10.1016/j.spen.2014.10.006]

78 **Bell MJ**, Carpenter J, Au AK, Keating RF, Myseros JS, Yaun A, Weinstein S. Development of a pediatric neurocritical care service. *Neurocrit Care* 2009; **10**: 4-10 [PMID: 18256793 DOI: 10.1007/s12028-008-9061-3]

79 **Erklauer JC**, Thammasitboon S, Shekerdemian LS, Riviello JJ, Lai YC. Creating a Robust Community of Practice as a Foundation for the Successful Development of a Pediatric Neurocritical Care Program. *Pediatr Neurol* 2022; **136**: 1-7 [PMID: 36029730 DOI: 10.1016/j.pediatrneurol.2022.07.014]

80 **Ferriero DM**, Fullerton HJ, Bernard TJ, Billinghurst L, Daniels SR, DeBaun MR, deVeber G, Ichord RN, Jordan LC, Massicotte P, Meldau J, Roach ES, Smith ER; American Heart Association Stroke Council and Council on Cardiovascular and Stroke Nursing. Management of Stroke in Neonates and Children: A Scientific Statement From the American Heart Association/American Stroke Association. *Stroke* 2019; **50**: e51-e96 [PMID: 30686119 DOI: 10.1161/STR.0000000000000183]

81 **Appavu B**, Foldes ST, Adelson PD. Clinical trials for pediatric traumatic brain injury: definition of insanity? *J Neurosurg Pediatr* 2019; **23**: 661-669 [PMID: 31153150 DOI: 10.3171/2019.2.PEDS18384]

82 **Chang N**, Rasmussen L. Exploring Trends in Neuromonitoring Use in a General Pediatric ICU: The Need for Standardized Guidance. *Children (Basel)* 2022; **9** [PMID: 35883918 DOI: 10.3390/children9070934]

83 **Appavu B**, Burrows BT, Foldes S, Adelson PD. Approaches to Multimodality Monitoring in Pediatric Traumatic Brain Injury. *Front Neurol* 2019; **10**: 1261 [PMID: 32038449 DOI: 10.3389/fneur.2019.01261]

84 **LaRovere KL**, Tasker RC, Wainwright M, Reuter-Rice K, Appavu B, Miles D, Lidsky K, Vittner P, Gundersen D, O'Brien NF; Pediatric Neurocritical Care Research Group (PNCRG). Transcranial Doppler Ultrasound During Critical Illness in Children: Survey of Practices in Pediatric Neurocritical Care Centers. *Pediatr Crit Care Med* 2020; **21**: 67-74 [PMID: 31568242 DOI: 10.1097/PCC.0000000000002118]

85 **Appavu B**, Burrows BT, Nickoles T, Boerwinkle V, Willyerd A, Gunnala V, Mangum T, Marku I, Adelson PD. Implementation of Multimodality Neurologic Monitoring Reporting in Pediatric Traumatic Brain Injury Management. *Neurocrit Care* 2021; **35**: 3-15 [PMID: 33791948 DOI: 10.1007/s12028-021-01190-8]

86 **Zeiler FA**, Cardim D, Donnelly J, Menon DK, Czosnyka M, Smielewski P. Transcranial Doppler Systolic Flow Index and ICP-Derived Cerebrovascular Reactivity Indices in Traumatic Brain Injury. *J Neurotrauma* 2018; **35**: 314-322 [PMID: 29050524 DOI: 10.1089/neu.2017.5364]

87 **Budohoski KP**, Reinhard M, Aries MJ, Czosnyka Z, Smielewski P, Pickard JD, Kirkpatrick PJ, Czosnyka M. Monitoring cerebral autoregulation after head injury. Which component of transcranial Doppler flow velocity is optimal? *Neurocrit Care* 2012; **17**: 211-218 [PMID: 21691895 DOI: 10.1007/s12028-011-9572-1]

88 **Zweifel C**, Lavinio A, Steiner LA, Radolovich D, Smielewski P, Timofeev I, Hiler M, Balestreri M, Kirkpatrick PJ, Pickard JD, Hutchinson P, Czosnyka M. Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury. *Neurosurg Focus* 2008; **25**: E2 [PMID: 18828700 DOI: 10.3171/FOC.2008.25.10.E2]

89 **Steiner LA**, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, Pickard JD. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med* 2002; **30**: 733-738 [PMID: 11940737 DOI: 10.1097/00003246-200204000-00002]

90 **Appavu B**, Temkit M', Foldes S, Burrows BT, Kuwabara M, Jacobson A, Adelson PD. Association of Outcomes with Model-Based Indices of Cerebral Autoregulation After Pediatric Traumatic Brain Injury. *Neurocrit Care* 2021; **35**: 640-650 [PMID: 34268644 DOI: 10.1007/s12028-021-01279-0]

91 **Brady KM**, Shaffner DH, Lee JK, Easley RB, Smielewski P, Czosnyka M, Jallo GI, Guerguerian AM. Continuous monitoring of cerebrovascular pressure reactivity after traumatic brain injury in children. *Pediatrics* 2009; **124**: e1205-

e1212 [PMID: 19948619 DOI: 10.1542/peds.2009-0550]

92 **Lewis PM**, Czosnyka M, Carter BG, Rosenfeld JV, Paul E, Singhal N, Butt W. Cerebrovascular Pressure Reactivity in Children With Traumatic Brain Injury. *Pediatr Crit Care Med* 2015; **16**: 739-749 [PMID: 26132743 DOI: 10.1097/PCC.0000000000000471]

93 **Young AM**, Donnelly J, Czosnyka M, Jalloh I, Liu X, Aries MJ, Fernandes HM, Garnett MR, Smielewski P, Hutchinson PJ, Agrawal S. Continuous Multimodality Monitoring in Children after Traumatic Brain Injury-Preliminary Experience. *PLoS One* 2016; **11**: e0148817 [PMID: 26978532 DOI: 10.1371/journal.pone.0148817]

94 **Tas J**, Beqiri E, van Kaam RC, Czosnyka M, Donnelly J, Haeren RH, van der Horst ICC, Hutchinson PJ, van Kuijk SMJ, Liberti AL, Menon DK, Hoedemaekers CWE, Depreitere B, Smielewski P, Meyfroidt G, Ercole A, Aries MJH. Targeting Autoregulation-Guided Cerebral Perfusion Pressure after Traumatic Brain Injury (COGiTATE): A Feasibility Randomized Controlled Clinical Trial. *J Neurotrauma* 2021; **38**: 2790-2800 [PMID: 34407385 DOI: 10.1089/neu.2021.0197]

95 **Appavu B**, Foldes S, Burrows BT, Jacobson A, Abruzzo T, Boerwinkle V, Willyerd A, Mangum T, Gunnala V, Marku I, Adelson PD. Multimodal Assessment of Cerebral Autoregulation and Autonomic Function After Pediatric Cerebral Arteriovenous Malformation Rupture. *Neurocrit Care* 2021; **34**: 537-546 [PMID: 32748209 DOI: 10.1007/s12028-020-01058-3]

96 **Joram N**, Beqiri E, Pezzato S, Moscatelli A, Robba C, Liet JM, Chenouard A, Bourgoin P, Czosnyka M, Léger PL, Smielewski P. Continuous Monitoring of Cerebral Autoregulation in Children Supported by Extracorporeal Membrane Oxygenation: A Pilot Study. *Neurocrit Care* 2021; **34**: 935-945 [PMID: 33029743 DOI: 10.1007/s12028-020-01111-1]

97 **Kirschen MP**, Majmudar T, Beaulieu F, Burnett R, Shaik M, Morgan RW, Baker W, Ko T, Balu R, Agarwal K, Lourie K, Sutton R, Kilbaugh T, Diaz-Arrastia R, Berg R, Topjian A. Deviations from NIRS-derived optimal blood pressure are associated with worse outcomes after pediatric cardiac arrest. *Resuscitation* 2021; **168**: 110-118 [PMID: 34600027 DOI: 10.1016/j.resuscitation.2021.09.023]

98 **Lee JK**, Brady KM, Chung SE, Jennings JM, Whitaker EE, Aganga D, Easley RB, Heitmiller K, Jamrogowicz JL, Larson AC, Lee JH, Jordan LC, Hogue CW, Lehmann CU, Bembea MM, Hunt EA, Koehler RC, Shaffner DH. A pilot study of cerebrovascular reactivity autoregulation after pediatric cardiac arrest. *Resuscitation* 2014; **85**: 1387-1393 [PMID: 25046743 DOI: 10.1016/j.resuscitation.2014.07.006]

99 **Paniukov D**, Lebel RM, Giesbrecht G, Lebel C. Cerebral blood flow increases across early childhood. *Neuroimage* 2020; **204**: 116224 [PMID: 31561017 DOI: 10.1016/j.neuroimage.2019.116224]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 June 9; 12(3): 130-138

DOI: 10.5492/wjccm.v12.i3.130

ISSN 2220-3141 (online)

MINIREVIEWS

Upper extremity deep vein thrombosis: An intensivist's perspective

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bloomfield DA, United States; Navarrete Arellano M, Mexico

Received: December 29, 2022
Peer-review started: December 29, 2022
First decision: March 15, 2023
Revised: March 16, 2023
Accepted: April 20, 2023
Article in press: April 20, 2023
Published online: June 9, 2023

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Abstract

Upper extremity deep vein thrombosis (UEDVT) is less common than lower extremity DVT but is a cause of significant morbidity and mortality in intensive care unit patients. Increasing cancer incidence, prolonged life expectancy and increasing use of intravascular catheters and devices has led to an increased incidence of UEDVT. It is also associated with high rates of complications like pulmonary embolism, post-thrombotic syndrome and recurrent thrombosis. Clinical prediction scores and D-dimer may not be as useful in identifying UEDVT; hence, a high suspicion index is required for diagnosis. Doppler ultrasound is commonly employed for diagnosis, but other tests like computed tomography and magnetic resonance imaging venography may also be required in some patients. Contrast venography is rarely used in patients with clinical and ultrasound findings discrepancies. Anticoagulant therapy alone is sufficient in most patients, and thrombolysis and surgical decompression is seldom indicated. The outcome depends on the cause and underlying comorbidities.

Key Words: Catheter associated deep vein thrombosis; Pacemaker associated deep vein thrombosis; Paget-von Schröetter syndrome; Thoracic outlet syndrome; Upper extremity deep vein thrombosis

Core Tip: Upper extremity deep vein thrombosis (UEDVT), is largely under-recognised and an often missed diagnosis. Even though it is less common than the lower extremity DVT, it is increasingly being diagnosed, especially in intensive care unit patients because of presence of venous catheters and devices in these patients. Traditionally used clinical probability scores and tests like D-dimer may not be as effective in diagnosing UEDVT. Bedside Doppler ultrasound is the most commonly employed diagnostic tool which may aid in clinching the diagnosis. Contrast venography remains the gold standard, but is rarely required. Pulmonary embolism is the most dreaded complication but the rates of other complications including post thrombotic syndrome and recurrent DVT also remain significant. Anticoagulant therapy alone is sufficient in most patients. However, UEDVT may be associated with high mortality rates unless early diagnostic and therapeutic measures are initiated.

Citation: Singh O, Juneja D. Upper extremity deep vein thrombosis: An intensivist's perspective. *World J Crit Care Med* 2023; 12(3): 130-138
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/130.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.130

INTRODUCTION

Lower extremity deep vein thrombosis (LEDVT) is a well-recognized and dreaded complication among critically ill patients. All efforts regarding its early recognition and prompt treatment are incorporated into the teachings of critical care physicians and nurses. However, upper extremity DVT (UEDVT) is largely under-recognized and an often missed diagnosis. Even though it is less common than the LEDVT, it is increasingly being diagnosed, especially in intensive care unit (ICU) patients, because of certain inherent risk factors present in these patients. It may lead to several complications causing significant morbidity and mortality. Simple tests like bedside doppler ultrasound may enable us to make an early diagnosis and initiate prompt therapeutic measures with anticoagulants to improve clinical outcomes. Hence, critical care physicians must be aware of this dreadful condition and keep a high index of suspicion to diagnose it.

EPIDEMIOLOGY

UEDVT refers to the formation of fibrin clots within the deep veins of the upper extremities. Superficial veins, like the basilic and cephalic, which have anastomoses with the deep veins, can also be affected with superficial thrombophlebitis, which may progress to cause DVT. As the UEDVT involving the distal veins (radial, ulna and interosseous veins) is generally asymptomatic and does not require any clinical intervention, clinically relevant UEDVT generally denotes thrombosis of subclavian, axillary, and brachial veins. Subclavian veins (SCVs) are most commonly implicated in 76% of cases, followed by axillary (47%) and brachial veins (36%). Multiple veins are usually involved; a single vein is involved in only 38% of cases. Other deep veins, like the internal jugular and brachiocephalic, may also be involved in up to 50% of cases[1,2].

LEDVT is a much more commonly recognized and reported complication, with UEDVT constituting only 10% of all cases of DVT[3,4]. However, the risk and incidence of UEDVT would depend on the population studied, with certain patient populations having a much higher incidence. Nonetheless, the incidence of UEDVT is increasing, especially in ICU patients with several risk factors for developing UEDVT[5,6]. In an observational study conducted in a surgical ICU, out of 862 patients, 15% developed UEDVT despite standardized heparin thromboprophylaxis[7]. Some reports even suggest that the UEDVT may be as common in hospitalized medical patients as the LEDVT[8].

RISK FACTORS

UEDVT may be classified as primary or spontaneous, without any apparent risk factors and secondary, due to identifiable risk factors.

Primary UEDVT

Primary UEDVT may be further categorized due to "effort thrombosis", Paget-Schroetter syndrome (PSS), and idiopathic thrombosis. Primary causes account for up to 33% of cases of UEDVT, among which PSS is reported to be more common[9-11]. PSS generally affects young, otherwise healthy, adult males. The underlying anatomical abnormalities at the thoracic outlet, like the cervical rib, congenital

bands, scalenus tendons hypertrophy, and abnormal insertion of the costoclavicular ligament, cause compression of the SCV and stasis to the flow of blood. The repetitive movements of the dominant arm, as in athletes, cause repetitive trauma to the endothelium of the SCV, leading to intimal hyperplasia, inflammation, and fibrosis, which may worsen venous stasis and lead to the formation and progression of thrombus. People involved in occupations requiring excessive upper extremity motion, such as painting, hairdressing or sports like golf, tennis, weightlifting, baseball or gymnastics, are more commonly affected. The onset of symptoms is generally acute or subacute, precipitated by repeated arm movement, but rarely patients may present with chronic symptoms[12,13]. A subset of patients in whom no cause can be identified are labelled as having idiopathic thrombosis. Underlying occult malignancies have been reported in up to 25% of such patients[14]. These patients are older and have a higher prevalence of underlying coagulation abnormalities[10,15]. Their prognosis is also worse than those with PSS[5].

Secondary UEDVT

Secondary UEDVT is much more common and is responsible for up to 80% of cases[10]. The risk factors for UEDVT differ from the traditionally recognised factors for LEDVT (Table 1). These risk factors are particularly important in critically ill patients admitted to ICUs. Central venous catheters (CVCs) have been recognized as the single most important factor associated with the development of UEDVT and are responsible for up to 50% of cases[5,6]. The use of CVC has been shown to increase the risk of developing UEDVT by up to 14 times[16]. The use of peripherally inserted central catheters is associated with an even higher risk of developing UEDVT[8]. Even among those with CVCs, patients with technically difficult insertions, those with left-sided catheters, misplaced catheter tips, previous catheter placements, and large or multiple lumen catheters have a higher risk of developing UEDVT[17]. Underlying malignancies, especially ovarian cancers and lung adenocarcinomas, have been associated with a higher risk of UEDVT[3]. The risk of developing UEDVT may be compounded if multiple risk factors exist. The reported risk as high as 66%, has been reported in cancer patients having CVCs[18]. Patients who develop non-CVC-associated UEDVT are more likely to be younger, thinner (body mass index of < 25 kg/m^2) and smokers[16].

PATHOPHYSIOLOGY

The presence of the contributing factors from Virchow's Triad (venous stasis, vascular injury, and hypercoagulability) is implicated in thrombus formation in patients with UEDVT. In patients with PSS, thoracic outlet obstruction leads to venous stasis, and repeated movement of the arm causes trauma and endothelium injury leading to thrombosis. CVC or venous devices also cause venous stasis, platelet adherence, and endothelial trauma, increasing the risk of thrombus formation. Patients with malignancies have underlying hypercoagulable states, and excessive cancer cells may lead to vascular damage and venous stasis, making these patients prone to develop thrombosis.

CLINICAL FEATURES

Patients with UEDVT generally present with unilateral upper limb erythema, oedema, reduced mobility, pain, discomfort and low-grade fever. Urschel's sign, dilated and visible veins over the affected shoulders and upper arms, may be seen, especially in patients with long-standing thrombosis [13]. If CVC is present, it may be blocked. Cyanosis and pain while movement or exercise may be reported by patients with PSS. Clinical features related to complications may also be present. Patients with pulmonary embolism (PE) may develop breathlessness, chest pain and haemoptysis. In patients with central vein obstruction or occlusion, superior vena cava (SVC) syndrome features may be present. Brachial plexus compression may present with paraesthesia and arm pain, worsening with hyperabduction of the shoulder. However, in up to 19% of patients, UEDVT may be asymptomatic[5].

DIAGNOSIS

The clinical prediction scores used for LEDVT have been shown to have poor sensitivity and specificity, 78% and 64%, respectively, for diagnosing UEDVT. Hence, specific scores like the Constans clinical decision score have been developed for predicting UEDVT. It uses four variables to risk stratify patients with suspected UEDVT (Table 2)[19]. Only a few studies have evaluated its efficacy in diagnosing UEDVT and have reported sensitivity and specificity of up to 86% and 93%, with an area under the curve ranging from 0.70-0.81[20]. Hence, because of its comparatively low diagnostic accuracy and lack of clinical evidence, it is not recommended to use this clinical probability score as a standalone tool to diagnose UEDVT. However, it may aid physicians in recognizing high-risk patients and undertaking

Table 1 Risk factors for developing upper extremity deep vein thrombosis

Risk factors
Central venous catheters/dialysis catheters
Implantable cardiac rhythm devices
Personal or family history of thrombosis and thrombophilia
Surgery or trauma of the arm
Immobilization of the arm
Pregnancy
Use of oral contraceptive
Malignancy
Post-operative *e.g.*, esophagectomy, retrosternal reconstruction

Table 2 Constans clinical decision score

Patient characteristic	Score	
Venous material present (CVC/pacemaker)	Yes	1 point
	No	0 point
Localised pain	Yes	1 point
	No	0 point
Unilateral oedema	Yes	1 point
	No	0 point
Other diagnosis at least as plausible	Yes	-1 point
	No	0 point
Risk for UEDVT		
Low: 12% probability of UEDVT	-1 to 0 points[1]	
Intermediate: 20% probability of UEDVT	1 point[1]	
High: 70% probability of UEDVT	2-3 points[1]	

[1]Total score.
CVC: Central venous catheter; UEDVT: Upper extremity deep vein thrombosis.

further diagnostic testing. Variations of this score, like the extended Constans score, have also been tried, but they require further testing and validation[20].

Even D-dimer has not been extensively evaluated in diagnosing UEDVT and has shown low specificity of only 14%[21]. Hence, it should be used cautiously to rule out UEDVT. Combination of D-dimer and Constans score has been shown to increase their accuracy in predicting UEDVT[20]. Duplex ultrasonography (US) is commonly employed as the initial diagnostic procedure. It has several advantages: Easy availability, non-invasive nature, easy portability, inexpensive and no radiation exposure (Table 3)[22]. It has high sensitivity and specificity of 97% and 96%, respectively[23]. The presence of echogenicity's in the vascular lumen can suggest a thrombus. Further, a normal vein easily compresses on pressure, but when a thrombus is present, the vein becomes incompressible. However, as the pressure cannot be applied to central veins like SVC, a compression test cannot be used for such veins. Blood flow dynamics can further be evaluated using pulsed wave and colour flow Doppler, which may show an absence of flow or change of normal biphasic flow into a non-pulsatile flow pattern suggestive of obstruction[10,24]. As per a systematic review by Di Nisio *et al*[23], compression US (97% and 96%), Doppler US (84% and 94%) and Doppler US with compression (91% and 93%) all showed high sensitivity and specificity.

Contrast venography is considered the gold standard for diagnosing UEDVT with good sensitivity and specificity and can even visualize areas not accessible to ultrasound. However, because of inherent disadvantages, it is not routinely performed but may be done when there are contradictory clinical and US findings[24]. Contrast venography may also be required before performing catheter-directed

Table 3 Advantages and disadvantages of various diagnostic tests for upper extremity deep vein thrombosis

Diagnostic tests	Advantages	Disadvantages
D-dimer	High sensitivity. Readily available	Poor specificity. Not extensively evaluated for UEDVT
Ultrasound	Non-invasive. Readily available. Bedside. Less expensive. Good sensitivity and specificity	Not appropriate for evaluating central veins. Operator dependant
Doppler ultrasound	Non-invasive. Readily available. Bedside. Less expensive. Good sensitivity and specificity	Operator dependant
Computed tomography venography	Can help in diagnosing other underlying pathologies or rule out other diagnosis	Radiation exposure. Logistical issues. Moderate sensitivity and specificity
Magnetic resonance venography	Can help in diagnosing other underlying pathologies or rule out other diagnosis	Not widely available. Expensive. Logistical issues. Not suitable for patients with surgical implants and pacemakers. Moderate sensitivity and specificity
Contrast venography	Gold standard. High sensitivity and specificity. Can visualize the entire deep venous system. Can define complex and difficult anatomy	Invasive. Radiation exposure. Allergic reactions

UEDVT: Upper extremity deep vein thrombosis.

thrombolysis or surgery for thoracic outlet decompression as a part of a comprehensive workup[13].

Computed tomography (CT) and magnetic resonance imaging (MRI) venography can also be performed for diagnosing UEDVT. However, they have not been extensively evaluated, have moderate sensitivity and specificity, and are less accurate than contrast venography[25,26]. Routine screening for the underlying hypercoagulable state should also be conducted. Homocysteinemia should also be ruled out in such patients. Patients with primary UEDVT have a higher incidence of antiphospholipid antibodies, factor V Leiden, and prothrombin gene mutations[27].

TREATMENT

The treatment of UEDVT is primarily based on the data extrapolated from the studies on LEDVT. Hence, the management principles remain the same. However, in contrast with LEDVT, there is a lack of evidence regarding the effectiveness of compression devices in patients with UEDVT; hence, they are not recommended[28]. In most patients, only anticoagulant therapy is required, along with supportive management[29]. Use of low molecular weight heparin (LMWH), unfractionated heparin, or fondaparinux is generally recommended in the acute phase, followed by vitamin K antagonists (VKA) for 3 mo in patients with idiopathic thrombosis. Prolonged VKA therapy beyond three months is generally not advocated after the first episode of idiopathic UEDVT[28]. However, in patients with underlying malignancy, prolonged LMWH monotherapy extended for up to 6 mo or till cancer remains active, is recommended in non-CVC associated UEDVT[28]. In CVC-associated UEDVT, anticoagulant therapy is recommended for 3 mo if the CVC has been removed. However, if the CVC remains in situ, anticoagulation should be continued until the CVC is present[28]. The routine removal of the catheter is not advocated, even in patients with CVC-associated UEDVT, as long as the catheter is required and is functional[28].

The role of direct oral anticoagulants has not been extensively evaluated in the management of UEDVT. Even though early data from small studies suggest that they may be effective in preventing complications and the need for catheter removal, larger studies are required before they are routinely prescribed for managing UEDVT[30]. However, they may provide an excellent therapeutic alternative to LMWHs in cancer patients in whom VKA may not be as effective[29,31]. Patients on anticoagulants for UEDVT have significant bleeding risks; up to 5% have been reported to develop major bleeding[32]. The risk of bleeding may be higher in patients with underlying malignancies; hence, they must be monitored accordingly[32].

Additional therapeutic measures are rarely required to manage UEDVT[29]. Evidence regarding the efficacy of thrombolysis in UEDVT is lacking. Even though it may improve the patency of the vein, it is associated with a high risk of bleeding[28]. Hence, the American College of Chest Physician guidelines suggests using anticoagulation alone over thrombolysis[28]. Thrombolysis should be considered only in patients with severe symptoms, in patients with extensive involvement of SCV or axillary vein, acute symptoms of less than 14 d duration, good functional status and low risk for bleeding complications [28]. Anticoagulation should be initiated after thrombolysis and continued for at least three months to prevent a recurrence. SVC filters may be considered in patients with PE, and in those with contraindications to anticoagulants[28].

Physical therapy and lifestyle modification may be helpful in patients with UEDVT secondary to PSS. However, if symptoms persist and there is persistent SCV stenosis, as evidenced by positional venography, surgical decompression may be indicated to open the thoracic outlet[13]. Some authors have reported better symptom relief with thrombolysis followed by early surgical decompression by removing the first rib and the costoclavicular ligament, restoring normal blood flow in the SCV[33].

COMPLICATIONS

Common complications associated with UEDVT include recurrent DVT, post-thrombotic syndrome (PTS), PE, SVC syndrome and compression of the brachial plexus[13]. Even though the incidence of PE is lesser than that in LEDVT, it is the most dreaded complication associated with UEDVT[34]. The reported incidence ranges from 2.6% to 17%, with higher incidence reported in secondary UEDVT, especially in CVC-associated cases[7,35]. PE following non-CVC-associated UEDVT is rare, with a reported incidence of less than 1%[36]. Studies evaluating long-term outcomes of patients with UEDVT have reported an incidence of PE of up to 36% over a 2 years follow-up[37]. A review of data from the RIETE registry reported that the incidence of recurrent PE was similar in patients with UEDVT and LEDVT[38].

Recurrent DVT is another significant complication after UEDVT, with some data suggesting that incidence is even higher than that after LEDVT[38]. The data from a recent systematic review suggests that the rate of recurrent UEDVT in patients with idiopathic thrombosis ranges from 0%-23%[39]. Another meta-analysis has reported a pooled incidence of 7.5% for the development of recurrent thrombosis after UEDVT[40]. The reported rate of recurrent UEDVT is significantly higher in secondary DVT, more so in patients with CVC-related UEDVT[40]. Cancer patients have also been reported to have a 2-3 times higher risk of recurrent thrombosis[41].

Persistent obstruction and valvular insufficiency in patients with UEDVT may lead to PTS in around 4% to 32% of cases[28,29]. The incidence of PTS is significantly lower than that in patients with LEDVT, in whom it may develop in up to 50% of cases[34]. PTS has been reported to be more common in primary UEDVT than secondary[40]. It is characterized by persistent pain, oedema, and functional limitation of the affected arm. However, compression therapy, as used in managing LEDVT, is not recommended for PTS of the arm because of lack of evidence of efficacy given the different underlying pathophysiology. Hence, management is mainly supportive[28].

PROGNOSIS

The reported long-term mortality, two and 12 mo, after diagnosis of UEDVT is 30 and 40%, respectively [42,43]. However, these studies included patients with significant comorbidities, and mortality attributable to UEDVT could not be determined. The prognosis depends on the cause of UEDVT and underlying comorbidities. A systematic review of 45 studies with 4580 patients compared clinical courses and outcomes of UEDVT in patients with and without cancer. Overall, the one-year mortality rate in prospective trials was 24%, whereas, in retrospective studies, it was 35%. However, patients with cancer had an 8-fold higher risk of death than non-cancer patients. Patients with PSS are generally younger and have good functional status without many comorbidities. Hence, they have good overall outcomes and longer life expectancies.

CONCLUSION

UEDVT is an under-recognized and under-diagnosed complication in critically ill patients. Its incidence may be attributable to the increasing incidence of cancer, improving life expectancy, and increasing use of intravenous devices and catheters in hospitalized patients. Any unilateral oedema or erythema in an ICU patient with underlying risk factors should raise a concern, and further workup should be initiated. Bedside ultrasound with Doppler may help make a rapid diagnosis and contrast venography or CT/MRI venography is rarely indicated. Most patients can be managed with anticoagulant therapy, which is safe and effective. However, many patients may develop complications like bleeding, PTS and PE, so they should be monitored closely. The long-term outcome of these patients may depend on the cause of UEDVT and the underlying comorbidities. Early recognition and prompt therapy may help achieve favorable outcomes and prevent complications.

FOOTNOTES

Author contributions: Singh O and Juneja D performed all the writing, researched the project, prepared the tables, performed data accusation, and reviewed the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Lee JA**, Zierler BK, Zierler RE. The risk factors and clinical outcomes of upper extremity deep vein thrombosis. *Vasc Endovascular Surg* 2012; **46**: 139-144 [PMID: 22328450 DOI: 10.1177/1538574411432145]
2 **Khan O**, Marmaro A, Cohen DA. A review of upper extremity deep vein thrombosis. *Postgrad Med* 2021; **133**: 3-10 [PMID: 33618595 DOI: 10.1080/00325481.2021.1892390]
3 **Engelberger RP**, Kucher N. Management of deep vein thrombosis of the upper extremity. *Circulation* 2012; **126**: 768-773 [PMID: 22869858 DOI: 10.1161/CIRCULATIONAHA.111.051276]
4 **Isma N**, Svensson PJ, Gottsäter A, Lindblad B. Upper extremity deep venous thrombosis in the population-based Malmö thrombophilia study (MATS). Epidemiology, risk factors, recurrence risk, and mortality. *Thromb Res* 2010; **125**: e335-e338 [PMID: 20406709 DOI: 10.1016/j.thromres.2010.03.005]
5 **Grant JD**, Stevens SM, Woller SC, Lee EW, Kee ST, Liu DM, Lohan DG, Elliott CG. Diagnosis and management of upper extremity deep-vein thrombosis in adults. *Thromb Haemost* 2012; **108**: 1097-1108 [PMID: 23093319 DOI: 10.1160/TH12-05-0352]
6 **Blom JW**, Doggen CJ, Osanto S, Rosendaal FR. Old and new risk factors for upper extremity deep venous thrombosis. *J Thromb Haemost* 2005; **3**: 2471-2478 [PMID: 16241945 DOI: 10.1111/j.1538-7836.2005.01625.x]
7 **Malinoski DJ**, Ewing T, Patel MS, Nguyen D, Le T, Cui E, Kong A, Dolich M, Barrios C, Cinat M, Lekawa M, Salim A. The natural history of upper extremity deep venous thromboses in critically ill surgical and trauma patients: what is the role of anticoagulation? *J Trauma* 2011; **71**: 316-21; discussion 321 [PMID: 21825933 DOI: 10.1097/TA.0b013e318222f3f4]
8 **Winters JP**, Callas PW, Cushman M, Repp AB, Zakai NA. Central venous catheters and upper extremity deep vein thrombosis in medical inpatients: the Medical Inpatients and Thrombosis (MITH) Study. *J Thromb Haemost* 2015; **13**: 2155-2160 [PMID: 26340226 DOI: 10.1111/jth.13131]
9 **Bernardi E**, Pesavento R, Prandoni P. Upper extremity deep venous thrombosis. *Semin Thromb Hemost* 2006; **32**: 729-736 [PMID: 17024601 DOI: 10.1055/s-2006-951458]
10 **Czihal M**, Hoffmann U. Upper extremity deep venous thrombosis. *Vasc Med* 2011; **16**: 191-202 [PMID: 21343260 DOI: 10.1177/1358863X10395657]
11 **Joffe HV**, Goldhaber SZ. Upper-extremity deep vein thrombosis. *Circulation* 2002; **106**: 1874-1880 [PMID: 12356644 DOI: 10.1161/01.cir.0000031705.57473.1c]
12 **Zell L**, Kindermann W, Marschall F, Scheffler P, Gross J, Buchter A. Paget-Schroetter syndrome in sports activities--case study and literature review. *Angiology* 2001; **52**: 337-342 [PMID: 11386385 DOI: 10.1177/000331970105200507]
13 **Urschel HC Jr**, Patel AN. Surgery remains the most effective treatment for Paget-Schroetter syndrome: 50 years' experience. *Ann Thorac Surg* 2008; **86**: 254-60; discussion 260 [PMID: 18573433 DOI: 10.1016/j.athoracsur.2008.03.021]
14 **Girolami A**, Prandoni P, Zanon E, Bagatella P, Girolami B. Venous thromboses of upper limbs are more frequently associated with occult cancer as compared with those of lower limbs. *Blood Coagul Fibrinolysis* 1999; **10**: 455-457 [PMID: 10636455 DOI: 10.1097/00001721-199912000-00001]
15 **Héron E**, Lozinguez O, Alhenc-Gelas M, Emmerich J, Fiessinger JN. Hypercoagulable states in primary upper-extremity deep vein thrombosis. *Arch Intern Med* 2000; **160**: 382-386 [PMID: 10668841 DOI: 10.1001/archinte.160.3.382]
16 **Joffe HV**, Kucher N, Tapson VF, Goldhaber SZ; Deep Vein Thrombosis (DVT) FREE Steering Committee. Upper-extremity deep vein thrombosis: a prospective registry of 592 patients. *Circulation* 2004; **110**: 1605-1611 [PMID: 15353493 DOI: 10.1161/01.CIR.0000142289.94369.D7]
17 **Saber W**, Moua T, Williams EC, Verso M, Agnelli G, Couban S, Young A, De Cicco M, Biffi R, van Rooden CJ, Huisman MV, Fagnani D, Cimminiello C, Moia M, Magagnoli M, Povoski SP, Malak SF, Lee AY. Risk factors for catheter-related thrombosis (CRT) in cancer patients: a patient-level data (IPD) meta-analysis of clinical trials and prospective studies. *J Thromb Haemost* 2011; **9**: 312-319 [PMID: 21040443 DOI: 10.1111/j.1538-7836.2010.04126.x]

18 **Verso M**, Agnelli G, Kamphuisen PW, Ageno W, Bazzan M, Lazzaro A, Paoletti F, Paciaroni M, Mosca S, Bertoglio S. Risk factors for upper limb deep vein thrombosis associated with the use of central vein catheter in cancer patients. *Intern Emerg Med* 2008; **3**: 117-122 [PMID: 18317868 DOI: 10.1007/s11739-008-0125-3]

19 **Constans J**, Salmi LR, Sevestre-Pietri MA, Perusat S, Nguon M, Degeilh M, Labarere J, Gattolliat O, Boulon C, Laroche JP, Le Roux P, Pichot O, Quéré I, Conri C, Bosson JL. A clinical prediction score for upper extremity deep venous thrombosis. *Thromb Haemost* 2008; **99**: 202-207 [PMID: 18217155 DOI: 10.1160/TH07-08-0485]

20 **van Es N**, Bleker SM, Di Nisio M, Kleinjan A, Beyer-Westendorf J, Camporese G, Aggarwal A, Verhamme P, Righini M, Büller HR, Bossuyt PM. Improving the diagnostic management of upper extremity deep vein thrombosis. *J Thromb Haemost* 2017; **15**: 66-73 [PMID: 27732764 DOI: 10.1111/jth.13536]

21 **Merminod T**, Pellicciotta S, Bounameaux H. Limited usefulness of D-dimer in suspected deep vein thrombosis of the upper extremities. *Blood Coagul Fibrinolysis* 2006; **17**: 225-226 [PMID: 16575263 DOI: 10.1097/01.mbc.0000220248.04789.79]

22 **Kucher N**. Clinical practice. Deep-vein thrombosis of the upper extremities. *N Engl J Med* 2011; **364**: 861-869 [PMID: 21366477 DOI: 10.1056/NEJMcp1008740]

23 **Di Nisio M**, Van Sluis GL, Bossuyt PM, Büller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost* 2010; **8**: 684-692 [PMID: 20141579 DOI: 10.1111/j.1538-7836.2010.03771.x]

24 **Noyes AM**, Dickey J. The Arm is Not the Leg: Pathophysiology, Diagnosis, and Management of Upper Extremity Deep Vein Thrombosis. *R I Med J (2013)* 2017; **100**: 33-36 [PMID: 28459919]

25 **Baarslag HJ**, Van Beek EJ, Reekers JA. Magnetic resonance venography in consecutive patients with suspected deep vein thrombosis of the upper extremity: initial experience. *Acta Radiol* 2004; **45**: 38-43 [PMID: 15164777 DOI: 10.1080/02841850410003428]

26 **Bosch FTM**, Nisio MD, Büller HR, van Es N. Diagnostic and Therapeutic Management of Upper Extremity Deep Vein Thrombosis. *J Clin Med* 2020; **9** [PMID: 32630244 DOI: 10.3390/jcm9072069]

27 **Hendler MF**, Meschengieser SS, Blanco AN, Alberto MF, Salviú MJ, Gennari L, Lazzari MA. Primary upper-extremity deep vein thrombosis: high prevalence of thrombophilic defects. *Am J Hematol* 2004; **76**: 330-337 [PMID: 15282664 DOI: 10.1002/ajh.20131]

28 **Kearon C**, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e419S-e496S [PMID: 22315268 DOI: 10.1378/chest.11-2301]

29 **Key NS**, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, Wong SL, Balaban EP, Flowers CR, Francis CW, Gates LE, Kakkar AK, Levine MN, Liebman HA, Tempero MA, Lyman GH, Falanga A. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol* 2020; **38**: 496-520 [PMID: 31381464 DOI: 10.1200/JCO.19.01461]

30 **Davies GA**, Lazo-Langner A, Gandara E, Rodger M, Tagalakis V, Louzada M, Corpuz R, Kovacs MJ. A prospective study of Rivaroxaban for central venous catheter associated upper extremity deep vein thrombosis in cancer patients (Catheter 2). *Thromb Res* 2018; **162**: 88-92 [PMID: 28416213 DOI: 10.1016/j.thromres.2017.04.003]

31 National Comprehensive Cancer Network (NCCN) Guidelines 2020. Cancer-Associated Venous Thromboembolic Disease. [cited 15 December 2022]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf

32 **Bleker SM**, van Es N, Kleinjan A, Büller HR, Kamphuisen PW, Aggarwal A, Beyer-Westendorf J, Camporese G, Cosmi B, Gary T, Ghirarduzzi A, Kaasjager K, Lerede T, Marschang P, Meijer K, Otten HM, Porreca E, Righini M, Verhamme P, van Wissen S, Di Nisio M. Current management strategies and long-term clinical outcomes of upper extremity venous thrombosis. *J Thromb Haemost* 2016; **14**: 973-981 [PMID: 26866515 DOI: 10.1111/jth.13291]

33 **de Kleijn RJCMF**, Schropp L, Westerink J, de Borst GJ, Petri BJ. Timing of Thoracic Outlet Decompression after Thrombolysis for Primary Upper Extremity Deep Venous Thrombosis: A Systematic Review. *Ann Vasc Surg* 2020; **66**: 654-661 [PMID: 32035261 DOI: 10.1016/j.avsg.2020.01.083]

34 **Duijzer D**, de Winter MA, Nijkeuter M, Tuinenburg AE, Westerink J. Upper Extremity Deep Vein Thrombosis and Asymptomatic Vein Occlusion in Patients With Transvenous Leads: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med* 2021; **8**: 698336 [PMID: 34490367 DOI: 10.3389/fcvm.2021.698336]

35 **Kooij JD**, van der Zant FM, van Beek EJ, Reekers JA. Pulmonary embolism in deep venous thrombosis of the upper extremity: more often in catheter-related thrombosis. *Neth J Med* 1997; **50**: 238-242 [PMID: 9232088 DOI: 10.1016/s0300-2977(97)00020-x]

36 **Newton DH**, Monreal Bosch M, Amendola M, Wolfe L, Perez Ductor C, Lecumberri R, Levy MM; RIETE Investigators. Analysis of noncatheter-associated upper extremity deep venous thrombosis from the RIETE registry. *J Vasc Surg Venous Lymphat Disord* 2017; **5**: 18-24.e1 [PMID: 27987605 DOI: 10.1016/j.jvsv.2016.08.002]

37 **Prandoni P**, Polistena P, Bernardi E, Cogo A, Casara D, Verlato F, Angelini F, Simioni P, Signorini GP, Benedetti L, Girolami A. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. *Arch Intern Med* 1997; **157**: 57-62 [PMID: 8996041]

38 **Cote LP**, Greenberg S, Caprini JA, Tafur A, Choi C, Muñoz FJ, Skride A, Valero B, Porras JA, Ciammaichella M, Hernández-Blasco LM, Monreal M; RIETE Investigators. Comparisons Between Upper and Lower Extremity Deep Vein Thrombosis: A Review of the RIETE Registry. *Clin Appl Thromb Hemost* 2017; **23**: 748-754 [PMID: 27572888 DOI: 10.1177/1076029616663847]

39 **Yuen HLA**, Tan E, Tran H, Chunilal SD. Idiopathic upper extremity deep vein thrombosis: A systematic review. *Eur J Haematol* 2022; **109**: 542-558 [PMID: 36053912 DOI: 10.1111/ejh.13842]

40 **Thiyagarajah K**, Ellingwood L, Endres K, Hegazi A, Radford J, Iansavitchene A, Lazo-Langner A. Post-thrombotic syndrome and recurrent thromboembolism in patients with upper extremity deep vein thrombosis: A systematic review and meta-analysis. *Thromb Res* 2019; **174**: 34-39 [PMID: 30553163 DOI: 10.1016/j.thromres.2018.12.012]

41 **Bleker SM**, van Es N, van Gils L, Daams JG, Kleinjan A, Büller HR, Di Nisio M. Clinical course of upper extremity deep

vein thrombosis in patients with or without cancer: a systematic review. *Thromb Res* 2016; **140** Suppl 1: S81-S88 [PMID: 27067985 DOI: 10.1016/S0049-3848(16)30104-9]

42 **Martinelli I**, Battaglioli T, Bucciarelli P, Passamonti SM, Mannucci PM. Risk factors and recurrence rate of primary deep vein thrombosis of the upper extremities. *Circulation* 2004; **110**: 566-570 [PMID: 15262837 DOI: 10.1161/01.CIR.0000137123.55051.9B]

43 **Hingorani A**, Ascher E, Markevich N, Yorkovich W, Schutzer R, Mutyala M, Nahata S, Jacob T. Risk factors for mortality in patients with upper extremity and internal jugular deep venous thrombosis. *J Vasc Surg* 2005; **41**: 476-478 [PMID: 15838483 DOI: 10.1016/j.jvs.2004.12.038]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 June 9; 12(3): 139-152

DOI: 10.5492/wjccm.v12.i3.139

ISSN 2220-3141 (online)

MINIREVIEWS

Sepsis-induced mitochondrial dysfunction: A narrative review

Wagner Nedel, Caroline Deutschendorf, Luis Valmor Cruz Portela

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu LP, China; Zhong GQ, China

Received: January 20, 2023
Peer-review started: January 20, 2023
First decision: February 20, 2023
Revised: March 8, 2023
Accepted: April 14, 2023
Article in press: April 14, 2023
Published online: June 9, 2023

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Abstract

Sepsis represents a deranged and exaggerated systemic inflammatory response to infection and is associated with vascular and metabolic abnormalities that trigger systemic organic dysfunction. Mitochondrial function has been shown to be severely impaired during the early phase of critical illness, with a reduction in biogenesis, increased generation of reactive oxygen species and a decrease in adenosine triphosphate synthesis of up to 50%. Mitochondrial dysfunction can be assessed using mitochondrial DNA concentration and respirometry assays, particularly in peripheral mononuclear cells. Isolation of monocytes and lymphocytes seems to be the most promising strategy for measuring mitochondrial activity in clinical settings because of the ease of collection, sample processing, and clinical relevance of the association between metabolic alterations and deficient immune responses in mononuclear cells. Studies have reported alterations in these variables in patients with sepsis compared with healthy controls and non-septic patients. However, few studies have explored the association between mitochondrial dysfunction in immune mononuclear cells and unfavorable clinical outcomes. An improvement in mitochondrial parameters in sepsis could theoretically serve as a biomarker of clinical recovery and response to oxygen and vasopressor therapies as well as reveal unexplored pathophysiological mechanistic targets. These features highlight the need for further studies on mitochondrial metabolism in immune cells as a feasible tool to evaluate patients in intensive care settings. The evaluation of mitochondrial metabolism is a promising tool for the evaluation and management of critically ill patients, especially those with sepsis. In this article, we explore the pathophysiological

aspects, main methods of measurement, and the main studies in this field.

Key Words: Sepsis; Mitochondria; Mitochondrial dysfunction; Oxidative phosphorylation; Inflammation; Respirometry

Core Tip: The evaluation of mitochondrial metabolism is a promising tool for the evaluation and management of critically ill patients, particularly those with sepsis. In this article, we explore the pathophysiological aspects, main methods of measurement, and main studies in this field.

Citation: Nedel W, Deutschendorf C, Portela LVC. Sepsis-induced mitochondrial dysfunction: A narrative review. *World J Crit Care Med* 2023; 12(3): 139-152
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/139.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.139

INTRODUCTION

Sepsis is a major health problem worldwide and can be characterized by a dysregulated host response to infection[1-3]. Particularly, an imbalanced systemic inflammatory response to infection contribute to the clinical progress to multi-organ dysfunction[2,4]. There is a great effort in the recognition and prompt treatment of sepsis, especially with regard to early antibiotic administration, hemodynamic resuscitation, and evacuation of septic foci[1]. The ultimate cause of death in patients with sepsis, however, remains unclear. Infections usually are eradicated through an intense, but localized, inflammatory response. Nonetheless, fatal infections are characterized by an inability to resolve the inflammatory response because cytokines released into the systemic circulation, activates inflammatory cells in remote locations[5]. This response leads to organ injury and dysfunction, which cannot be completely explained by a decrease in tissue oxygenation due to an impairment of blood flow[2,4,5] but likely to problems in oxygen utilization.

Mitochondria is a highly specialized organelle that is considered the power plant of cells thus supporting energy in the form of adenosine triphosphate (ATP) according to functional demands[6]. In the blood, except for erythrocytes, all cell types possess mitochondria which imply they are dependent on oxidative metabolism. Remarkably, mitochondria tightly connect ATP biosynthesis with oxygen consumption, and even minor changes in mitochondrial functional integrity affect many aspects of cellular homeostasis. Although, the main proposed function of mitochondria is to generate ATP *via* oxidative phosphorylation (OXPHOS) of adenosine diphosphate (ADP), additional functions include generation and detoxification of reactive oxygen species (ROS), calcium homeostasis, involvement in apoptosis, synthesis and catabolism of metabolites, and transport of organelles within the cell[6,7]. Any alteration in one of these processes can be defined as mitochondrial dysfunction[8]. Actually, we know that impaired mitochondrial metabolism is an important mechanism that leads to organ dysfunction[2,5]. In acute diseases, such as sepsis, the measurement of mitochondrial metabolism, through cellular respiration, has the potential to identify those patients at risk of progressing in their organ failures. In addition, it can potentially help in monitoring the therapeutic response of these patients[6,9].

Considering that mitochondria interact with various other pathways involved in inflammation, Ca^{2+} balance, redox signaling, and apoptosis, it can be assumed that mitochondria are fundamental in cell survival and death[10]. Mitochondrial metabolism has been shown to be severely impaired during the early phase of an acute disease, with a reduction in biogenesis, increased generation of ROS, and a decrease in ATP synthesis[11,12]. The presence of an impaired mitochondrial metabolism is associated with the presence of a multiple organ failure syndrome, highlighting mitochondrial components as potential targets for therapeutic strategies[4,11,13]. There has been an increased interest in this field, with new studies exploring mitochondrial impairment and organ dysfunction and their relationship with prognosis in sepsis[14-17].

The main objective of this review is analyze the current state of the art in this field, explore potential methods for assessing mitochondrial metabolism in intensive care settings, and explore future perspectives on mitochondrial metabolism as a biomarker of clinical outcomes in sepsis.

PHYSIOPATHOLOGY

ATP is produced by mitochondria through OXPHOS by F1Fo-ATP synthase. ATP is generated to a greater extent by the oxidation of metabolic substrates in the tricarboxylic acid cycle leading to reduction of the electron acceptors NAD^+ and FAD to nicotinamide adenine dinucleotide (NADH) and 1,5-dihydroflavin adenine dinucleotide (FADH2)[18]. Both NADH and FADH2 are subsequently oxidized in the electron transport system of mitochondria. The electron transport chain is composed by enzyme complexes I to IV and the transporters ubiquinone and cytochrome c. With the electrons movement across the respiratory chain, protons are pumped across the inner mitochondrial membrane, generating an electrical potential. This proton-motive force provides the energy for F1Fo-ATP synthase, as known as Complex V, to phosphorylate ADP to ATP (Figure 1). This mechanism is favored by the electrochemical gradient produced by the proton motive force. Oxygen is the terminal electron acceptor of the chain in Complex IV and is reduced to water[19]. An incomplete reduction of oxygen increases superoxide radical production in Complex III and at Complex I. As part of this process, ROS are generated as by-products of the incomplete four-electron reduction of molecular oxygen to water[20,21].

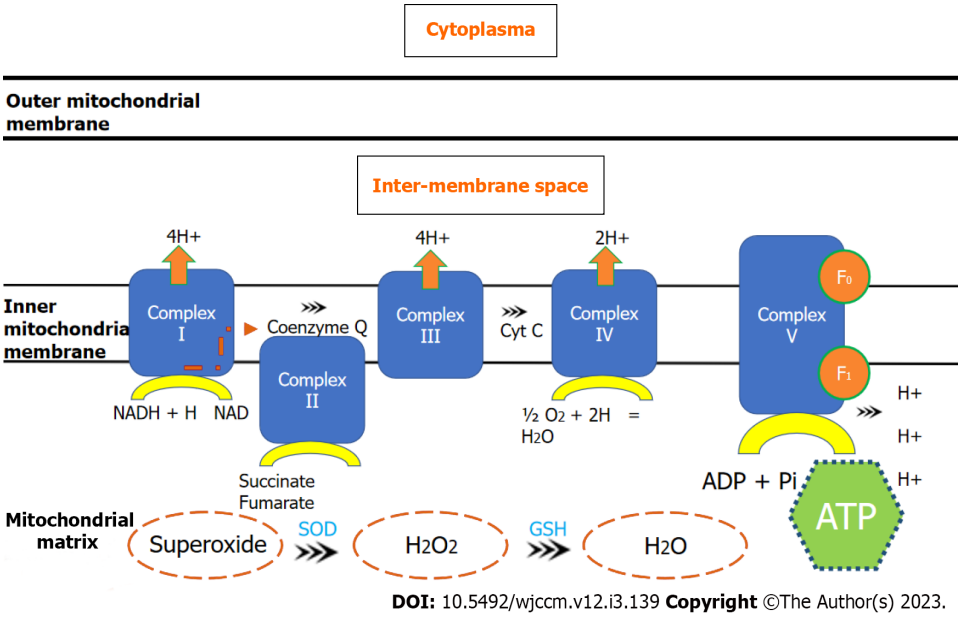
Under physiological conditions, mitochondria consume approximately 90% of the cellular O_2; however, 1%-4% of the respiratory chain reactions lead to a leak of electrons that directly react with O_2 to form O_2(*-), which can oxidize lipids, DNA, or proteins[22]. To avoid self-damage, mitochondria have intrinsic defense mechanisms that protect against ROS-induced damage through a large array of antioxidants[12]. In sepsis, not only ROS are generated, but also reactive nitrogen species (RNS), nitric oxide, and peroxynitrite[7,20,21]. Enzymatic defenses, such as the superoxide dismutase 2 (SOD2), convert O_2(*-) into hydrogen peroxide (H_2O_2), which can then be detoxified to water by catalase or selenium-containing glutathione peroxidase[23,24]. SOD2 expression is higher in survivors of critical illness[22]. Glutathione and Coenzyme Q10 (CoQ10) also have an important mitochondrial antioxidant function. CoQ10 Levels are lower in sepsis, suggesting a potential role in mitochondrial dysfunction[25].

Mitochondria are also essential for other cellular functions, such as calcium homeostasis, apoptosis, autophagy, and cellular signaling[6,9,12]. Mitochondrial DNA (mtDNA) is susceptible to mutations and deletions due to ROS increased levels and requires a set of self-regulated repair mechanisms[6]. mtDNA damage resulting from this phenomenon is associated with reduced mitochondrial respiratory capacity, which are potentially irreversible, depending on the intensity of oxidant "attack"[23]. Mitochondrial function is maintained by an equilibrium between fission, fusion, biogenesis, and autophagy[26]. In the case of an impairment in mitochondrial metabolism, various signaling routes allow an interaction between the mitochondria and nucleus, triggering mitochondrial biogenesis[10]. Defective mitochondria can become toxic by excessive ROS production, that can lead to apoptosis. Autophagy compensates for nutrient depletion or copes with cellular stress by recycling cellular components, to produce amino acids and fatty acids that can be metabolized and used in OXPHOS[27]. Despite being important for critical illness recovery, excessive induction of autophagy can trigger apoptosis[28]. ROS is one of some signaling pathways that regulate autophagy, and, since mitochondria are the primary source of ROS, mitochondria themselves play a key role in regulating autophagy[10]. Disturbances in mitochondrial function leading to impaired ATP biosynthesis, increased ROS production, and oxidative stress are associated with skeletal muscle damage, which correlates with septic shock severity and is associated with impaired clinical outcomes[18].

Many inflammatory mediators are linked to the altered mitochondrial metabolism. Tumoral necrosis factor-alpha (TNF-α) is a major interleukin that participates in the host response to sepsis and is capable of causing mitochondrial impairment[29]. TNF-α binds to several TNF receptors, ultimately promoting the intracellular release of ceramides and production of ROS, which may lead to mitochondrial dysfunction. TNF receptor activation promotes pro-inflammatory responses in polymorphonuclear leukocytes and monocytes, that induce ROS formation, leading to mtDNA damage and inhibition of mitochondrial metabolism in these cells[30]. Inhibition of mitochondrial complexes causes deviation of electrons, also producing even more ROS. These phenomena can lead to an imbalance between ROS production and mitochondrial antioxidant capacity, through manganese superoxide dismutase and glutathione reductase. This imbalance can trigger mitochondrial uncoupling related to the opening of mitochondrial permeability transition pores (PTP)[31]. The resulting mitochondrial permeability transition leads to dissolution of the electrochemical gradient required to form ATP, and these dysfunctional mitochondria are targeted for removal *via* autophagy. The induction of mitochondrial PTP win this context can promote apoptosis. Therefore, the pro-inflammatory activity in sepsis, especially in its initial phase, can lead to both a reduction in mitochondrial mass and a decrease in its function.

MECHANISMS OF MITOCHONDRIAL DYSFUNCTION

Hypoxia has been assumed to be the main causative agent of mitochondrial dysfunction[32]. However, it was later shown that tissue oxygen levels are normal or even elevated in sepsis[33]. Instead of a lower availability of oxygen, there is a lower use of it in septic patients[24]. Thus, OXPHOS dysfunction explain the inability to maintain ATP levels in this context, leading to increased glycolysis and increased



DOI: 10.5492/wjccm.v12.i3.139

Figure 1 Electron transport chain through mitocondrial complexes and oxidative phosphorylation. ADP: Adenosine diphosphtate; ATP: Adenosine triphosphate; Cyt c: Cytochrome c; GSH: Gluthatione synthetase; NAD: Nicotinamide adenine dinucleotide; NADH: Nicotinamide adenine dinucleotide (reduced); SOD: Superoxide dismuthase.

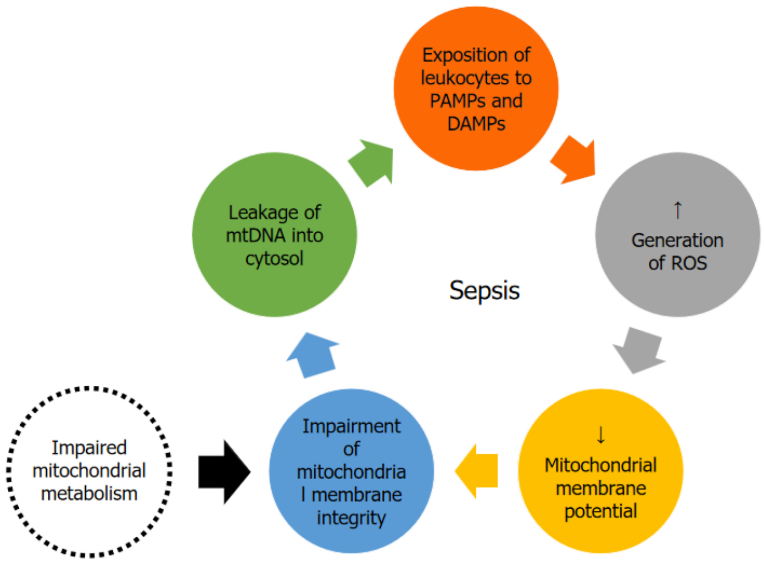
lactate levels[6]. This imbalance between ROS production and antioxidant capacity leads to an oxidative stress that damage the electron transport chain and mtDNA, creating a vicious circle of mitochondrial damage and ROS production[20]. ROS and calcium overload cause an increased membrane permeability, and mitochondrial products such as mtDNA leak into the circulation, acting as danger-associated molecular patterns and contributing to multiorganic failure[13] in a vicious cycle (Figure 2). This cascade can trigger cell apoptosis[7], a component of tissue damage and organ failure.

Changes in mitochondrial form and function in critical illnesses suggest that mitochondria try to rescue mechanisms and adapt to harmful environments. Mitochondrial fission and fusion are upregulated during critical illness, although it appears to be insufficient for restoring mitochondrial function[34]. Mitochondrial biogenesis was observed in skeletal muscle taken on days 1 to 2 in intensive care unit (ICU) survivors, but not in non-survivors[35]. During extreme conditions, such as refractory shock, mitochondrial damage is disseminated, causing the induction of mitochondrial PTP in many mitochondria and a great decrease in ATP production[36]. In contrast, a reduction in mitochondrial density was observed after the onset of sepsis, suggesting that although upregulated, biogenesis may be insufficient to maintain homeostasis[10].

Mitochondrial metabolism and inflammatory activity in sepsis-what is the relationship?

The hallmark of sepsis inflammatory response is an imbalance between a systemic inflammatory response and compensatory anti-inflammatory response[37,38]. The imbalance of pro- and anti-inflammatory responses often results in immunoparalysis among critically ill patients, making them more vulnerable to additional infections, and is linked to higher mortality rates[39]. Actually, the cause of immune dysfunction is matter of debate[38], and immune response is dependent of metabolic pathways [40], that is known as "immunometabolism". Mitochondria are a hub of the immune system, playing a crucial role in regulating the function of immune cells and shaping and modulating the response of the immune system to infection[7]. Evidence suggests that leukocytes from critically ill patients display mitochondrial dysfunction, which is thought to be the root cause of immunoparalysis and could be responsible for the onset of organ dysfunction[41,42]. Moreover, the recovery of mitochondrial function is associated with improved recovery in critically ill patients[14]. These changes are mostly detected in lymphocytes, monocytes, and macrophages[43].

Lymphocytes respond to cytokine stimuli induced by monocyte-macrophages, dendritic cells, and neutrophils, which are responsible for the innate immune response. Activated phagocytic cells, such as monocytes and macrophages, release the proinflammatory cytokines interleukin-1 (IL-1) and IL-6[44]. This phenomenon has been associated with energy deprivation[45]. Lymphocytes also attenuate the potentially harmful effects of the proinflammatory response, and this modulation of the immune response has a major impact on prognosis in septic patients[46]. On the other hand, IL-10 plays a major role in modulating the immune system by inhibiting monocyte-macrophage activation and suppressing the production of TNF-α, IL-1, and interferon-gamma (IFN-γ) from lymphocytes acting at the level of accessory cells[47]. In addition to cytokines, Krebs cycle intermediates, such as citrate, succinate, and itaconate, can activate pro-inflammatory gene expression[48]. Metabolites from the Krebs cycle impact



DOI: 10.5492/wjccm.v12.i3.139

Figure 2 Mitochondrial DNA damage as a potential trigger for the inflammatory response. DAMP: Damage associated molecular patterns; mtDNA: Mitochondrial deoxyribonucleic acid; PAMP: Pathogen associated molecular patterns; ROS: Reactive oxygen species.

the reprogramming of macrophages from the M1 phenotype (pro-inflammatory) to the M2 phenotype (anti-inflammatory). M1 macrophages have impaired OXPHOS, and M2 macrophages have an intact Krebs cycle, with OXPHOS as the main source of ATP generation[43].

Two major pathways are implicated in this interaction between mitochondrial function and inflammatory responses. The mammalian target of rapamycin (mTOR) pathway plays a pivotal role in metabolic regulation by modulating glycolysis. Furthermore, metabolic reprogramming and a transition to glycolysis for energy production in $CD4^+$ and $CD8^+$ T cells are also induced by the activation of mTOR and OXPHOS[30]. The nuclear factor kappabeta (NF-κβ) is a stress-induced pathway (*i.e.*, tissue damage, cytokine, and PAMPs release) that promotes the expression of target genes involved in the immune response. Upon activation of the NF-κβ pathway and subsequent induction of cytokine expression, macrophages undergo differentiation into either M1 or M2 subtypes, contingent on the local cytokine milieu present at the site of infection. IFN-γ typically drives the differentiation of M1 macrophages, which in turn produce pro-inflammatory cytokines. Conversely, M2 cells refer to macrophages exposed to immune complexes, IL-4, IL-13, and IL-10[30].

MEASUREMENT OF MITOCHONDRIAL DYSFUNCTION

Regrettably, it is currently impractical to perform a thorough and accurate real-time analysis of the modified cells and tissues within malfunctioning organs of living human patients in a hospital setting. Therefore, mechanisms must be inferred from tissue specimens obtained from nonvital organs (*e.g.*, blood, skeletal muscle) or from postmortem examinations. In postmortem studies, septic patients exhibit mild to moderate mitochondrial swelling and autophagocytosis, with minimal cell death or indications of permanent damage, such as tissue fibrosis[49].

Mitochondrial biogenesis

The process of mitochondrial biogenesis encompasses the synthesis of mitochondrial proteins encoded by nuclear DNA, which are subsequently imported and integrated into the mitochondria. Additionally, biogenesis can also occur through mitochondrial DNA, which encodes 13 proteins primarily located within the OXPHOS pathway. In this way, biogenesis serves to replace damaged proteins and enhances the ability to generate energy if energy demand increases over time[4]. Increased mitochondrial biogenesis is detected in postmortem studies in critically ill patients, with increased expression of transcription factors[34]. A decrease in mitochondrial content has also been reported in the muscles of critically ill patients with sepsis-induced multiple organ failure[50]. Taken together, these data suggest that biogenesis activation may have a role in the recovery phase of critical illness[22], time when there was also an increase in RNA expression, participating in the restorative process[16]. These data point to compromised mitochondrial biogenesis in critically ill patients; and an activation of the biogenesis pathway may represent a key prognostic factor in critically ill patients, associated with recovering of the initial injury[22].

From this point of view, it seems reasonable to imagine that the dynamic processes of mitochondrial fusion and fission must change during acute inflammatory injury observed in sepsis. This activity can be measured by assessing the concentrations of mitochondrial fusion proteins (mitofusins 1 and 2, optic atrophy 1 protein) and mitochondrial fission proteins (dynamin-related protein 1 and fission 1 protein) [22]. Currently, adequate characterization in relation to the pro-fusion or mitochondrial fission profile in sepsis is merely speculative, lacking clinical studies that may show some signs regarding its *in vivo* effects.

Mitochondrial DNA

Mitochondria experience various morphological changes during fusion and fission events, which help to sustain a healthy mitochondrial population by facilitating mitochondrial DNA exchange, preserving mitochondrial DNA integrity, and regulating the size, quantity, distribution, and upkeep of OXPHOS capacity[22]. These morphological changes also play a crucial role in cell division and proliferation, as well as in the selective elimination of damaged or excess mitochondria through a process referred to as mitophagy[4]. Proteins that facilitate fusion events (such as mitofusin-2) and fission events (such as dynamin related protein-1) have been linked to changes in mitochondrial membrane potentials and diminished oxygen consumption[51]. Fission and fusion processes become more prevalent under stressful conditions and play a crucial role in eliminating damaged mitochondria and enhancing repair mechanisms. Currently, there is insufficient data regarding these mitochondrial dynamics in septic patients, and the data may vary based on the tissue type. From a hypothetical perspective, the balance of mitochondrial dynamics in septic patients may shift in favor of mitochondrial fusion, which could represent a cellular response aimed at improving mitochondrial function and decreasing oxidative stress[52].

However, mitochondrial DNA levels in the serum should be interpreted as a potential damage-associated molecular pattern, propagating an inflammatory response through interactions with the immune system[12,53]. Thus, mtDNA damage can lead to a pathological cycle, resulting in metabolic dysfunction, especially in white blood cells[54]. A reduction in mtDNA content in the peripheral blood, observed in the acute phase of sepsis, could be due to an increased concentration of neutrophils in the peripheral blood[55]. Therefore, it remains uncertain whether there is an interaction between DNA concentration and changes in mitochondrial function, especially in immune cells. Mitochondria contain their own DNA, and the depletion of mtDNA in an injury process may theoretically cause a respiratory chain defect and compromise ATP synthesis[23,55].

Qualitative measurements of mitochondrial metabolism

In addition to changes in mitochondrial mass, the quality of mitochondrial function and a shift towards glycolytic pathways are regulated by several hormones, enzymes, and regulatory pathways within cells. Reactive derivatives of nitric oxide and superoxide anion (such as peroxynitrite), which cause oxidative stress, promote glycolysis by activating the rate-limiting step of the pentose pathway, glucose-6-phosphate dehydrogenase. The pentose pathway results in the formation of NADPH relative to NADH. While NADH is the substrate for mitochondrial OXPHOS of high-energy phosphates, NADPH is crucial for the formation and repair of proteins, DNA, and lipids. Thus, by diverting glycolytic intermediates from the Krebs cycle to suppress aerobic mitochondrial respiration, cells and tissues transition to a state of decreased oxygen consumption and ATP production. This phenomenon is commonly referred to as the "Warburg effect", particularly in the context of cancer[41]. In this context, cells are less dependent on oxidative metabolism, thus reducing oxidative stress and promoting the formation of reducing equivalents (*e.g.*, lactic acid and NADPH) that induce cell repair[56]. The Warburg effect and related mediators, such as HIF-1α, are induced under conditions that model sepsis, confer cytoprotection to vital organs, and inhibit inflammation under conditions of acute cell stress[57]. However, the HIF-1α activation in immune cells could perpetuate the activation of the pro-inflammatory pathway[58].

The proton pumps of the electron transport chain, in conjunction with F1Fo-ATP synthase, establish a proton gradient across the inner membrane, generating both an electrochemical potential (proton motive force, pmf, in mV) and a flux of protons (proton current in nmol of protons/min). The mitochondrial membrane potential is a critical component of healthy mitochondrial metabolism and contributes to determining the pmf[8].

Reductions in both the expression and activity of complexes I, II, III, and IV have been reported in critically ill patients[14,22]. However, it is still doubtful whether these alterations are determinants of the patient's prognosis, or if they are just epiphenomena in the acute context of critical illness. However, they are useful and commonly used measurements to assess mitochondrial activity[35,59-61], especially when normalized by enzymatic activity, protein, or DNA concentration.

Respirometry

Measurement of mitochondrial respiration is a cost-effective and time-efficient method compared to traditional methods of assessing mitochondrial function in biopsies, making it readily available for use. Advanced instruments equipped with highly sensitive micro-cathode oxygen electrodes enable high-resolution measurements of mitochondrial respiration and can be utilized in acute care settings.

Mitochondrial respiration can be quantified by performing substrate-uncoupler-inhibitor titrations, commonly known as the SUIT protocol. This protocol involves titration with various combinations of substrates, uncouplers, and inhibitors to assess mitochondrial respiratory function[9]. This protocol allows the study of complex interactions of coupling and substrate control in a single assay, measuring multiple aspects of mitochondrial physiology[62].

Respirometry enables the real-time measurement of mitochondrial respiration, with key parameters obtainable through the use of established inhibitors and uncouplers that act as sensitive indicators of response to mitochondrial stress. Figure 3 depicts the mitochondrial respiration trace derived from the SUIT protocol, which was employed in the following procedures[9,62]: (1) Routine respiration: Routine respiration also known as basal respiration, measures the oxygen consumption resulting from ATP production and proton leak. This represents energy demand under steady-state conditions. Changes in routine respiration in patients with disease compared to controls may indicate altered mitochondrial function and should be interpreted in the context of the following mitochondrial parameters; (2) proton leak: After measuring routine respiration, cells are exposed to oligomycin, an inhibitor of complex V. The remaining mitochondrial respiration after the addition of oligomycin is attributable to proton leak. While some proton leaks are expected under physiological conditions, significant proton leak may indicate damage to the mitochondrial membrane and/or complex damage. The use of oligomycin also allows for the estimation of oxygen consumption secondary to ATP production, often referred to as ATP-linked respiration; (3) maximal respiration: The addition of a mitochondrial uncoupler, such as dinitrophenol or carbonyl cyanide-4-(trifluoromethoxy) phenylhydrazone, stimulates maximal respiration by mimicking the physiological energy demand, leading to an increase in oxygen consumption. The difference between maximal respiration and routine respiration represents the spare respiratory capacity (SRC) of the cell. SRC indicates the ability of the cell to respond to energetic stress and is a measure of a cell's fitness. A decrease in SRC may limit the cell's ability to handle stressors, resulting in mitochondrial dysfunction; and (4) residual oxygen consumption: The addition of mitochondrial inhibitors, such as the combination of rotenone (complex I) and antimycin (complex III), completely inhibits electron transport system. The remaining oxygen is consumed by non-mitochondrial respiration in the form of oxidases and other cellular enzymes that use oxygen. Residual oxygen consumption may increase in the presence of a stress response.

Under normal conditions with excess ADP and oxygen, mitochondrial respiration occurs rapidly, known as state 3 respiration. Conversely, when ADP is fully consumed, state 4 respiration occurs, which is significantly slower. This state 4 respiration can be induced by "uncoupling" oxygen consumption from OXPHOS, leading to proton leakage back into the mitochondrial matrix without the production of cellular energy. One of the most promising indicators of mitochondrial function is the biochemical coupling efficiency (BCE), which is calculated as the quotient between OXPHOS and proton leak. BCE reflects the true effectiveness of mitochondria in utilizing oxygen for ATP production[62]. It is a useful way to gain more insight into the site of the dysfunction, namely, respiratory control decreases because of dysfunction in localized sites of substrate oxidation, ATP synthesis, proton conductance, or F1Fo-ATP synthase[8].

Although we understand that small clinical centers may have limited access to equipment for measuring real-time mitochondrial respiratory rates, this limitation could be easily overcome using simpler biochemical colorimetric methods that still maintain a reasonable level of sensitivity, the time to assay is usually short, and easy to implement in the laboratory hospital routine. For instance, the measurements of enzymatic activity of succinate dehydrogenase: Complex II (succinate: DCIP-oxidoreductase), complex, and complex V are routinely performed in research laboratories, and at the current state require standardization as a step forward to reach clinical settings[63,64]. However, the aforementioned colorimetric methods restrict the evaluation of metabolic activity to one complex each time, whereas in mitochondrial respirometry assays the metabolic activity of complexes can be assayed both, individually or more than one at the same time.

Which cells are ideal for measuring the mitochondrial activity? And what is the most suitable method?

Although it is logical that dysfunction in mitochondrial metabolism leads to a certain degree of organ failure, its measurement is often not feasible, because the ethical questions, costs, and viability of obtaining adequate mitochondrial samples from vital organs in critically ill patients[61]. Therefore, it is feasible to assess mitochondrial dysfunction in cells that are easy to collect, especially those that may reflect the "systemic" effect of sepsis on the body. Peripheral blood cells have been used to access bioenergetic functions in translational research. Peripheral blood mononuclear cells (PBMCs) are mitochondria-rich with high rates of respiration[16]; therefore, they are prime candidates in circulating blood to provide reliable estimation of global oxidative metabolism, particularly the metabolism linked to immune response. Lymphocytes comprise the majority of PBMCs and are traditionally used to measure defects in mitochondrial OXPHOS[30]. Exhaustion of lymphocytes, especially T cells, leads to an increased risk of secondary infections, which is correlated with mortality[65]. Circulating immune cells play an important role in the pathophysiology of sepsis because their activation may remotely induce inflammation in non-infected organs[66]. The measurement of mitochondrial respiration in

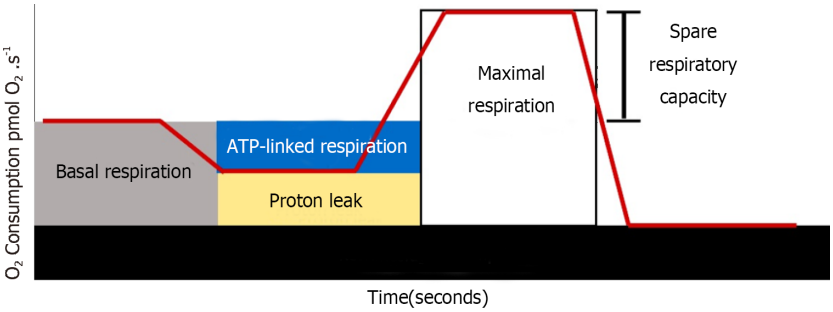


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Figure 3 Example of a respirometry assay. ATP: Adenosine triphosphate.

PBMCs of septic patients has the potential to identify those at risk of negative outcomes, and also can monitor the clinical course and response to treatment, making it a useful marker for acute care settings [9]. Thus, it is a candidate biomarker in sepsis.

In addition, this approach allows us to unravel mechanist readouts associated with impaired metabolism that follow this syndrome and also challenges how or whether this could be improved by therapeutic intervention. These primary observations collected from the literature are encouraging, and more clinical studies will help to advance methodological issues, clinical validation, and the level of reproducibility and sensitivity (Table 1).

SEPSIS AND MULTI-ORGANIC FAILURE

Various systemic inflammatory processes can exert different effects on mitochondria. In the early stages of sepsis, reduced perfusion resulting from intrinsic and extrinsic fluid losses, decreased intake, myocardial depression, microcirculatory redistribution of blood flow, and loss of vascular tone, can lead to tissue hypoxia. This condition, characterized by insufficient oxygen levels at the mitochondrial level, impedes the ability of mitochondria to carry out OXPHOS, leading to a deficit in ATP production[12]. Although Complex IV exhibits distinctive enzyme properties that facilitate its functionality under hypoxic conditions, severely diminished oxygen concentrations may compromise ATP generation and activate cell death pathways, thereby adversely impacting cellular homeostasis[12,67,68]. Hormonal alterations in sepsis also affect mitochondrial function and efficiency. For example, thyroid hormones are believed to work predominantly through the modulation of mitochondrial activity[4,33]. Thirdly, genes that transcribe mitochondrial proteins are downregulated early in the inflammatory response. This was first recognized in human volunteers receiving endotoxins[69] and subsequently described in critically ill patients[35].

Impairment of mitochondrial metabolism in sepsis

Different studies, in different contexts, have evaluated mitochondrial activity in septic compared to nonseptic or control patients. Muscular cells are prone to impaired mitochondrial metabolism during critical illness[70] and are an important research field. Carré *et al*[35] used muscle tissue biopsies from critically ill patients, comparing them to those of controls subjected to hip surgery. They found a decrease in mitochondrial density in critically ill patients, without a decrease in Complex I and Complex IV activity. In a study evaluating patients with ICU-acquired weakness, comparing ATP synthesis in this population with metabolically healthy controls, ICU patients had an approximately 50% reduction in the ability of skeletal muscle to synthesize ATP in mitochondria, with a depletion of complex III and IV concentrations[71]. A similar loss of mitochondrial activity was detected in a previous study in a population with sepsis and multiorgan failure[72]. Complex I and complex IV activity was reduced in the intercostal and leg muscles, respectively, compared to controls.

Belikova demonstrated a higher baseline PBMC oxygen consumption and attenuated response to ADP stimulation in patients with sepsis than in healthy volunteers[66]. In blood mononuclear cells, Kraft *et al*[16] demonstrated an early sepsis-mediated disruption of mitochondrial quality control in septic patients, with a later activation of mitochondrial biogenesis in this population. These patients also showed increased mitochondrial damage (measured by mtDNA levels) during the early phase of sepsis management. In a cohort of septic and non-septic ICU patients with measurement of mitochondrial function in isolated lymphocytes, critically ill patients had increased mitochondrial oxygen consumption but no significant difference in mitochondrial membrane potential[17]. Jang *et al*[15] also found a lower routine, uncoupled Complex I, and maximal respiration in septic patients, when compared to controls in the early sepsis management. A respirometric study in PBMC developed by Japiassú *et al*[73] reported reduced F1Fo-ATP synthase activity, thereby reducing ATP production. This

Table 1 Different methods of mensuration of mitochondrial damage and recovery

Item	Description
Mitochondrial biogenesis	PPAR-γ coactivator 1-α, nuclear respiratory factor 1, mitochondrial transcription factor A. Material obtained from tissue biopsy or from peripheral PBMC
Mitochondrial content	Mitochondrial mass, concentration and area
Mitochondrial DNA content	PGC-1α, NRF-1, absolute DNA number of copies
Mitochondrial fusion	Mitofusins 1 and 2, optic atrophy 1 protein
Mitochondrial fission	Dynamin-related protein 1 and fission 1 protein

PPAR-γ: Peroxisome proliferator-activated receptor gamma; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator-1 alpha; NRF-1: Nuclear respiratory factor-1; PBMC: Peripheral blood mononuclear cells.

may contribute to the energetic failure reported in these cells during the course of septic insult. In addition, septic shock PBMC have reduced O_2 consumption, ADP-induced state 3 respiration, and respiratory control ratio compared to control PBMC. Inhibition of complexes I, III, and IV in PBMCs from septic patients compared with controls was also detected in another study[74]. In a pediatric population, Weiss *et al*[75] detected a decrease in spare respiratory capacity on days 1-2 of sepsis compared with controls. Spare respiratory capacity normalized on days 5-7. Patients with sepsis also had a higher ratio of leak to maximal respiration than controls, with normalization in the later phase of sepsis. Patients with sepsis did not show differences in basal or ATP-linked oxygen consumption or membrane potential.

In patients admitted to the emergency department with and without sepsis, Puskarich[76] did not find differences in plasma levels of cytochrome B, NADH, and Cox-III mtDNA between groups. Pyle *et al*[55], in a protocol that evaluated mononuclear cell mtDNA content, found that these levels were lower in patients with sepsis, with depletion of monocyte and lymphocyte mtDNA. Platelet studies have also evaluated mitochondrial metabolism in patients with sepsis. Sjövall *et al*[61] found an increase in state 3 and a decrease in RCR in patients with sepsis compared to controls during sequential evaluations in the first week of sepsis diagnosis. Additionally, patients with sepsis had increased rates of complex I and complex II respiration compared to controls. However, the mtDNA concentration did not differ between the platelets of patients with sepsis and controls.

Are mitochondrial metabolisms associated with mortality?

A criticism can be made of the differences in mitochondrial measurements between survivors and non-survivors observed in studies. Whether they are pathological or just another measure of disease severity requires further investigation[77]. In human subjects, a significant constraint of this research approach is the uncertainty surrounding whether mitochondria sourced from PBMCs, platelets, or muscle cells can accurately serve as proxies for the mitochondria present in essential organs like the liver, kidneys, and heart[77]. The establishment of a workable, all-encompassing strategy to investigate the complete energy production pathway in human beings would signify a more significant achievement, as it would facilitate a deeper comprehension of the origin of lactate in distinct patients and across time, thereby enabling more targeted clinical trials for novel treatments for bioenergetic dysfunction.

Defects in leukocyte energy metabolism[78], particularly in T lymphocyte cells[79], are intrinsically associated with the state of immunoparalysis in sepsis. Metabolic events in the mitochondria of macrophages, dendritic cells, and T-lymphocytes have profound effects on immunity. When exposed to infectious injury, OXPHOS levels decrease, with a concomitant increase in glycolysis. An outcome of the reduced ATP production *via* OXPHOS is the redirection of mitochondria towards generating mitochondrial ROS, which function as signaling molecules essential for eliciting an appropriate immune response[54]. Therefore, mitochondrial respiration is essential for the functioning of these cells.

Despite the fact that the current knowledge suggests a potential role of mitochondrial metabolism impairment in septic patients (when compared with controls) with a potential impact on prognosis, the literature is quite heterogeneous with regard to the findings of mitochondrial dysfunction (Table 2). It is still necessary to define the most practical way of measuring, with the greatest clinical applicability, the greatest prognostic impact, and, above all, the most accurate in predicting the clinical course of the disease.

Are mitochondrial metabolisms associated with recovery?

Therefore, mitochondrial biogenesis is critical for recovery, and the recovery from organ dysfunction is preceded by an increased mitochondrial biogenesis[33]. In our study of patients with multi-organ failure in intensive care, we found that those who ultimately survived had higher levels of PGC-1α and better-preserved levels of Complex protein, along with a more robust antioxidant response (specifically, manganese superoxide) in the early stages of their disease progression[35]. The ability to clear damaged

Table 2 Studies that explored association of mitochondrial dysfunction and prognosis in sepsis

Ref.	*n* of critically ill septic patients	Mitochondrial measurement	Main findings (survivors *vs* nonsurvivors)
Belikova *et al*[66], 2007			
Brealey *et al* [18], 2003	28	ATP concentration, Complex I, II, and IV activities in biopsied muscle cells	Sepsis survivors had an increased level of ATP and Complex I and IV activity
Carré *et al* [35], 2010	16	Mitochondrial morphology (surface density and volume), RT-PCR of mitochondrial biogenesis factors and concentration of Complex I and Complex IV mitochondrial proteins and OXPHOS transcripts in muscle biopsy specimens	Nonsurvivors had an increased decline in mitochondrial surface density, with a similar mitochondrial volume in these groups; OXPHOS transcripts were more abundant in survivors; increased ATP content in survivors; no difference between groups in Complex I and Complex IV activity
Kraft *et al* [16], 2019	37	qRT-PCR for genes that regulate mitochondrial biogenesis in PBMCs	Increased genetic activation of mitochondrial biogenesis in day 3 compared with day 1; decrease in mtDNA in septic patients compared with controls, with a recovery on day 5; early activation of mitochondrial biogenesis by day 1 associated with ICU discharge; increased mRNA levels in survivors
Japiassú *et al*[73], 2011	20	Respirometry of PBMC evaluating state 3, 4 and respiratory control ratio	No difference in ADP-stimulated respiration in nonsurvivors, when compared with survivors
Nedel *et al* [14], 2021	90 patients	Respirometry of permeabilized lymphocytes	Improvement in Complex I, Complex II, basal and in BCE in day 3, compared with day 1, were associated with lower mortality. In multivariate analysis, BCE improvement was associated with lower 6-mo mortality
Puskarich *et al*[77], 2015	28 patients	Respirometry of platelets	Routine and state 3 respiration were significantly higher in non-survivors compared to survivors; state 4 respiration had a non-significant increase in non-survivors
Pyle *et al* [55], 2010	Not reported (147 patients, including septic)	mtDNA content from mononuclear cells	No relationship between mtDNA content and survival outcome at 180 d
Sjövall *et al* [61], 2010	18 patients	Respirometry of isolated platelets evaluating Complex I, state 3, 4 and respiratory control ratio	Non-survivors had an increased Complex I, Complex II, state 3 respiration and an increased respiratory control ratio at day 6-7 of sepsis when compared with survivors
Sjövall *et al* [82], 2013	20 patients	Respirometry of permeabilized peripheral blood immune cells	Survivors and non-survivors at 90 d after sepsis did not have difference in Complex I plus Complex II respiration normalized to citrate synthase, mtDNA, and cytochrome c

ATP: Adenosine triphosphate; BCE: Biochemical coupling efficiency; ICU: Intensive care unit; qRT-PCR: Quantitative reverse transcriptase-polymerase chain reaction; mtDNA: Mitochondrion desoxyribonucleic acid; OXPHOS: Oxidative phosphorylation; PBMC: Peripheral blood mononuclear cells; ADP: Adenosine diphosphtate.

mitochondria is another important phenomenon[80]. Mitophagy (autophagic degradation) and mitoptosis (programmed destruction) are the processes by which cells deal with impaired mitochondria [12]. The efficiency of these processes may be an important contributing factor to the pathogenesis of various states of the disease. The process of mitophagy entails the targeted sequestration and subsequent degradation of damaged mitochondria, which occurs prior to their ability to activate cell death pathways and potentially jeopardize the viability of the entire cell. Thus, mitophagy operates as an initial protective response. Conversely, heightened levels of oxidative stress and apoptotic proteases can impede the function of mitophagy and stimulate additional inflammatory responses[81].

CONCLUSION

Alterations caused by acute inflammatory conditions, such as sepsis, is associated with impaired function of mitochondrial components including protein content, mtDNA concentration, oxidative complexes activity, and F1Fo-ATP synthase. Often, these alterations are associated with clinical outcomes. Given these features mitochondria deserve to be better explored regarding its role as potential biomarker in prognosis, sepsis rehabilitation, and its association with different spectrum of organ failure.

FOOTNOTES

Author contributions: Nedel W contributed to research, wrote the manuscript, reviewed the final version, and made the graphs and figures; Deutschendorf C contributed to write the manuscript and reviewed the final version; Portela LVC contributed to write the manuscript, reviewed the final version.

Supported by the Fundação de Amparo a Pesquisa do Estado do Rio Grande do Sul, No. 1010267.

Conflict-of-interest statement: The authors state that there was no conflict of interest.

Country/Territory of origin: Brazil

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S-Editor: Chen YL
L-Editor: A
P-Editor: Xu ZH

REFERENCES

1 **Evans L**, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med* 2021; **49**: e1063-e1143 [PMID: 34605781 DOI: 10.1097/CCM.0000000000005337]

2 **Cecconi M**, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *Lancet* 2018; **392**: 75-87 [PMID: 29937192 DOI: 10.1016/S0140-6736(18)30696-2]

3 **Angus DC**, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013; **369**: 840-851 [PMID: 23984731 DOI: 10.1056/NEJMra1208623]

4 **Singer M**. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. *Virulence* 2014; **5**: 66-72 [PMID: 24185508 DOI: 10.4161/viru.26907]

5 **Leite HP**, de Lima LF. Metabolic resuscitation in sepsis: a necessary step beyond the hemodynamic? *J Thorac Dis* 2016; **8**: E552-E557 [PMID: 27501325 DOI: 10.21037/jtd.2016.05.37]

6 **Supinski GS**, Schroder EA, Callahan LA. Mitochondria and Critical Illness. *Chest* 2020; **157**: 310-322 [PMID: 31494084 DOI: 10.1016/j.chest.2019.08.2182]

7 **Arulkumaran N**, Deutschman CS, Pinsky MR, Zuckerbraun B, Schumacker PT, Gomez H, Gomez A, Murray P, Kellum JA; ADQI XIV Workgroup. MITOCHONDRIAL FUNCTION IN SEPSIS. *Shock* 2016; **45**: 271-281 [PMID: 26871665 DOI: 10.1097/SHK.0000000000000463]

8 **Brand MD**, Nicholls DG. Assessing mitochondrial dysfunction in cells. *Biochem J* 2011; **435**: 297-312 [PMID: 21726199 DOI: 10.1042/BJ20110162]

9 **Jang DH**, Greenwood JC, Spyres MB, Eckmann DM. Measurement of Mitochondrial Respiration and Motility in Acute Care: Sepsis, Trauma, and Poisoning. *J Intensive Care Med* 2017; **32**: 86-94 [PMID: 27443317 DOI: 10.1177/0885066616658449]

10 **Moonen HPFX**, Van Zanten ARH. Mitochondrial dysfunction in critical illness during acute metabolic stress and convalescence: consequences for nutrition therapy. *Curr Opin Crit Care* 2020; **26**: 346-354 [PMID: 32487844 DOI: 10.1097/MCC.0000000000000741]

11 **Maestraggi Q**, Lebas B, Clere-Jehl R, Ludes PO, Chamaraux-Tran TN, Schneider F, Diemunsch P, Geny B, Pottecher J. Skeletal Muscle and Lymphocyte Mitochondrial Dysfunctions in Septic Shock Trigger ICU-Acquired Weakness and Sepsis-Induced Immunoparalysis. *Biomed Res Int* 2017; **2017**: 7897325 [PMID: 28589148 DOI: 10.1155/2017/7897325]

12 **Kozlov AV**, Bahrami S, Calzia E, Dungel P, Gille L, Kuznetsov AV, Troppmair J. Mitochondrial dysfunction and biogenesis: do ICU patients die from mitochondrial failure? *Ann Intensive Care* 2011; **1**: 41 [PMID: 21942988 DOI: 10.1186/2110-5820-1-41]

13 **McClave SA**, Wischmeyer PE, Miller KR, van Zanten ARH. Mitochondrial Dysfunction in Critical Illness: Implications for Nutritional Therapy. *Curr Nutr Rep* 2019; **8**: 363-373 [PMID: 31713718 DOI: 10.1007/s13668-019-00296-y]

14 **Nedel WL**, Kopczynski A, Rodolphi MS, Strogulski NR, De Bastiani M, Montes THM, Abruzzi J Jr, Galina A, Horvath TL, Portela LV. Mortality of septic shock patients is associated with impaired mitochondrial oxidative coupling efficiency in lymphocytes: a prospective cohort study. *Intensive Care Med Exp* 2021; **9**: 39 [PMID: 34304333 DOI:

10.1186/s40635-021-00404-9]
15 **Jang DH**, Orloski CJ, Owiredu S, Shofer FS, Greenwood JC, Eckmann DM. Alterations in Mitochondrial Function in Blood Cells Obtained From Patients With Sepsis Presenting to an Emergency Department. *Shock* 2019; **51**: 580-584 [PMID: 29905672 DOI: 10.1097/SHK.0000000000001208]
16 **Kraft BD**, Chen L, Suliman HB, Piantadosi CA, Welty-Wolf KE. Peripheral Blood Mononuclear Cells Demonstrate Mitochondrial Damage Clearance During Sepsis. *Crit Care Med* 2019; **47**: 651-658 [PMID: 30730439 DOI: 10.1097/CCM.0000000000003681]
17 **Ayala JC**, Grismaldo A, Aristizabal-Pachon AF, Mikhaylenko EV, Nikolenko VN, Mikhaleva LM, Somasundaram SG, Kirkland CE, Aliev G, Morales L. Mitochondrial Dysfunction in Intensive Care Unit Patients. *Curr Pharm Des* 2021; **27**: 3074-3081 [PMID: 33292115 DOI: 10.2174/1381612826666201207112931]
18 **Brealey D**, Singer M. Mitochondrial Dysfunction in Sepsis. *Curr Infect Dis Rep* 2003; **5**: 365-371 [PMID: 13678565 DOI: 10.1007/s11908-003-0015-9]
19 **Hsiao CP**, Hoppel C. Analyzing mitochondrial function in human peripheral blood mononuclear cells. *Anal Biochem* 2018; **549**: 12-20 [PMID: 29505781 DOI: 10.1016/j.ab.2018.03.003]
20 **Galley HF**. Oxidative stress and mitochondrial dysfunction in sepsis. *Br J Anaesth* 2011; **107**: 57-64 [PMID: 21596843 DOI: 10.1093/bja/aer093]
21 **Mantzarlis K**, Tsolaki V, Zakynthinos E. Role of Oxidative Stress and Mitochondrial Dysfunction in Sepsis and Potential Therapies. *Oxid Med Cell Longev* 2017; **2017**: 5985209 [PMID: 28904739 DOI: 10.1155/2017/5985209]
22 **Preau S**, Vodovar D, Jung B, Lancel S, Zafrani L, Flatres A, Oualha M, Voiriot G, Jouan Y, Joffre J, Uhel F, De Prost N, Silva S, Azabou E, Radermacher P. Energetic dysfunction in sepsis: a narrative review. *Ann Intensive Care* 2021; **11**: 104 [PMID: 34216304 DOI: 10.1186/s13613-021-00893-7]
23 **Crouser ED**. Mitochondrial dysfunction in septic shock and multiple organ dysfunction syndrome. *Mitochondrion* 2004; **4**: 729-741 [PMID: 16120428 DOI: 10.1016/j.mito.2004.07.023]
24 **Nagar H**, Piao S, Kim CS. Role of Mitochondrial Oxidative Stress in Sepsis. *Acute Crit Care* 2018; **33**: 65-72 [PMID: 31723865 DOI: 10.4266/acc.2018.00157]
25 **Vassiliou AG**, Mastora Z, Jahaj E, Keskinidou C, Pratikaki ME, Kampisiouli E, Orfanos SE, Kotanidou A, Dimopoulou I. Serum Coenzyme Q10 Levels are Decreased in Critically-Ill Septic Patients: Results From a Preliminary Study. *Biol Res Nurs* 2021; **23**: 198-207 [PMID: 32705879 DOI: 10.1177/1099800420944489]
26 **Zamponi N**, Zamponi E, Cannas SA, Billoni OV, Helguera PR, Chialvo DR. Mitochondrial network complexity emerges from fission/fusion dynamics. *Sci Rep* 2018; **8**: 363 [PMID: 29321534 DOI: 10.1038/s41598-017-18351-5]
27 **Roca-Agujetas V**, de Dios C, Lestón L, Marí M, Morales A, Colell A. Recent Insights into the Mitochondrial Role in Autophagy and Its Regulation by Oxidative Stress. *Oxid Med Cell Longev* 2019; **2019**: 3809308 [PMID: 31781334 DOI: 10.1155/2019/3809308]
28 **Gunst J**, Derese I, Aertgeerts A, Ververs EJ, Wauters A, Van den Berghe G, Vanhorebeek I. Insufficient autophagy contributes to mitochondrial dysfunction, organ failure, and adverse outcome in an animal model of critical illness. *Crit Care Med* 2013; **41**: 182-194 [PMID: 23222264 DOI: 10.1097/CCM.0b013e3182676657]
29 **Pool R**, Gomez H, Kellum JA. Mechanisms of Organ Dysfunction in Sepsis. *Crit Care Clin* 2018; **34**: 63-80 [PMID: 29149942 DOI: 10.1016/j.ccc.2017.08.003]
30 **Koutroulis I**, Batabyal R, McNamara B, Ledda M, Hoptay C, Freishtat RJ. Sepsis Immunometabolism: From Defining Sepsis to Understanding How Energy Production Affects Immune Response. *Crit Care Explor* 2019; **1**: e0061 [PMID: 32166242 DOI: 10.1097/CCE.0000000000000061]
31 **Exline MC**, Crouser ED. Mitochondrial dysfunction during sepsis: still more questions than answers. *Crit Care Med* 2011; **39**: 1216-1217 [PMID: 21603080 DOI: 10.1097/CCM.0b013e31821487cb]
32 **Wesselink E**, Koekkoek WAC, Grefte S, Witkamp RF, van Zanten ARH. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. *Clin Nutr* 2019; **38**: 982-995 [PMID: 30201141 DOI: 10.1016/j.clnu.2018.08.032]
33 **Singer M**. Critical illness and flat batteries. *Crit Care* 2017; **21**: 309 [PMID: 29297363 DOI: 10.1186/s13054-017-1913-9]
34 **Vanhorebeek I**, Gunst J, Derde S, Derese I, Boussemaere M, D'Hoore A, Wouters PJ, Van den Berghe G. Mitochondrial fusion, fission, and biogenesis in prolonged critically ill patients. *J Clin Endocrinol Metab* 2012; **97**: E59-E64 [PMID: 22013100 DOI: 10.1210/jc.2011-1760]
35 **Carré JE**, Orban JC, Re L, Felsmann K, Iffert W, Bauer M, Suliman HB, Piantadosi CA, Mayhew TM, Breen P, Stotz M, Singer M. Survival in critical illness is associated with early activation of mitochondrial biogenesis. *Am J Respir Crit Care Med* 2010; **182**: 745-751 [PMID: 20538956 DOI: 10.1164/rccm.201003-0326OC]
36 **Exline MC**, Crouser ED. Mitochondrial mechanisms of sepsis-induced organ failure. *Front Biosci* 2008; **13**: 5030-5041 [PMID: 18508567 DOI: 10.2741/3061]
37 **Duggal NA**, Snelson C, Shaheen U, Pearce V, Lord JM. Innate and adaptive immune dysregulation in critically ill ICU patients. *Sci Rep* 2018; **8**: 10186 [PMID: 29976949 DOI: 10.1038/s41598-018-28409-7]
38 **Surbatovic M**, Vojvodic D, Khan W. Immune Response in Critically Ill Patients. *Mediators Inflamm* 2018; **2018**: 9524315 [PMID: 30116156 DOI: 10.1155/2018/9524315]
39 **Frazier WJ**, Hall MW. Immunoparalysis and adverse outcomes from critical illness. *Pediatr Clin North Am* 2008; **55**: 647-668, xi [PMID: 18501759 DOI: 10.1016/j.pcl.2008.02.009]
40 **Faas MM**, de Vos P. Mitochondrial function in immune cells in health and disease. *Biochim Biophys Acta Mol Basis Dis* 2020; **1866**: 165845 [PMID: 32473386 DOI: 10.1016/j.bbadis.2020.165845]
41 **McBride MA**, Owen AM, Stothers CL, Hernandez A, Luan L, Burelbach KR, Patil TK, Bohannon JK, Sherwood ER, Patil NK. The Metabolic Basis of Immune Dysfunction Following Sepsis and Trauma. *Front Immunol* 2020; **11**: 1043 [PMID: 32547553 DOI: 10.3389/fimmu.2020.01043]
42 **Angajala A**, Lim S, Phillips JB, Kim JH, Yates C, You Z, Tan M. Diverse Roles of Mitochondria in Immune Responses: Novel Insights Into Immuno-Metabolism. *Front Immunol* 2018; **9**: 1605 [PMID: 30050539 DOI: 10.3389/fimmu.2018.01605]

43 **Iwasaki Y**, Takeshima Y, Fujio K. Basic mechanism of immune system activation by mitochondria. *Immunol Med* 2020; **43**: 142-147 [PMID: 32393116 DOI: 10.1080/25785826.2020.1756609]

44 **de Pablo R**, Monserrat J, Prieto A, Alvarez-Mon M. Role of circulating lymphocytes in patients with sepsis. *Biomed Res Int* 2014; **2014**: 671087 [PMID: 25302303 DOI: 10.1155/2014/671087]

45 **Kelly B**, O'Neill LA. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. *Cell Res* 2015; **25**: 771-784 [PMID: 26045163 DOI: 10.1038/cr.2015.68]

46 **de Pablo R**, Monserrat J, Reyes E, Diaz-Martin D, Rodriguez Zapata M, Carballo F, de la Hera A, Prieto A, Alvarez-Mon M. Mortality in patients with septic shock correlates with anti-inflammatory but not proinflammatory immunomodulatory molecules. *J Intensive Care Med* 2011; **26**: 125-132 [PMID: 21464065 DOI: 10.1177/0885066610384465]

47 **Andrea AD**, Aste-Amezaga M, Valiante NM, Ma X, Kubin M, Trinchieri G. Interleukin 10 (IL-10) Inhibits Human Lymphocyte Interferon 3,-Production by Suppressing Natural Killer Cell Stimulatory Factor/IL-12 Synthesis in Accessory Cells. *J Exp Med* 1993; **178**: 1041-1048

48 **Murphy MP**, O'Neill LAJ. Krebs Cycle Reimagined: The Emerging Roles of Succinate and Itaconate as Signal Transducers. *Cell* 2018; **174**: 780-784 [PMID: 30096309 DOI: 10.1016/j.cell.2018.07.030]

49 **Takasu O**, Gaut JP, Watanabe E, To K, Fagley RE, Sato B, Jarman S, Efimov IR, Janks DL, Srivastava A, Bhayani SB, Drewry A, Swanson PE, Hotchkiss RS. Mechanisms of cardiac and renal dysfunction in patients dying of sepsis. *Am J Respir Crit Care Med* 2013; **187**: 509-517 [PMID: 23348975 DOI: 10.1164/rccm.201211-1983OC]

50 **Fredriksson K**, Tjäder I, Keller P, Petrovic N, Ahlman B, Schéele C, Wernerman J, Timmons JA, Rooyackers O. Dysregulation of mitochondrial dynamics and the muscle transcriptome in ICU patients suffering from sepsis induced multiple organ failure. *PLoS One* 2008; **3**: e3686 [PMID: 18997871 DOI: 10.1371/journal.pone.0003686]

51 **Liesa M**, Palacín M, Zorzano A. Mitochondrial dynamics in mammalian health and disease. *Physiol Rev* 2009; **89**: 799-845 [PMID: 19584314 DOI: 10.1152/physrev.00030.2008]

52 **Willems PH**, Rossignol R, Dieteren CE, Murphy MP, Koopman WJ. Redox Homeostasis and Mitochondrial Dynamics. *Cell Metab* 2015; **22**: 207-218 [PMID: 26166745 DOI: 10.1016/j.cmet.2015.06.006]

53 **Harrington JS**, Choi AMK, Nakahira K. Mitochondrial DNA in Sepsis. *Curr Opin Crit Care* 2017; **23**: 284-290 [PMID: 28562385 DOI: 10.1097/MCC.0000000000000427]

54 **Mills EL**, Kelly B, O'Neill LAJ. Mitochondria are the powerhouses of immunity. *Nat Immunol* 2017; **18**: 488-498 [PMID: 28418387 DOI: 10.1038/ni.3704]

55 **Pyle A**, Burn DJ, Gordon C, Swan C, Chinnery PF, Baudouin SV. Fall in circulating mononuclear cell mitochondrial DNA content in human sepsis. *Intensive Care Med* 2010; **36**: 956-962 [PMID: 20224905 DOI: 10.1007/s00134-010-1823-7]

56 **Meloche J**, Pflieger A, Vaillancourt M, Paulin R, Potus F, Zervopoulos S, Graydon C, Courboulin A, Breuils-Bonnet S, Tremblay E, Couture C, Michelakis ED, Provencher S, Bonnet S. Role for DNA damage signaling in pulmonary arterial hypertension. *Circulation* 2014; **129**: 786-797 [PMID: 24270264 DOI: 10.1161/CIRCULATIONAHA.113.006167]

57 **Cicchillitti L**, Di Stefano V, Isaia E, Crimaldi L, Fasanaro P, Ambrosino V, Antonini A, Capogrossi MC, Gaetano C, Piaggio G, Martelli F. Hypoxia-inducible factor 1-α induces miR-210 in normoxic differentiating myoblasts. *J Biol Chem* 2012; **287**: 44761-44771 [PMID: 23148210 DOI: 10.1074/jbc.M112.421255]

58 **Tannahill GM**, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, Frezza C, Bernard NJ, Kelly B, Foley NH, Zheng L, Gardet A, Tong Z, Jany SS, Corr SC, Haneklaus M, Caffrey BE, Pierce K, Walmsley S, Beasley FC, Cummins E, Nizet V, Whyte M, Taylor CT, Lin H, Masters SL, Gottlieb E, Kelly VP, Clish C, Auron PE, Xavier RJ, O'Neill LA. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. *Nature* 2013; **496**: 238-242 [PMID: 23535595 DOI: 10.1038/nature11986]

59 **Svistunenko DA**, Davies N, Brealey D, Singer M, Cooper CE. Mitochondrial dysfunction in patients with severe sepsis: an EPR interrogation of individual respiratory chain components. *Biochim Biophys Acta* 2006; **1757**: 262-272 [PMID: 16626626 DOI: 10.1016/j.bbabio.2006.03.007]

60 **Brealey D**, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, Davies NA, Cooper CE, Singer M. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet* 2002; **360**: 219-223 [PMID: 12133657 DOI: 10.1016/S0140-6736(02)09459-X]

61 **Sjövall F**, Morota S, Hansson MJ, Friberg H, Gnaiger E, Elmér E. Temporal increase of platelet mitochondrial respiration is negatively associated with clinical outcome in patients with sepsis. *Crit Care* 2010; **14**: R214 [PMID: 21106065 DOI: 10.1186/cc9337]

62 **Makrecka-Kuka M**, Krumschnabel G, Gnaiger E. High-Resolution Respirometry for Simultaneous Measurement of Oxygen and Hydrogen Peroxide Fluxes in Permeabilized Cells, Tissue Homogenate and Isolated Mitochondria. *Biomolecules* 2015; **5**: 1319-1338 [PMID: 26131977 DOI: 10.3390/biom5031319]

63 **Rustin P**, Chretien D, Bourgeron T, Gérard B, Rötig A, Saudubray JM, Munnich A. Biochemical and molecular investigations in respiratory chain deficiencies. *Clin Chim Acta* 1994; **228**: 35-51 [PMID: 7955428 DOI: 10.1016/0009-8981(94)90055-8]

64 **Fischer JC**, Ruitenbeek W, Berden JA, Trijbels JM, Veerkamp JH, Stadhouders AM, Sengers RC, Janssen AJ. Differential investigation of the capacity of succinate oxidation in human skeletal muscle. *Clin Chim Acta* 1985; **153**: 23-36 [PMID: 3000647 DOI: 10.1016/0009-8981(85)90135-4]

65 **Brady J**, Horie S, Laffey JG. Role of the adaptive immune response in sepsis. *Intensive Care Med Exp* 2020; **8**: 20 [PMID: 33336293 DOI: 10.1186/s40635-020-00309-z]

66 **Belikova I**, Lukaszewicz AC, Faivre V, Damoisel C, Singer M, Payen D. Oxygen consumption of human peripheral blood mononuclear cells in severe human sepsis. *Crit Care Med* 2007; **35**: 2702-2708 [PMID: 18074472 DOI: 10.1097/01.ccm.0000295593.25106.c4]

67 **Srinivasan S**, Avadhani NG. Cytochrome c oxidase dysfunction in oxidative stress. *Free Radic Biol Med* 2012; **53**: 1252-1263 [PMID: 22841758 DOI: 10.1016/j.freeradbiomed.2012.07.021]

68 **Szabó C**, Módis K. Pathophysiological roles of peroxynitrite in circulatory shock. *Shock* 2010; **34** Suppl 1: 4-14 [PMID: 20523270 DOI: 10.1097/SHK.0b013e3181e7e9ba]

69 **Calvano SE**, Xiao W, Richards DR, Felciano RM, Baker HV, Cho RJ, Chen RO, Brownstein BH, Cobb JP, Tschoeke SK, Miller-Graziano C, Moldawer LL, Mindrinos MN, Davis RW, Tompkins RG, Lowry SF; Inflamm and Host Response to Injury Large Scale Collab. Res. Program. A network-based analysis of systemic inflammation in humans. *Nature* 2005; **437**: 1032-1037 [PMID: 16136080 DOI: 10.1038/nature03985]

70 **De Jonghe B**, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, Cerf C, Renaud E, Mesrati F, Carlet J, Raphaël JC, Outin H, Bastuji-Garin S; Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA* 2002; **288**: 2859-2867 [PMID: 12472328 DOI: 10.1001/jama.288.22.2859]

71 **Jiroutková K**, Krajčová A, Ziak J, Fric M, Waldauf P, Džupa V, Gojda J, Němcova-Fürstová V, Kovář J, Elkalaf M, Trnka J, Duška F. Mitochondrial function in skeletal muscle of patients with protracted critical illness and ICU-acquired weakness. *Crit Care* 2015; **19**: 448 [PMID: 26699134 DOI: 10.1186/s13054-015-1160-x]

72 **Fredriksson K**, Hammarqvist F, Strigård K, Hultenby K, Ljungqvist O, Wernerman J, Rooyackers O. Derangements in mitochondrial metabolism in intercostal and leg muscle of critically ill patients with sepsis-induced multiple organ failure. *Am J Physiol Endocrinol Metab* 2006; **291**: E1044-E1050 [PMID: 16803854 DOI: 10.1152/ajpendo.00218.2006]

73 **Japiassú AM**, Santiago AP, d'Avila JC, Garcia-Souza LF, Galina A, Castro Faria-Neto HC, Bozza FA, Oliveira MF. Bioenergetic failure of human peripheral blood monocytes in patients with septic shock is mediated by reduced F1Fo adenosine-5'-triphosphate synthase activity. *Crit Care Med* 2011; **39**: 1056-1063 [PMID: 21336129 DOI: 10.1097/CCM.0b013e31820eda5c]

74 **Garrabou G**, Morén C, López S, Tobías E, Cardellach F, Miró O, Casademont J. The effects of sepsis on mitochondria. *J Infect Dis* 2012; **205**: 392-400 [PMID: 22180620 DOI: 10.1093/infdis/jir764]

75 **Weiss SL**, Selak MA, Tuluc F, Perales Villarroel J, Nadkarni VM, Deutschman CS, Becker LB. Mitochondrial dysfunction in peripheral blood mononuclear cells in pediatric septic shock. *Pediatr Crit Care Med* 2015; **16**: e4-e12 [PMID: 25251517 DOI: 10.1097/PCC.0000000000000277]

76 **Puskarich MA**, Shapiro NI, Trzeciak S, Kline JA, Jones AE. Plasma levels of mitochondrial DNA in patients presenting to the emergency department with sepsis. *Shock* 2012; **38**: 337-340 [PMID: 22777124 DOI: 10.1097/SHK.0b013e318266a169]

77 **Puskarich MA**. The Challenge and the Promise of Studying Mitochondrial Dysfunction in Humans with Sepsis. *Ann Am Thorac Soc* 2015; **12**: 1595-1596 [PMID: 26540415 DOI: 10.1513/AnnalsATS.201509-592ED]

78 **Cheng SC**, Scicluna BP, Arts RJ, Gresnigt MS, Lachmandas E, Giamarellos-Bourboulis EJ, Kox M, Manjeri GR, Wagenaars JA, Cremer OL, Leentjens J, van der Meer AJ, van de Veerdonk FL, Bonten MJ, Schultz MJ, Willems PH, Pickkers P, Joosten LA, van der Poll T, Netea MG. Broad defects in the energy metabolism of leukocytes underlie immunoparalysis in sepsis. *Nat Immunol* 2016; **17**: 406-413 [PMID: 26950237 DOI: 10.1038/ni.3398]

79 **Luperto M**, Zafrani L. T cell dysregulation in inflammatory diseases in ICU. *Intensive Care Med Exp* 2022; **10**: 43 [PMID: 36279072 DOI: 10.1186/s40635-022-00471-6]

80 **Kubli DA**, Gustafsson ÅB. Mitochondria and mitophagy: the yin and yang of cell death control. *Circ Res* 2012; **111**: 1208-1221 [PMID: 23065344 DOI: 10.1161/CIRCRESAHA.112.265819]

81 **Zhou R**, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. *Nature* 2011; **469**: 221-225 [PMID: 21124315 DOI: 10.1038/nature09663]

82 **Sjövall F**, Morota S, Persson J, Hansson MJ, Elmér E. Patients with sepsis exhibit increased mitochondrial respiratory capacity in peripheral blood immune cells. *Crit Care* 2013; **17**: R152 [PMID: 23883738 DOI: 10.1186/cc12831]

World Journal of Critical Care Medicine

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World J Crit Care Med 2023 June 9; 12(3): 153-164

DOI: 10.5492/wjccm.v12.i3.153

ISSN 2220-3141 (online)

MINIREVIEWS

Acute exacerbation of interstitial lung disease in the intensive care unit: Principles of diagnostic evaluation and management

Muhammad K Hayat Syed, Or Bruck, Anupam Kumar, Salim Surani

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Juneja D, India; Wu J, China

Received: February 27, 2023
Peer-review started: February 27, 2023
First decision: March 28, 2023
Revised: April 18, 2023
Accepted: May 17, 2023
Article in press: May 17, 2023
Published online: June 9, 2023

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Abstract

Interstitial lung disease (ILD) is typically managed on an outpatient basis. Critical care physicians manage patients with ILD in the setting of an acute exacerbation (ILD flare) causing severe hypoxia. The principles of management of acute exacerbation of ILD are different from those used to manage patients with acute respiratory distress syndrome from sepsis, *etc*. Selected patients may be candidates for aggressive measures like extracorporeal membrane oxygenation and lung transplantation, while almost all patients will benefit from early palliative care. This review focused on the types of ILD, diagnosis, and management pathways for this challenging condition.

Key Words: Interstitial lung disease; Pulmonary fibrosis; Acute exacerbation of interstitial lung disease; Extracorporeal membrane oxygenation; Interstitial lung disease flare; Immunosuppression

Core Tip: Interstitial lung disease (ILD) refers to a heterogeneous group of parenchymal lung disorders. Most patients with ILD receive management in outpatient clinics. Patients with acute exacerbation of ILD may experience significant respiratory distress, requiring urgent management in an intensive care unit. Timely diagnosis and management of these patients using a multimodality team approach may improve both morbidity and mortality. When acute exacerbation of ILD progresses to irreversible end-stage respiratory failure, lung transplantation and/or palliative care may be appropriate treatment options depending on the individual patient's clinical presentation.

Citation: Hayat Syed MK, Bruck O, Kumar A, Surani S. Acute exacerbation of interstitial lung disease in the intensive care unit: Principles of diagnostic evaluation and management. *World J Crit Care Med* 2023; 12(3): 153-164
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/153.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.153

INTRODUCTION

Interstitial lung disease (ILD) is a heterogeneous group of approximately 200 disorders affecting lung parenchyma. The classification schema of this group of diseases has changed over time, with the most current iteration agreed upon in 2013 in a consensus statement from the American Thoracic Society and European Respiratory Society[1]. This classification system will be the basis for the nomenclature used in this review (Figure 1).

ILD can be more broadly categorized into those with a known cause and those without an identifiable etiology, also known as "idiopathic." Those ILDs with known causes can be due to drugs and toxins, rheumatic disease, granulomatous diseases such as sarcoidosis, and other forms such as lymphangioleiomyomatosis, eosinophilic pneumonia, or pulmonary Langerhans cell histiocytosis. The major idiopathic ILDs can be distributed into three categories: Chronic fibrosing [idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP)], acute/subacute fibrosing [cryptogenic organizing pneumonia, acute interstitial pneumonia (AIP)], and lastly smoking-related (delta sleep-inducing peptide, respiratory bronchiolitis-ILD)[1]. Notably, not all ILDs have the propensity to present as an acute exacerbation (AE). Moreover, common conditions like pulmonary edema, pneumonia, pulmonary embolism, and aspiration should be considered in the differential diagnosis of acute worsening. Furthermore, patients may present to the intensive care unit (ICU) with no known history of ILD.

An abnormal chest radiograph may be the initial finding in these patients[2]. Much attention is paid to the specific patterns noted on chest computed tomography (CT) that, when coupled with clinical history, can sometimes obviate the need for tissue sampling[3]. It is important to note that the lung has a limited and predictable response to injury; thus, a variety of disease processes may produce similar imaging findings[4]. Patients will almost universally present in a similar fashion, with dyspnea and acute hypoxemic respiratory failure. CT becomes an essential tool in the differentiation of the diagnosis.

AE-ILD

Definition

The definition of AE-ILD has evolved over time. AE-ILD was defined by 2007 IPFnet[5] as an "acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality typically less than 1-mo's duration with exclusion of alternative etiologies"[2]. The revised criteria in 2016[2] did not set a definite 30-d duration of onset of symptoms. The critical component of establishing a diagnosis of AE-ILD is excluding other etiologies that could be causing increased respiratory distress such as heart failure, pulmonary embolism, pneumothorax, and infection, *etc* (Table 1). However, in some cases infections and other pulmonary insults might act as a trigger for AE-ILD. It is difficult to lump all ILDs into one framework, and it is important to acknowledge that some of the acute presentations may be exacerbations of a previously unrecognized process[6]. AE-ILD symptoms tend to be shared across the spectrum of the disease. Commonly patients will present with worsening cough and dyspnea, but presentations may be more fulminant in the case of some AIP. However, given the non-specific nature of these symptoms, chest imaging and clinical history play an important role in discerning the diagnosis and thus the appropriate management.

Triggers

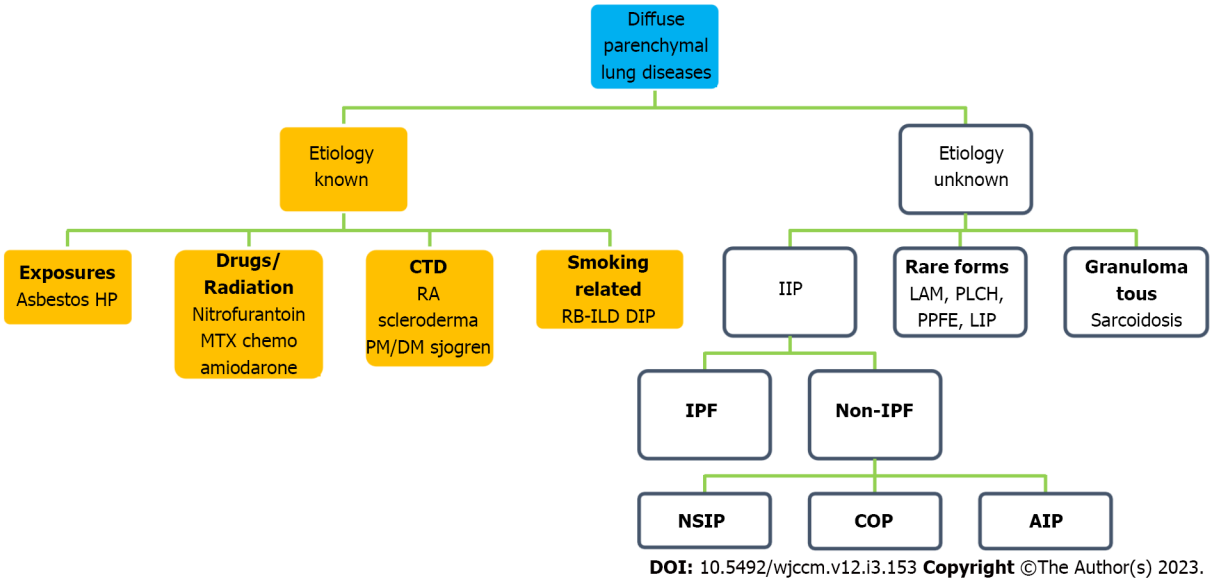
The incidence of AE-IPF ranges from 2% to 15% per year, depending on the cohort studied[7-10]. Nonetheless, AEs appear at a lower rate in non-IPF ILDs[11]. AEs are often devastating, with a median survival of usually about 4 mo[12]. If an IPF patient requires mechanical ventilation, mortality exceeds 75%[13]. Given that patients with ILD exist on the fringe between functionality and fulminant worsening, even the most minor perturbations in homeostasis can lead to a significant decline. Intuitively it makes sense that any of the common causes of respiratory failure in the general population also occur in the ILD population, with the implications of such in the latter being far more pronounced.

Risk factors for AE-IPF have been described in several studies but have not been validated in independent cohorts[11]. Whether the AE represents a progression of the underlying ILD or an aberrant response to external insults such as aspiration of gastric content, infection, or mechanical stretch remains unknown. Song *et al*[12] demonstrated that patients with lower baseline lung function as measured by

Table 1 Reversible causes of hypoxia in interstitial lung disease

No.	Potentially reversible (partial or complete) causes of worsening ILD
1	Pulmonary edema
2	Pneumonia
3	Aspiration
4	Pulmonary hemorrhage
5	Pulmonary embolism

ILD: Interstitial lung disease.



DOI: 10.5492/wjccm.v12.i3.153

Figure 1 Classification of interstitial lung disease/diffuse parenchymal lung disease. AIP: Acute interstitial pneumonia; COP: Cryptogenic organizing pneumonia; CTD: Connective tissue disease; DIP: Desquamative interstitial pneumonia; DM: Dermatomyositis; HP: Hypersensitivity pneumonitis; IIP: Idiopathic interstitial pneumonias; IPF: Idiopathic pulmonary fibrosis; LAM: Lymphangioleiomyomatosis; LIP: Lymphoid interstitial pneumonia; MTX: Methotrexate; NSIP: Non-specific interstitial pneumonia; PLCH: Pulmonary Langerhans cell histiocytosis; PM: Polymyositis; PPFE: Pleuroparenchymal fibroelastosis; RA: Rheumatoid arthritis; RB-ILD: Respiratory bronchiolitis-ILD.

forced vital capacity and those who never smoked had a greater risk for AE-IPF[12]. They described a subset of patients with AE-ILD as rapid deterioration of ILD, where the respiratory failure occurs in shorter duration (days to weeks) requiring hospitalization, with the presence of new radiographic abnormalities. Interestingly, within this cohort, many patients were found to have an infection as a trigger; more than half of those patients had opportunistic infections. The demonstration that AE is the most common cause of clinic deterioration in IPF patients is not a novel discovery[14]; thus, acceptance that disease progression may explain the patient's presentation can obviate the need for expensive and possibly morbid diagnostic investigations.

Other previously described exposures that can precipitate AE include bronchoalveolar lavage, cryobiopsy, lung resection surgery, pollution, aspiration, vaccination, and infection[15-21]. Churg *et al* [22] described the pathologic features found on lung biopsy in patients with fibrotic lung disease who were admitted with worsening respiratory failure. They noted three microscopic patterns found in these patients: Diffuse alveolar damage; organizing pneumonia; and a pattern of numerous very large fibroblast foci superimposed on underlying fibrosis. Ultimately, the onus on the admitting team is to differentiate idiopathic exacerbations from secondary ones, potentially more amenable to treatment. It has been shown to be related to mortality; that is, patients with suspected AE had worse in-hospital mortality as compared to those patients who had other causes for respiratory worsening[23].

Work-up

The diagnostic evaluation of patients with ILD admitted to the ICU is largely the same as that for all other patients admitted with acute hypoxemic respiratory failure. A caveat to this approach is for the patient with previously undiagnosed ILD, in which case, they will require a more thoughtful appraisal.

It is reasonable to exclude all the common, secondary causes of worsening that can be seen in ILD patients (Table 1).

Chest CT is now routinely utilized in all patients admitted to the ICU with AE-ILD. In those patients without a known diagnosis of ILD, a basic working knowledge of some of the classic radiographic findings can be helpful. As previously noted, ILDs are both a radiographic and histopathologic diagnosis.

There are several characteristics that can be used to quickly narrow the diagnosis: (1) Is increased attenuation present? *i.e.* reticulation, ground-glass, consolidation, nodules, or linear opacities; (2) Are cysts present?; and (3) Are areas of decreased attenuation (as is seen with honeycombing) a sign of lung fibrosis? While ILD is considered a rare family of diseases, IPF is the most common archetype of these rare diseases. The terms NSIP and usual interstitial pneumonia (UIP) are often encountered in the impression of CT scans of these patients. It should be mentioned that these are both descriptive of radiographic and histologic processes. With the advent of high-resolution chest CT, many ILDs can be diagnosed based on imaging alone. Radiologically, in UIP, honeycombing is the prototypical appearance of IPF (which represents areas of the destroyed and fibrotic lung) and is a predominant feature with an apical to basal gradient. It classically involves the subpleural region and is more often in the middle and lower lungs (Figure 2A). Ground glass opacities are minimal or absent, and traction bronchiectasis is often seen, which signifies architectural changes secondary to fibrosis[4]. NSIP refers to a pattern that is predominantly composed of diffuse, bilateral, ground-glass opacities and, at times, associated with peripheral irregular linear or reticular opacities. The distribution is mainly peripheral and basal and typically spares the subpleural region. Honeycombing, if present, is generally mild in comparison to UIP (Figure 2B).

However, there are some radiographic findings that are nearly pathognomonic and obviating the need for a tissue diagnosis[24]. While tissue sampling does provide a definitive diagnosis, surgical lung biopsy is generally not pursued in the setting of AE-ILD as it does not alter the course of treatment[25], and the procedure itself carries with it significant morbidity[26]. The typical UIP and NSIP CT patterns were outlined above. The findings seen during an AE may be of prognostic value. In AEs, the CT scan may show areas of consolidation, ground glass opacification, or a combination of the two (Figure 2C and D). In fact, Akira *et al*[27] were able to demonstrate Kaplan-Meir survival curve differences as it relates to the patterns found on CT scans in patients admitted with AE-UIP[27]. The chest CT will also exclude pulmonary embolism (if protocoled correctly) and pneumothorax.

Laboratory workups should follow the same standard of care as for patients admitted to the ICU with respiratory failure. Sputum and blood cultures should be drawn at the time of admission. Urine antigens for *Legionella* and *Streptococcus* and respiratory samples should be sent for PCR to assess for viral infection. Evidence exists that serum procalcitonin may be a helpful marker in differentiating bacterial pneumonia from AE-ILD[28,29]. Bronchoscopy likely has limited utility in the evaluation of these patients and if performed should be conducted with anticipation that further respiratory decompensation may occur. In the single-center cohort, it was demonstrated that bronchoscopy revealed potential causes of respiratory decline in 13% of patients and a change in management from the initial empiric regimen in 25% of patients. There was no difference in mortality between those with and without bronchoscopy findings. However, bronchoscopy in non-ICU patients led to immediate respiratory decompensation and the need for a higher level of care or invasive mechanical ventilation (IMV) in 25% of patients[30].

In patients without previously diagnosed ILD, there may be a role of assessing autoimmune serology for the purpose of differentiating between IPF and connective tissue disease-related ILD or pulmonary alveolar hemorrhage syndromes. The latter two are more likely to respond to high doses of immunosuppression[31].

Management

Management can be viewed as a multifaceted approach that is mainly comprised of supportive care for respiratory failure. Given the relative heterogeneity of disease processes, there is not one treatment plan that can be universally applied. Below we will outline the different considerations and treatment modalities that have been applied to patients with AE-ILD. It should be noted that much of this practice is done with a paucity of high-quality evidence and ultimately relies on expert opinion on consensus guidelines. Figure 3 is a generalized flowsheet that can be used to guide through the various steps of management of AE-ILD patients.

Immunosuppression

Presently there are no proven, effective therapies for the treatment of AE-IPF. Despite this, many patients with AE-IPF receive corticosteroids in accordance with the guidelines, which admit there are no controlled trials to judge efficacy and that the recommendation comes largely from anecdotal evidence of benefit[3]. Given the high mortality associated with AE-IPF, it is reasonable to administer corticosteroids to these patients. However, the dose, route, and duration are of unknown amounts. The same can be said for AIP, which is a rapidly progressing, lethal form of ILD with a dismal prognosis and is not responsive to steroids[6]. A general approach adopted is to use daily corticosteroid dosage in the 1-2 mg/kg range in divided doses. In patients who respond to this treatment, a gradual taper is attempted

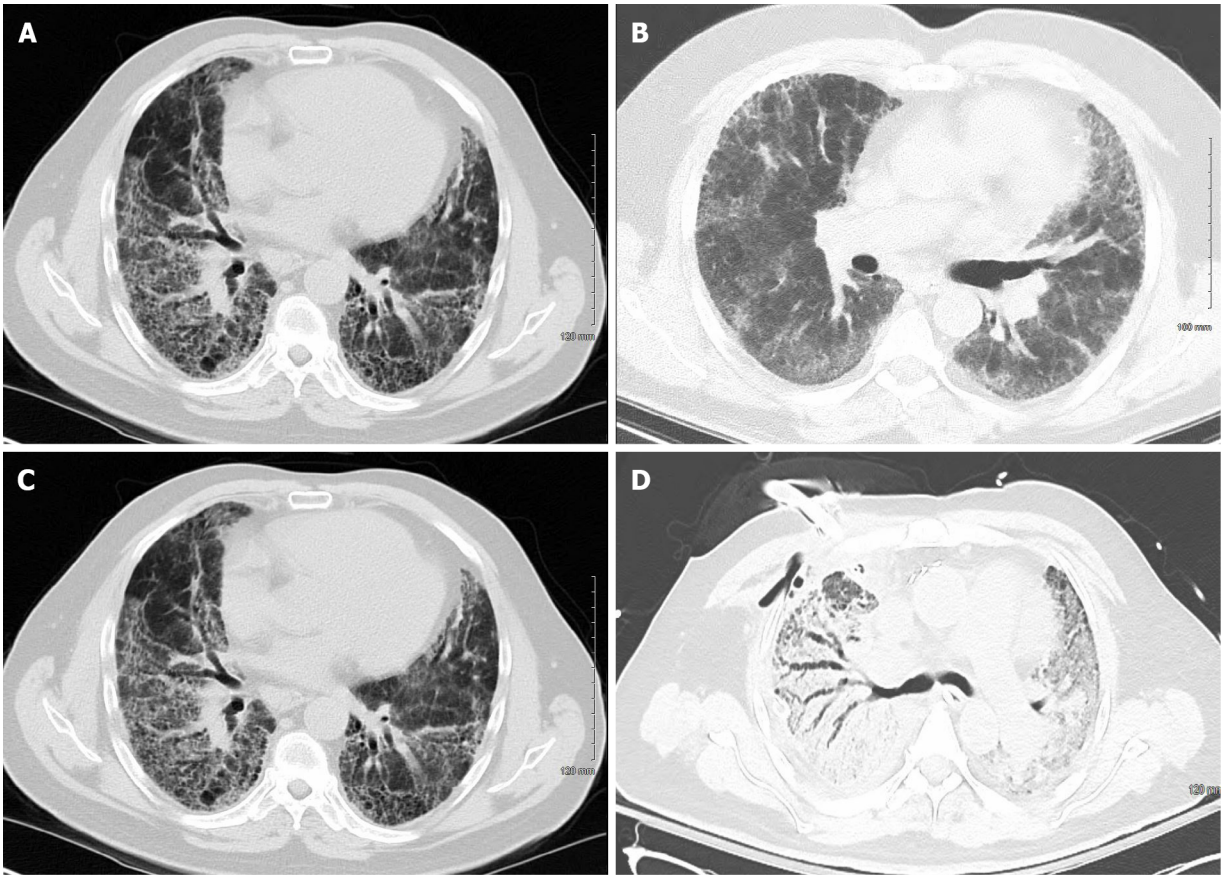


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Figure 2 Chest computed tomography. A: Chest computed tomography (CT) of a patient with idiopathic pulmonary fibrosis with usual interstitial pneumonia pattern; B: A 54-year-old male with non-specific interstitial pneumonia. Chest CT showed faint ground glass opacity and mild reticulations (non-specific interstitial pneumonia); C: Idiopathic pulmonary fibrosis patient in Figure 2A during acute exacerbation showing ground glass opacities requiring extracorporeal membrane oxygenation as bridge to transplant; D: Chest CT of patient in Figure 2B during acute exacerbation of interstitial lung disease with areas of ground glass opacity and consolidation.

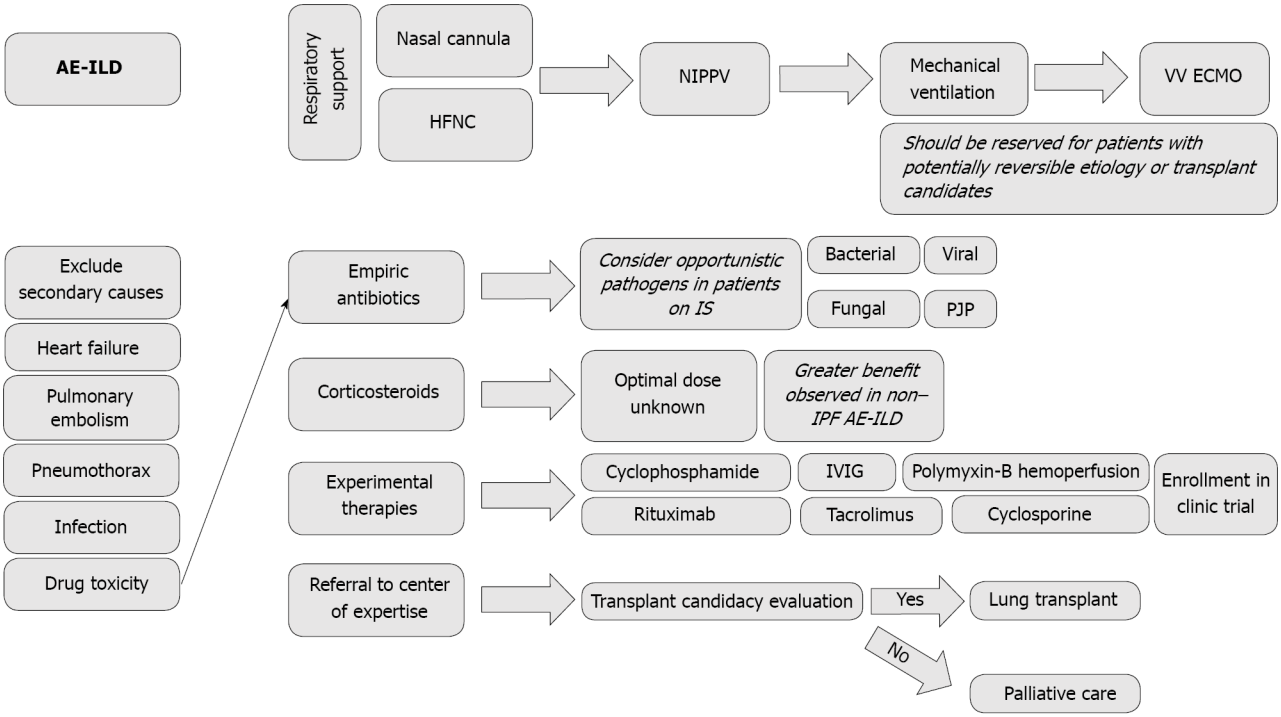
over the course of weeks.

A recent trial looked at the addition of cyclophosphamide to corticosteroids for the management of AE-IPF and showed that 3-mo mortality increased in the treatment arm, which provides further evidence against its use in this setting[32,33]. Another drug of interest is cyclosporine, which has been investigated in conjunction with corticosteroids in several non-randomized, retrospective studies in patients with AE-IPF and has shown potential benefits. However, larger randomized controlled studies are needed to confirm this[34]. It has been postulated that immune dysregulation may lead to autoantibody production, which may drive the progression of IPF or the development of AE. As such, rituximab, in conjunction with plasma exchange, has been investigated as a potential therapeutic with promising results[35].

Currently, there are ongoing, prospective, randomized controlled studies, STRIVE-IPF [NCT03-286556] and Europe Exchange-IPF [NCT03584802], testing the efficacy and safety of the combination of plasma exchange, rituximab, intravenous immunoglobulin, and corticosteroids for the treatment of AE-IPF based on the hypothesis that autoantibody reduction might help in its management. Regarding patients with AE of other ILDs, stronger evidence of benefits from corticosteroids exists, as is the case for fibrotic hypersensitivity pneumonitis, connective tissue disease-ILD, and organizing pneumonia, to name a few. We recommend the engagement of a pulmonologist familiar with the role of immunosuppression in connective tissue disease-ILD if this is suspected. Depending on the condition, the choice of agents may range from corticosteroids alone to consideration of agents like cyclophosphamide, rituximab, and even plasma exchange if alveolar hemorrhage is suspected. These decisions are best undertaken in a multidisciplinary discussion to facilitate the best outcome for the patient.

ANTIFIBROTIC THERAPY

Currently, there are two medications available on the market, nintedanib and pirfenidone, which are



DOI: 10.5492/wjccm.v12.i3.153

Figure 3 Flowsheet for management of acute exacerbation of interstitial lung disease. AE-ILD: Acute exacerbation of interstitial lung disease; HFNC: High-flow nasal cannula; IPF: Idiopathic pulmonary fibrosis; IS: Immunosuppressants; IVIG: Intravenous immunoglobulin; NIPPV: Noninvasive positive pressure ventilation; PJP: *Pneumocystis jiroveci* pneumonia; VV ECMO: Veno-venous extracorporeal membrane oxygenation.

classified as antifibrotics that are approved for the treatment of IPF. Nintedanib is a tyrosine kinase inhibitor that blocks the processes that propagate fibrosis. In the clinical trial, which ultimately led to its approval, it was shown to reduce the decline of lung function and thus slow disease progression[36]. Pirfenidone works by inhibiting transforming growth factor beta, which plays a role in collagen-directed fibroblast formation. While there is no reversal of disease, this medication has also shown the ability to slow the progression of lung decline. Both medications have been shown to reduce the rate of exacerbations[3]. Many patients with IPF will be on these medications at the time of hospitalization. Polke *et al*[33] looked at the management practices of AE-IPF in specialized and non-specialized ILD centers worldwide. They found that 80% of physicians in specialized centers continue antifibrotics during hospitalization, and 66% initiate therapy during the AE[33]. These therapies have not been investigated specifically for use in the setting of AE-IPF or other ILDs, for that matter. There is, however, a growing body of evidence for the use of these drugs in other fibrosing lung diseases other than IPF[37].

Antibiotics

Antimicrobial agents are used routinely in patients with AE-ILD in conjunction with a thorough infectious workup. Antimicrobial coverage should be tailored to the specific pathogens and sensitivities at each respective institution. Azithromycin is a familiar drug, and its use in the management of AEs of chronic obstructive lung disease is well documented. Azithromycin is postulated to exert its benefits through anti-inflammatory and immunomodulatory effects in the lung[38,39]. Evidence does exist that there may be a benefit to macrolide use in patients with AE-IPF. However, these studies are small and confounded by other therapies the patients received[40,41]. Other patient-specific considerations, such as recent hospitalization, prior culture data, and immunosuppression, should also play a role in determining the most appropriate therapy. In a Chinese cohort of patients with idiopathic inflammatory myopathy-related ILD, they found that roughly one-third of patients admitted with clinical worsening (mainly respiratory) had what they deemed to be concomitant infection and exacerbation of the idiopathic inflammatory myopathy. Nearly half of those patients with documented infections had a fungal infection with either *Aspergillus* or *Pneumocystis*[42]. This highlights the importance of considering opportunistic infections in patients with ILD who are admitted to the ICU.

Antacids

It is postulated that microaspiration might play a role in the incitement of lung fibrosis. Studies have frequently demonstrated a higher prevalence of gastroesophageal reflux disease in ILD patients; however, this association cannot be interpreted as causation[43,44]. The role of acid-reducing therapy in

AE has not been formally investigated. However, many physicians will continue antacids during hospitalization, and at the very least, the patients will qualify for alimentary prophylaxis based on mechanical ventilation and corticosteroid administration.

HIGH-FLOW NASAL CANNULA

The coronavirus disease 2019 pandemic has changed the way non-invasive ventilation (NIV) is viewed and utilized. With the popularization of high-flow nasal cannula (HFNC), the oxygen demands of severely hypoxemic patients can be met without the need for endotracheal intubation. IMV has a dismal prognosis for patients with AE-ILD[45], and a trial of HFNC is warranted. The benefit and feasibility of using HFNC for acute hypoxemic respiratory failure has been shown. However, patients with chronic hypoxemic respiratory failure were excluded from this study. While the patients that were randomized to HFNC *vs* continuous positive airway pressure (CPAP) or bi-level positive airway pressure devices did not result in a decreased need for intubation, there was a reduction in mortality at 90 d in the HFNC group. HFNC can deliver a fraction of inspired oxygen up to 100% with high flow rates that can match the patients' respiratory demands. Given the high flow rates, there is also a degree of dead-space washout that results in decreased work breathing. There is limited high-quality evidence regarding the matter, but it has been shown in several retrospective studies that it is a safe and well-tolerated modality with comparable outcomes to CPAP and bi-level positive airway pressure[46,47]. HFNC has been shown to have salutatory effects in IPF patients without an AE, specifically decreased minute ventilation and respiratory rate, and capillary carbon dioxide was seen. The minor increase in positive end-expiratory pressure seen with it is also considered beneficial[48,49]. Finally, there is the added advantage of the patient being able to eat and communicate with HFNC *vs* IMV.

NIV

NIV is often applied in patients with acute hypoxemic respiratory failure in the hopes of staving off endotracheal intubation. There is robust evidence for the utility of its use in respiratory failure secondary to chronic obstructive lung disease and congestive heart failure. However, the benefit is less certain in AE-ILD. Yokoyama *et al*[50] demonstrated that NIV might have potential benefits in patients with acute hypoxemic respiratory failure secondary to AE-ILD. Eleven patients received CPAP therapy. Of those patients, 6 failed and required IMV but did not survive. The remaining 5 patients survived and were alive at the 3-mo follow-up. Similar results were shown in another study that also used NIV for patients with IPF[51,52]. These studies are not without limitations, given small sample sizes and retrospective natures that may not be representative of the general AE-ILD population. Further, it may reflect a selection bias that patients who benefitted from the use of NIV may have had less severe diseases. Nonetheless, it is proof of concept that perhaps for a subset of AE-ILD patients, a trial of NIV is a potential alternative to an otherwise morbid intervention that in some cohorts see a mortality rate of up to 90% for ICU patients[51].

MECHANICAL VENTILATION

The outcomes for ILD patients that require IMV are so poor that outside of transplant candidates, some experts have advised against endotracheal intubation for these patients apart from those patients that have clearly reversible causes for respiratory decompensation[53]. The lungs of ILD patients are plagued by two detrimental factors: Significant V/Q mismatch and poor compliance. No specific guidelines dictate the optimal way to provide IMV to this subset of patients. The intrinsic substrate properties of ILD lungs make them especially prone to ventilator-induced lung injury with decreased compliance making the lung more prone to both barotraumas as well as atelecatrauma[54,55]. Therefore, it is reasonable to utilize strategies from the ARDSNET group for the management of patients with acute lung injury and acute respiratory distress syndrome (ARDS)[56]. Some authors use this fact as a caution against absolute denial of IMV for ILD patients, given that some of the data were collected before the publication of the landmark trial in 2000, which demonstrated the mortality benefit of low tidal volume ventilation[13].

There have been studies that looked at the lung mechanics of stable ILD patients and found that based on both static and dynamic lung compliance, the lung is less distensible than normal. Furthermore, it was demonstrated that the elastance of the mechanically ventilated IPF patient was four times higher than even those patients with ARDS[57]. This is further corroborated by retrospective studies that have shown that higher levels of positive end-expiratory pressure have been associated with higher mortality in AE-ILD patients[54].

In conclusion, the outcomes of ILD patients requiring IMV are extremely poor, with cohorts that report up to 100% mortality[58]. As such, the decision to proceed with endotracheal intubation should not be made lightly and should only occur after thoughtful discussion with the patient and family members. In the case of transplant candidates, IMV can be seen as a bridge therapy. Otherwise, early involvement in palliative services are advised.

EXTRACORPOREAL MEMBRANE OXYGENATION

Veno-venous extracorporeal membrane oxygenation (VV ECMO) is presently viewed as a salvage tool in the management of patients with refractory hypoxemic respiratory failure. When the known strategies, such as low-tidal volume ventilation, prone positioning, and neuromuscular blockade, all fail to improve oxygenation and/or refractory acidemia due to impossible ventilation in the capable centers, VV ECMO is often employed. ECMO helps to diminish ventilator-induced lung injury in these patients. There is no consensus recommendation on the use of VV ECMO for ARDS, and the data supporting its use leaves most intensivists with a great deal of uncertainty regarding the degree of and who will benefit[59,60].

There is even less certainty regarding its use in AE-ILD patients. Trudzinski *et al*[61] showed that ECMO is a viable option for patients who are suitable for a lung transplant. However, it should not be offered to those who are not, given that it does not reverse the otherwise poor prognosis faced by patients who are not transplant candidates. In an international poll, roughly 50% of physicians at specialized centers offered ECMO as a bridge to patients who were suitable for transplantation[33]. To summarize, ECMO should be considered for patients with AE-ILD with a clear reversible cause (*e.g.*, infection or pulmonary embolism) or as a bridging therapy for patients appropriate for lung transplant.

LUNG TRANSPLANTATION

ILD, particularly IPF, is now the most common indication for lung transplantation worldwide[62]. The median post-transplant survival for patients with idiopathic interstitial pneumonia, which includes IPF, is 5.2 years and 6.7 years for all other ILDs transplanted between 1992 and 2017[63]. Current guidelines recommend that transplant only be offered to those patients with a > 80% likelihood of 5-year post-transplant survival[64]. There are several relative contraindications to transplant, such as severe psychosocial problems or life-threatening extrapulmonary organ dysfunction. The latter may frequently be encountered in AE-ILD patients who require ICU admission. The need for IMV and/or ECMO for respiratory failure before the transplantation are associated with adverse post-transplant outcomes, which may prevent some of the sickest patients from undergoing transplantation[64]. For those patients who were already listed for transplantation and who experienced an AE, ECMO as a bridge to transplantation could be considered on a case-by-case basis. The emphasis in these patients is to avoid the development of critical illness myopathy and extrapulmonary organ damage. For de novo patients, performing invasive tests like heart catheterization and screening colonoscopies can be perilous. Ultimately, candidacy for an organ transplant will be a decision made in a multidisciplinary fashion incorporating the values of the patient and family, transplant surgeons, and transplant pulmonologists.

PALLIATIVE CARE

Palliative care (PC) medicine specialists are dedicated to improving patient quality of life during serious illnesses. In a recent survey, it was shown that the majority of ILD providers use PC and are comfortable discussing PC with their patients[65]. Given the poor prognosis that ILD patients face when they are admitted to the ICU, it warrants early involvement of PC services. Furthermore, the median life expectancy for all patients with IPF is between 2-7 years, which hastens in the AE setting. The American Thoracic Society/European Respiratory Society guidelines recommend that advanced directives and end-of-life issues be addressed in the ambulatory setting in all patients with IPF[3]. A subset of patients will require ICU level of care due to AE-ILD that was not previously diagnosed and will require more nuanced discussions given the emotional burden of a new, life-limiting diagnosis. In one IPF cohort, it was found that the hospital was the place of death for 80% of the patients, and most of these patients (93%) were hospitalized for an average of 30 d during the last 6 mo of their life. More striking was the statistic that 42% had a do not resuscitate order that was decided upon ≤ 3 d prior to their death[66]. This further confirms the importance of early and thoughtful communication with these patients and their families to ease the emotional and physical suffering they may endure at the end of their lives.

CONCLUSION

Flares or AEs of ILD have feared complications, owing both to their poor prognosis and uncertain management. The mainstay of therapy is supportive care and early recognition of a potentially reversible cause. Immunosuppression plays a role in a subset of patients; however, the optimal dosage and duration have not yet been defined. It behooves the intensivist to trial NIV forms on respiratory support to avoid the highly morbid effects of mechanical ventilation in these patients. The most aggressive therapies, such as IMV and ECMO, should be reserved for those patients who are potential transplant candidates. Early involvement in PC will assist in managing complex discussions and minimize suffering for patients with a high propensity for mortality.

FOOTNOTES

Author contributions: Hayat Syed MK contributed to idea origination, literature review, write-up, and revision; Bruck O and Kumar A contributed to the literature review and write-up; Surani S contributed to idea origination, review, revision, and supervision.

Conflict-of-interest statement: All the authors report having no relevant conflicts of interest for this article.

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S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

REFERENCES

1 **Travis WD**, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; **188**: 733-748 [PMID: 24032382 DOI: 10.1164/rccm.201308-1483ST]

2 **Collard HR**, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, Lee JS, Maher TM, Wells AU, Antoniou KM, Behr J, Brown KK, Cottin V, Flaherty KR, Fukuoka J, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kolb M, Lynch DA, Myers JL, Raghu G, Richeldi L, Taniguchi H, Martinez FJ. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. *Am J Respir Crit Care Med* 2016; **194**: 265-275 [PMID: 27299520 DOI: 10.1164/rccm.201604-0801CI]

3 **Raghu G**, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; **183**: 788-824 [PMID: 21471066 DOI: 10.1164/rccm.2009-040GL]

4 **Jawad H**, Chung JH, Lynch DA, Newell JD Jr. Radiological approach to interstitial lung disease: a guide for the nonradiologist. *Clin Chest Med* 2012; **33**: 11-26 [PMID: 22365242 DOI: 10.1016/j.ccm.2012.01.002]

5 **Collard HR**, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, Lasky JA, Loyd JE, Noth I, Olman MA, Raghu G, Roman J, Ryu JH, Zisman DA, Hunninghake GW, Colby TV, Egan JJ, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kondoh Y, Lynch DA, Müller-Quernheim J, Myers JL, Nicholson AG, Selman M, Toews GB, Wells AU, Martinez FJ; Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; **176**: 636-643 [PMID: 17585107 DOI: 10.1164/rccm.200703-463PP]

6 **Taniguchi H**, Kondoh Y. Acute and subacute idiopathic interstitial pneumonias. *Respirology* 2016; **21**: 810-820 [PMID:

27123874 DOI: 10.1111/resp.12786]
7 **Idiopathic Pulmonary Fibrosis Clinical Research Network**, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; **366**: 1968-1977 [PMID: 22607134 DOI: 10.1056/NEJMoa1113354]
8 **Richeldi L**, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Klüglich M, du Bois RM. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011; **365**: 1079-1087 [PMID: 21992121 DOI: 10.1056/NEJMoa1103690]
9 **King TE Jr**, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, du Bois RM; INSPIRE Study Group. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009; **374**: 222-228 [PMID: 19570573 DOI: 10.1016/S0140-6736(09)60551-1]
10 **King TE Jr**, Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, Behr J. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; **184**: 92-99 [PMID: 21474646 DOI: 10.1164/rccm.201011-1874OC]
11 **Ryerson CJ**, Collard HR. Acute exacerbations complicating interstitial lung disease. *Curr Opin Pulm Med* 2014; **20**: 436-441 [PMID: 25032813 DOI: 10.1097/MCP.0000000000000073]
12 **Song JW**, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J* 2011; **37**: 356-363 [PMID: 20595144 DOI: 10.1183/09031936.00159709]
13 **Gaudry S**, Vincent F, Rabbat A, Nunes H, Crestani B, Naccache JM, Wolff M, Thabut G, Valeyre D, Cohen Y, Mal H. Invasive mechanical ventilation in patients with fibrosing interstitial pneumonia. *J Thorac Cardiovasc Surg* 2014; **147**: 47-53 [PMID: 23968871 DOI: 10.1016/j.jtcvs.2013.06.039]
14 **Panos RJ**, Mortenson RL, Niccoli SA, King TE Jr. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. *Am J Med* 1990; **88**: 396-404 [PMID: 2183601 DOI: 10.1016/0002-9343(90)90495-y]
15 **Sakamoto K**, Taniguchi H, Kondoh Y, Wakai K, Kimura T, Kataoka K, Hashimoto N, Nishiyama O, Hasegawa Y. Acute exacerbation of IPF following diagnostic bronchoalveolar lavage procedures. *Respir Med* 2012; **106**: 436-442 [PMID: 22138357 DOI: 10.1016/j.rmed.2011.11.006]
16 **Casoni GL**, Tomassetti S, Cavazza A, Colby TV, Dubini A, Ryu JH, Carretta E, Tantalocco P, Piciucchi S, Ravaglia C, Gurioli C, Romagnoli M, Chilosi M, Poletti V. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. *PLoS One* 2014; **9**: e86716 [PMID: 24586252 DOI: 10.1371/journal.pone.0086716]
17 **Johannson KA**, Vittinghoff E, Lee K, Balmes JR, Ji W, Kaplan GG, Kim DS, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *Eur Respir J* 2014; **43**: 1124-1131 [PMID: 24176998 DOI: 10.1183/09031936.00122213]
18 **Lee JS**, Song JW, Wolters PJ, Elicker BM, King TE Jr, Kim DS, Collard HR. Bronchoalveolar lavage pepsin in acute exacerbation of idiopathic pulmonary fibrosis. *Eur Respir J* 2012; **39**: 352-358 [PMID: 22183478 DOI: 10.1183/09031936.00050911]
19 **Sugino K**, Ono H, Saito M, Ando M, Tsuboi E. Coronavirus disease 2019 vaccination-induced acute exacerbation in idiopathic pulmonary fibrosis. *Respirol Case Rep* 2022; **10**: e01051 [PMID: 36254333 DOI: 10.1002/rcr2.1051]
20 **Sugiura H**, Takeda A, Hoshi T, Kawabata Y, Sayama K, Jinzaki M, Kuribayashi S. Acute exacerbation of usual interstitial pneumonia after resection of lung cancer. *Ann Thorac Surg* 2012; **93**: 937-943 [PMID: 22305054 DOI: 10.1016/j.athoracsur.2011.12.010]
21 **Wootton SC**, Kim DS, Kondoh Y, Chen E, Lee JS, Song JW, Huh JW, Taniguchi H, Chiu C, Boushey H, Lancaster LH, Wolters PJ, DeRisi J, Ganem D, Collard HR. Viral infection in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; **183**: 1698-1702 [PMID: 21471095 DOI: 10.1164/rccm.201010-1752OC]
22 **Churg A**, Müller NL, Silva CI, Wright JL. Acute exacerbation (acute lung injury of unknown cause) in UIP and other forms of fibrotic interstitial pneumonias. *Am J Surg Pathol* 2007; **31**: 277-284 [PMID: 17255773 DOI: 10.1097/01.pas.0000213341.70852.9d]
23 **Moua T**, Westerly BD, Dulohery MM, Daniels CE, Ryu JH, Lim KG. Patients With Fibrotic Interstitial Lung Disease Hospitalized for Acute Respiratory Worsening: A Large Cohort Analysis. *Chest* 2016; **149**: 1205-1214 [PMID: 26836940 DOI: 10.1016/j.chest.2015.12.026]
24 **Hunninghake GW**, Zimmerman MB, Schwartz DA, King TE Jr, Lynch J, Hegele R, Waldron J, Colby T, Müller N, Lynch D, Galvin J, Gross B, Hogg J, Toews G, Helmers R, Cooper JA Jr, Baughman R, Strange C, Millard M. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001; **164**: 193-196 [PMID: 11463586 DOI: 10.1164/ajrccm.164.2.2101090]
25 **Parambil JG**, Myers JL, Ryu JH. Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. *Chest* 2005; **128**: 3310-3315 [PMID: 16304277 DOI: 10.1378/chest.128.5.3310]
26 **Hutchinson JP**, Fogarty AW, McKeever TM, Hubbard RB. In-Hospital Mortality after Surgical Lung Biopsy for Interstitial Lung Disease in the United States. 2000 to 2011. *Am J Respir Crit Care Med* 2016; **193**: 1161-1167 [PMID: 26646481 DOI: 10.1164/rccm.201508-1632OC]
27 **Akira M**, Kozuka T, Yamamoto S, Sakatani M. Computed tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008; **178**: 372-378 [PMID: 18451320 DOI: 10.1164/rccm.200709-1365OC]
28 **Nagata K**, Tomii K, Otsuka K, Tachikawa R, Nakagawa A, Takeshita J, Tanaka K, Matsumoto T, Monden K, Kawamura T, Tamai K. Serum procalcitonin is a valuable diagnostic marker in acute exacerbation of interstitial pneumonia. *Respirology* 2013; **18**: 439-446 [PMID: 23163578 DOI: 10.1111/resp.12018]
29 **Sim JK**, Oh JY, Lee EJ, Hur GY, Lee SH, Lee SY, Kim JH, Shin C, Shim JJ, In KH, Kang KH, Min KH. Serum Procalcitonin for Differential Diagnosis of Acute Exacerbation and Bacterial Pneumonia in Patients With Interstitial Lung Disease. *Am J Med Sci* 2016; **351**: 499-505 [PMID: 27140709 DOI: 10.1016/j.amjms.2016.02.029]
30 **Arcadu A**, Moua T. Bronchoscopy assessment of acute respiratory failure in interstitial lung disease. *Respirology* 2017;

22: 352-359 [PMID: 27712021 DOI: 10.1111/resp.12909]

31 **Vij R**, Strek ME. Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. *Chest* 2013; **143**: 814-824 [PMID: 23460159 DOI: 10.1378/chest.12-0741]

32 **Naccache JM**, Jouneau S, Didier M, Borie R, Cachanado M, Bourdin A, Reynaud-Gaubert M, Bonniaud P, Israël-Biet D, Prévot G, Hirschi S, Lebargy F, Marchand-Adam S, Bautin N, Traclet J, Gomez E, Leroy S, Gagnadoux F, Rivière F, Bergot E, Gondouin A, Blanchard E, Parrot A, Blanc FX, Chabrol A, Dominique S, Gibelin A, Tazi A, Berard L, Brillet PY, Debray MP, Rousseau A, Kerjouan M, Freynet O, Dombret MC, Gamez AS, Nieves A, Beltramo G, Pastré J, Le Borgne-Krams A, Dégot T, Launois C, Plantier L, Wémeau-Stervinou L, Cadranel J, Chenivesse C, Valeyre D, Crestani B, Cottin V, Simon T, Nunes H; EXAFIP investigators and the OrphaLung network. Cyclophosphamide added to glucocorticoids in acute exacerbation of idiopathic pulmonary fibrosis (EXAFIP): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2022; **10**: 26-34 [PMID: 34506761 DOI: 10.1016/S2213-2600(21)00354-4]

33 **Polke M**, Kondoh Y, Wijsenbeek M, Cottin V, Walsh SLF, Collard HR, Chaudhuri N, Avdeev S, Behr J, Calligaro G, Corte TJ, Flaherty K, Funke-Chambour M, Kolb M, Krisam J, Maher TM, Molina Molina M, Morais A, Moor CC, Morisset J, Pereira C, Quadrelli S, Selman M, Tzouvelekis A, Valenzuela C, Vancheri C, Vicens-Zygmunt V, Wälscher J, Wuyts W, Bendstrup E, Kreuter M. Management of Acute Exacerbation of Idiopathic Pulmonary Fibrosis in Specialised and Non-specialised ILD Centres Around the World. *Front Med (Lausanne)* 2021; **8**: 699644 [PMID: 34646836 DOI: 10.3389/fmed.2021.699644]

34 **Sakamoto S**, Homma S, Miyamoto A, Kurosaki A, Fujii T, Yoshimura K. Cyclosporin A in the treatment of acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2010; **49**: 109-115 [PMID: 20075573 DOI: 10.2169/internalmedicine.49.2359]

35 **Donahoe M**, Valentine VG, Chien N, Gibson KF, Raval JS, Saul M, Xue J, Zhang Y, Duncan SR. Autoantibody-Targeted Treatments for Acute Exacerbations of Idiopathic Pulmonary Fibrosis. *PLoS One* 2015; **10**: e0127771 [PMID: 26083430 DOI: 10.1371/journal.pone.0127771]

36 **Mazzei ME**, Richeldi L, Collard HR. Nintedanib in the treatment of idiopathic pulmonary fibrosis. *Ther Adv Respir Dis* 2015; **9**: 121-129 [PMID: 25862013 DOI: 10.1177/1753465815579365]

37 **Flaherty KR**, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, Richeldi L, Kolb M, Tetzlaff K, Stowasser S, Coeck C, Clerisme-Beaty E, Rosenstock B, Quaresma M, Haeufel T, Goeldner RG, Schlenker-Herceg R, Brown KK; INBUILD Trial Investigators. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *N Engl J Med* 2019; **381**: 1718-1727 [PMID: 31566307 DOI: 10.1056/NEJMoa1908681]

38 **Albert RK**, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, Curtis JL, Dransfield MT, Han MK, Lazarus SC, Make B, Marchetti N, Martinez FJ, Madinger NE, McEvoy C, Niewoehner DE, Porsasz J, Price CS, Reilly J, Scanlon PD, Sciurba FC, Scharf SM, Washko GR, Woodruff PG, Anthonisen NR; COPD Clinical Research Network. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; **365**: 689-698 [PMID: 21864166 DOI: 10.1056/NEJMoa1104623]

39 **Martinez FJ**, Curtis JL, Albert R. Role of macrolide therapy in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2008; **3**: 331-350 [PMID: 18990961 DOI: 10.2147/copd.s681]

40 **Kawamura K**, Ichikado K, Suga M, Yoshioka M. Efficacy of azithromycin for treatment of acute exacerbation of chronic fibrosing interstitial pneumonia: a prospective, open-label study with historical controls. *Respiration* 2014; **87**: 478-484 [PMID: 24802885 DOI: 10.1159/000358443]

41 **Kawamura K**, Ichikado K, Yasuda Y, Anan K, Suga M. Azithromycin for idiopathic acute exacerbation of idiopathic pulmonary fibrosis: a retrospective single-center study. *BMC Pulm Med* 2017; **17**: 94 [PMID: 28629448 DOI: 10.1186/s12890-017-0437-z]

42 **Peng JM**, Du B, Wang Q, Weng L, Hu XY, Wu CY, Shi Y. Dermatomyositis and Polymyositis in the Intensive Care Unit: A Single-Center Retrospective Cohort Study of 102 Patients. *PLoS One* 2016; **11**: e0154441 [PMID: 27115138 DOI: 10.1371/journal.pone.0154441]

43 **Hershcovici T**, Jha LK, Johnson T, Gerson L, Stave C, Malo J, Knox KS, Quan S, Fass R. Systematic review: the relationship between interstitial lung diseases and gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2011; **34**: 1295-1305 [PMID: 21999527 DOI: 10.1111/j.1365-2036.2011.04870.x]

44 **Lee JS**, Collard HR, Anstrom KJ, Martinez FJ, Noth I, Roberts RS, Yow E, Raghu G; IPFnet Investigators. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. *Lancet Respir Med* 2013; **1**: 369-376 [PMID: 24429201 DOI: 10.1016/S2213-2600(13)70105-X]

45 **Rangappa P**, Moran JL. Outcomes of patients admitted to the intensive care unit with idiopathic pulmonary fibrosis. *Crit Care Resusc* 2009; **11**: 102-109 [PMID: 19485873]

46 **Koyauchi T**, Hasegawa H, Kanata K, Kakutani T, Amano Y, Ozawa Y, Matsui T, Yokomura K, Suda T. Efficacy and Tolerability of High-Flow Nasal Cannula Oxygen Therapy for Hypoxemic Respiratory Failure in Patients with Interstitial Lung Disease with Do-Not-Intubate Orders: A Retrospective Single-Center Study. *Respiration* 2018; **96**: 323-329 [PMID: 29954000 DOI: 10.1159/000489890]

47 **Koyauchi T**, Yasui H, Enomoto N, Hasegawa H, Hozumi H, Suzuki Y, Karayama M, Furuhashi K, Fujisawa T, Nakamura Y, Inui N, Yokomura K, Suda T. Pulse oximetric saturation to fraction of inspired oxygen (SpO(2)/FIO(2)) ratio 24 h after high-flow nasal cannula (HFNC) initiation is a good predictor of HFNC therapy in patients with acute exacerbation of interstitial lung disease. *Ther Adv Respir Dis* 2020; **14**: 1753466620906327 [PMID: 32046604 DOI: 10.1177/1753466620906327]

48 **Ito J**, Nagata K, Morimoto T, Kogo M, Fujimoto D, Nakagawa A, Otsuka K, Tomii K. Respiratory management of acute exacerbation of interstitial pneumonia using high-flow nasal cannula oxygen therapy: a single center cohort study. *J Thorac Dis* 2019; **11**: 103-112 [PMID: 30863578 DOI: 10.21037/jtd.2018.12.114]

49 **Bräunlich J**, Beyer D, Mai D, Hammerschmidt S, Seyfarth HJ, Wirtz H. Effects of nasal high flow on ventilation in volunteers, COPD and idiopathic pulmonary fibrosis patients. *Respiration* 2013; **85**: 319-325 [PMID: 23128844 DOI: 10.1159/000342027]

50 **Yokoyama T**, Kondoh Y, Taniguchi H, Kataoka K, Kato K, Nishiyama O, Kimura T, Hasegawa R, Kubo K. Noninvasive

ventilation in acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2010; **49**: 1509-1514 [PMID: 20686281 DOI: 10.2169/internalmedicine.49.3222]

51 **Vianello A**, Arcaro G, Battistella L, Pipitone E, Vio S, Concas A, Paladini L, Gallan F, Marchi MR, Tona F, Iliceto S. Noninvasive ventilation in the event of acute respiratory failure in patients with idiopathic pulmonary fibrosis. *J Crit Care* 2014; **29**: 562-567 [PMID: 24768565 DOI: 10.1016/j.jcrc.2014.03.019]

52 **Yokoyama T**, Tsushima K, Yamamoto H, Koizumi T, Kubo K. Potential benefits of early continuous positive pressure ventilation in patients with rapidly progressive interstitial pneumonia. *Respirology* 2012; **17**: 315-321 [PMID: 21883678 DOI: 10.1111/j.1440-1843.2011.02051.x]

53 **Al-Hameed FM**, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. *Can Respir J* 2004; **11**: 117-122 [PMID: 15045042 DOI: 10.1155/2004/379723]

54 **Fernández-Pérez ER**, Yilmaz M, Jenad H, Daniels CE, Ryu JH, Hubmayr RD, Gajic O. Ventilator settings and outcome of respiratory failure in chronic interstitial lung disease. *Chest* 2008; **133**: 1113-1119 [PMID: 17989156 DOI: 10.1378/chest.07-1481]

55 **Syed MKH**, Selickman J, Evans MD, Dries D, Marini JJ. Elastic Power of Mechanical Ventilation in Morbid Obesity and Severe Hypoxemia. *Respir Care* 2021; **66**: 626-634 [PMID: 33262172 DOI: 10.4187/respcare.08234]

56 **Acute Respiratory Distress Syndrome Network**, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1301-1308 [PMID: 10793162 DOI: 10.1056/NEJM200005043421801]

57 **Nava S**, Rubini F. Lung and chest wall mechanics in ventilated patients with end stage idiopathic pulmonary fibrosis. *Thorax* 1999; **54**: 390-395 [PMID: 10212101 DOI: 10.1136/thx.54.5.390]

58 **Mollica C**, Paone G, Conti V, Ceccarelli D, Schmid G, Mattia P, Perrone N, Petroianni A, Sebastiani A, Cecchini L, Orsetti R, Terzano C. Mechanical ventilation in patients with end-stage idiopathic pulmonary fibrosis. *Respiration* 2010; **79**: 209-215 [PMID: 19546508 DOI: 10.1159/000225932]

59 **Combes A**, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. *N Engl J Med* 2018; **378**: 1965-1975 [PMID: 29791822 DOI: 10.1056/NEJMoa1800385]

60 **Peek GJ**, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support *vs* extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; **374**: 1351-1363 [PMID: 19762075 DOI: 10.1016/S0140-6736(09)61069-2]

61 **Trudzinski FC**, Kaestner F, Schäfers HJ, Fähndrich S, Seiler F, Böhmer P, Linn O, Kaiser R, Haake H, Langer F, Bals R, Wilkens H, Lepper PM. Outcome of Patients with Interstitial Lung Disease Treated with Extracorporeal Membrane Oxygenation for Acute Respiratory Failure. *Am J Respir Crit Care Med* 2016; **193**: 527-533 [PMID: 26492547 DOI: 10.1164/rccm.201508-1701OC]

62 **Kapnadak SG**, Raghu G. Lung transplantation for interstitial lung disease. *Eur Respir Rev* 2021; **30** [PMID: 34348979 DOI: 10.1183/16000617.0017-2021]

63 **Chambers DC**, Cherikh WS, Harhay MO, Hayes D Jr, Hsich E, Khush KK, Meiser B, Potena L, Rossano JW, Toll AE, Singh TP, Sadavarte A, Zuckermann A, Stehlik J; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: Donor and recipient size match. *J Heart Lung Transplant* 2019; **38**: 1042-1055 [PMID: 31548030 DOI: 10.1016/j.healun.2019.08.001]

64 **Leard LE**, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, Campos SV, Christon LM, Cypel M, Dellgren G, Hartwig MG, Kapnadak SG, Kolaitis NA, Kotloff RM, Patterson CM, Shlobin OA, Smith PJ, Solé A, Solomon M, Weill D, Wijsenbeek MS, Willemse BWM, Arcasoy SM, Ramos KJ. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2021; **40**: 1349-1379 [PMID: 34419372 DOI: 10.1016/j.healun.2021.07.005]

65 **Gersten RA**, Seth B, Arellano L, Shore J, O'Hare L, Patel N, Safdar Z, Krishna R, Mageto Y, Cochran D, Lindell K, Danoff SK; Pulmonary Fibrosis Foundation. Provider Perspectives on and Access to Palliative Care for Patients With Interstitial Lung Disease. *Chest* 2022; **162**: 375-384 [PMID: 35305969 DOI: 10.1016/j.chest.2022.03.009]

66 **Rajala K**, Lehto JT, Saarinen M, Sutinen E, Saarto T, Myllärniemi M. End-of-life care of patients with idiopathic pulmonary fibrosis. *BMC Palliat Care* 2016; **15**: 85 [PMID: 27729035 DOI: 10.1186/s12904-016-0158-8]

World Journal of Critical Care Medicine

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World J Crit Care Med 2023 June 9; 12(3): 165-175

DOI: 10.5492/wjccm.v12.i3.165

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Case Control Study

Causative bacteria of ventilator-associated pneumonia in intensive care unit in Bahrain: Prevalence and antibiotics susceptibility pattern

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ewers A, Austria; Karim HMR, India

Received: December 23, 2022
Peer-review started: December 23, 2022
First decision: January 31, 2023
Revised: February 3, 2023
Accepted: March 24, 2023
Article in press: March 24, 2023
Published online: June 9, 2023

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Abstract

BACKGROUND

Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs two calendar days following endotracheal intubation or after that. It is the most common infection encountered among intubated patients. VAP incidence showed wide variability between countries.

AIM
To define the VAP incidence in the intensive care unit (ICU) in the central gove-rnment hospital in Bahrain and review the risk factors and the predominant bacterial pathogens with their antimicrobial susceptibility pattern.

METHODS
The research was a prospective cross-sectional observational study over six months from November 2019 to June 2020. It included adult and adolescent patients (> 14 years old) admitted to the ICU and required intubation and mechanical ventilation. VAP was diagnosed when it occurred after 48 h after endotracheal intubation using the clinical pulmonary infection score, which considers the clinical, laboratory, microbiological, and radiographic evidence.

RESULTS
The total number of adult patients admitted to the ICU who required intubation and mechanical ventilation during the study period was 155. Forty-six patients developed VAP during their ICU stay (29.7%). The calculated VAP rate was 22.14 events per 1000 ventilator days during the study period, with a mean age of 52 years ± 20. Most VAP cases had late-onset VAP with a mean number of ICU days before the development of VAP of 9.96 ± 6.55. Gram-negative contributed to most VAP cases in our unit, with multidrug-resistant Acinetobacter being the most identified pathogen.

CONCLUSION
The reported VAP rate in our ICU was relatively high compared to the international benchmark, which should trigger a vital action plan for reinforcing the implementation of the VAP prevention bundle.

Key Words: Ventilator-associated pneumonia; Intensive care unit; Antibiotics susceptibility pattern; Kingdom of Bahrain; Adults; Bacterial resistance; Acinetobacter

Core Tip: Ventilator-associated pneumonia (VAP) is the most common infection among intubated patients. Early-onset VAP is usually caused by sensitive pathogens, while multidrug-resistant bacteria usually cause late-onset. Early, appropriate, and empirical antibiotics therapy for VAP is crucial to decreasing mortality risk. The VAP rate in Bahrain is relatively high compared to the international rates, which should trigger a vital action plan for reinforcing the implementation of the VAP prevention bundle. Gram-negative bacteria were the most common organisms that cause VAP in the current study, where *Acinetobacter baumannii* was the most common organism, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Knowing the prevalent organisms helps choose the appropriate antibiotics until culture and sensitivity become available.

Citation: Hassan ME, Al-Khawaja SA, Saeed NK, Al-Khawaja SA, Al-Awainati M, Radhi SSY, Alsaffar MH, Al-Beltagi M. Causative bacteria of ventilator-associated pneumonia in intensive care unit in Bahrain: Prevalence and antibiotics susceptibility pattern. *World J Crit Care Med* 2023; 12(3): 165-175
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/165.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.165

INTRODUCTION

Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs two calendar days following endotracheal intubation or after that. It is the most common infection encountered among intubated patients[1]. It occurs in 10%-30% of mechanically ventilated patients[2-4]. The VAP incidence showed wide variability, ranging from 10 to 41.7 per 1000 ventilator days in developing countries[5], while the rate is much lower in developed countries ranging between 1.2 and 8.5 per 1000 ventilator days[6].

Early-onset VAP is defined as pneumonia that occurs within four days of endotracheal intubation. It is usually attributed to sensitive pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and methicillin-sensitive *Staphylococcus aureus*. In contrast, late-onset VAP emerges after four days of intubation. It is caused by multidrug-resistant (MDR) bacteria such as methicillin-resistant *S. aureus* (MRSA), *Acinetobacter*, *Pseudomonas aeruginosa*, and extended-spectrum beta-lactamase-producing

bacteria. VAP caused by fungal and viral pathogens has a low contribution and tend to occur among immunocompromised host[5].

The risk for VAP is most significant during the first five days after intubation (3%), with the mean duration between intubation and development of VAP being 3.3 d. This risk declines to 2%/d between days 5 to 10 of ventilation and 1%/d after that[7]. Many previous studies showed that the related mortality for VAP ranges between 33%–50%, but this rate fluctuates and depends heavily on the underlying medical illness[5]. The diagnosis of VAP in the intensive care unit (ICU) remains challenging due to the absence of universally accepted gold-standard diagnostic criteria for VAP[8]. The clinical pulmonary infection score (CPIS) is one of the best diagnostic tools considering the clinical, physiological, microbiological, and radiographic evidence to allow a numerical value to predict the presence or absence of VAP[9,10].

Early, appropriate, and empirical antibiotics therapy for VAP is crucial as any delay in initiating proper antibiotics may increase the mortality risk with VAP. Consequently, selecting the appropriate regimen should be guided by the updated local antibiogram for each hospital and ICU. This study aimed to define VAP incidence in the ICU at Salmaniya Medical Complex, Bahrain's leading tertiary care government hospital. The study also reviewed the risk factors and the predominant pathogens that cause VAP, which helps choose the appropriate empiric antimicrobial therapy for VAP-related sepsis in adult ICU.

MATERIALS AND METHODS

The study was a prospective, observational, cross-sectional study conducted at the adult ICU in Salmaniya Medical Complex from November 2019 to June 2020 to determine the microbiological profile of adult patients with VAP and evaluate the magnitude of MDR microbes among those patients. We used patients who needed mechanical ventilation and did not develop VAP as a control group. The Research and Ethics Committee at Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, approved the study. We did not collect consent, as the study was observational, without exposure to any personal data.

Sample size and inclusion criteria

We did not determine a preset sample size as we included all the patients admitted to the adult ICU during the study periods (November 2019-June 2020) when they met the inclusion criteria. We included adult and adolescent patients (> 14 years old) who were admitted to the ICU and required intubation and mechanical ventilation.

Diagnostic criteria of VAP

VAP was diagnosed when it occurs after 48 h after endotracheal intubation and mechanical ventilation based on the scoring system by using the CPIS, considering the clinical, laboratory, microbiological, and radiographic evidence to allow a numerical value to predict the presence or absence of VAP[7,11-13] as summarized in Table 1. We considered the VAP as early-onset when it occurred in the first four days following intubation and late-onset after the fourth day of intubation.

The laboratory parameters (leukocyte count and microbial profile) were obtained daily from the patient's laboratory data and documented in the study datasheets. The treating clinical teams assessed the radiological finding and oxygenation status. Temperature documentation and assessment of tracheal secretions were obtained from the assigned nurses' notes, which are part of their daily assessment of intubated patients. All culture reports were reviewed by the medical microbiologist and infectious diseases (ID) consultant. A summative score was calculated for each patient enrolled in the study. The scores range between 0 and 12, with a score of ≥ 6 showing a good correlation with the presence of VAP.

Microbiology

The microbial profile of endotracheal specimens isolated from the enrolled patients was identified as part of CPIS diagnostic criteria. Positive cultures (aerobic, anaerobic, and/or fungal) were further analyzed by full antibiotics sensitivity pattern with identification of MDR according to the standard definition of the Clinical Laboratory Standards Institute[14]. The medical microbiologist and the ID consultants reviewed all microbial data.

Calculation of VAP rate

VAP rate was calculated as a percentage of patients who developed VAP out of all intubated patients in the ICU during the study period.

VAP rate per 1000 ventilator days was also calculated according to the centers for disease control and prevention surveillance formula[15] by dividing the VAP cases (defined by CPIS ≥ 6) over the patient-ventilator days during the same period and multiplying by 1000.

Table 1 The clinical pulmonary infection score

Assessed parameter	Result	Score
Temperature (°Celsius)	36.5–38.4 °C	0
	38.5–38.9 °C	1
	≤ 36 or ≥ 39 °C	2
Leukocytes in blood (cells/mm^3)	4000–11000/mm^3	0
	< 4000 or > 11000/mm^3	1
	≥ 500 band cells	2
Tracheal secretions (subjective visual scale)	None	0
	Mild/non-purulent	1
	Purulent	2
Radiographic findings (on chest radiography, excluding CHF and ARDS)	No infiltrate	0
	Diff use/patchy infiltrate	1
	Localized infiltrate	2
Culture results (endotracheal aspirate)	No or mild growth	0
	Moderate or florid growth	1
	Moderate or florid growth and pathogen consistent with gram stain	2
Oxygenation status	> 240 or ARDS	1
	≤ 240 and absence of ARDS	2

CHF: Congestive heart failure; ARDS: Acute respiratory distress syndrome.

Risk factors and complications

To analyze the predisposing factors for VAP and the risk of complications, we evaluated the following variables among all enrolled patients and compared between the two groups: The VAP patients (case group) and non-VAP patients (control group) such as age, gender, presence of comorbidities, source of admission, and the number of ICU days before intubation, the outcome including the mortality, development of complication and the need for tracheostomy.

Statistical analysis

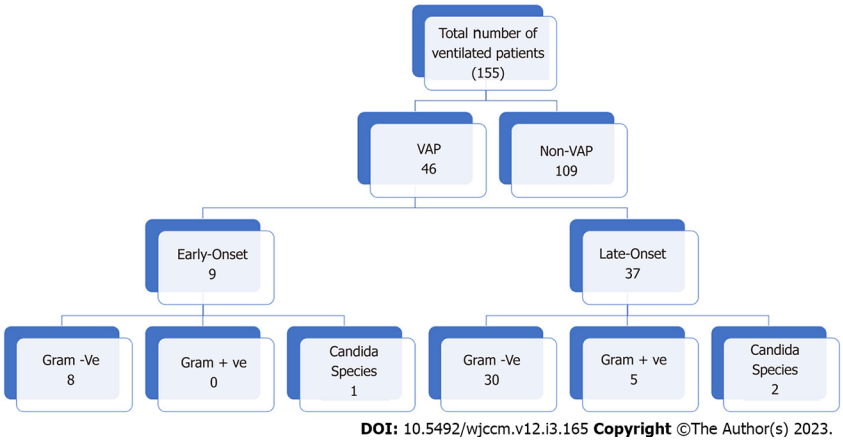
We performed a descriptive analysis, expressing the categorical variables in numbers and percentages and the quantitative variables in means and standard deviations. We compared the categorical variables as appropriate, using the χ^2 test or Fisher's exact test (when the expected n is less than 5). In addition, we used the *t*-test or Mann-Whitney U test to compare continuous variables. Statistical significance was established at 95% ($P < 0.05$). All statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY).

Ethical clearance

The investigation followed the latest version of the Declaration of Helsinki and was approved by the Secondary Research Committee of Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain. We did not get consent from the patients as it was a descriptive non-interventional study without disclosure of any patients' data.

RESULTS

Figure 1 shows the flow chart of the study. The total number of adult patients admitted to the ICU who required intubation and mechanical ventilation during the study period was 155. Forty-six patients developed VAP during their ICU stay (29.7%), with a VAP rate of 22.14 events per 1000 ventilator days. The mean age of patients who developed VAP was 52 ± 20 (range 27–88 years.), and 32 were male (69.6%). The mean number of ICU days before VAP development was 9.96 ± 6.55 d. Most VAP cases were late-onset, with a mean time interval between intubation and VAP diagnosis of 11.37 ± 6.67 d.



DOI: 10.5492/wjccm.v12.i3.165

Figure 1 The flow chart of the study. VAP: Ventilator-associated pneumonia.

Thirty-seven cases (80.4%) were late-onset VAP that was developed after 96 h from intubation, while 9 cases (19.6%) were early-onset VAP (developed within initial 96 d post-intubation). The most common comorbidities among VAP cases were diabetes mellitus and hypertension (19 patients, 41.3 % of VAP cases). Other identified comorbid conditions include chronic kidney disease (7, 15.2%), ischemic heart disease (6, 13%), and neurological disorder (5, 10.9%). Less identified comorbidities included malignancy (4, 8.7%), chronic liver disease (3, 6.5%), and sickle cell disease (3, 6.5%).

Table 2 showed no statistically significant difference between VAP and non-VAP groups regarding age, sex, and the number of hospital or ICU stays before intubation. Hypertension was the only significant risk factor for VAP acquisition among ICU intubated patients regarding the underlying comorbidities. Complications differ significantly among the VAP and non-VAP groups, where the duration of mechanical ventilation and the length of ICU stay were significantly higher in the VAP group ($P = 0.009$, < 0.001, respectively).

The rate of septic shock, acute respiratory distress syndrome (ARDS), and acute kidney injury was significantly higher in the VAP group than in the non-VAP group. On the other hand, the rate of pneumothorax did not show a significant difference between both groups. Notably, the extubation failure and the rate of tracheostomy and reintubation among extubated patients were significantly higher among the VAP group than in non-VAP groups. The overall ICU mortality rate was 22.6% (35/155) in all mechanically ventilated patients. However, there was no significant difference in mortality between both groups.

Table 3 shows the most common organisms isolated from patients with VAP. The total number of isolates was 46. Twenty percent of the isolates were from early-onset VAP, while 80% were from late-onset VAP. About 58.7% of the total isolates showed MDR. In early-onset VAP, gram-negative bacteria formed 89% of the total isolates (75% were MDR), followed by candida (11%). No gram-positive isolates were detected. *Acinetobacter baumannii* was the most common isolated gram-negative bacteria (50%); all were MDR. *Klebsiella pneumoniae* was the second most common gram-negative bacteria (37.5%) isolated; two-thirds were MDR. In late-onset VAP, gram-negative bacteria formed 81% of the total isolates (70% were MDR), followed by gram-positive (13.5%) and candida (5.4%). *Acinetobacter baumannii* was the most common isolated gram-negative bacteria (50%); 93% were MDR. *Klebsiella pneumoniae* was the second most common gram-negative bacteria (16.6%) isolated; all were MDR. *Pseudonomas aeruginosa* was detected in 8% of late-VAP, 33% of them were MDR. We detected only one MRSA isolate in the samples collected from VAP (20% of all five gram-positive isolates). We also detected candida in 2 cases with late-onset VAP (5.4%).

Tables 4 and 5 showed the antibiotic susceptibility among the bacterial isolates from patients with VAP. *Acinetobacter baumannii,* which was the most common organism isolated from VAP, had 100% susceptibility to Colistin, 37% susceptibility to Trimethoprim/sulfamethoxazole, Gentamicin, and Amikacin, 21% susceptibility to Tigecycline, low susceptibility (5%) to Ciprofloxacin, Piperacillin-Tazobactam, Cefepime, Meropenem, Imipenem, and Ertapenem, and resistance to Levofloxacin. *Klebsiella pneumonia,* which was the second most common organism isolated from VAP, had 87.5% susceptibility to Tigecycline, 62.5% susceptibility to Colistin, 50% susceptibility to Trimethoprim/sulfamethoxazole, 37% susceptibility to Gentamicin, and Amikacin, 12.5% susceptibility to Levofloxacin, Cefepime, Meropenem, Imipenem, Ertapenem, Amoxiclav, Cefuroxime, and Ceftriaxone. However, it showed complete resistance to Ceftazidime and Piperacillin-Tazobactam. *Stenotrophomonas maltophilia* had 100% susceptibility to Trimethoprim/sulfamethoxazole, Levofloxacin, and Minocycline. It had 20% susceptibility to Ceftazidime. At the same time, *Pseudomonas aeruginosa* had 100% susceptibility to Ceftazidime, Piperacillin-Tazobactam, Cefepime, Colistin, Gentamicin, Amikacin, and Ciprofloxacin, 66.6% susceptibility to Meropenem, Imipenem, and Ertapenem. MRSA was 100% susceptible to Erythromycin, Clindamycin, Tetracycline, and Vancomycin.

Table 2 Comparison between ventilator-associated pneumonia and non-ventilator-associated pneumonia groups for risk factors and complications, *n* (%)

Risk factors and complications		VAP group, *n* = 46	Non-VAP group, *n* = 109	*P* value
Age, mean ± SD		52.74 ± 20.42	61.45 ± 65.05	> 0.5
Sex, males%		32 (69.57)	73 (66.97)	> 0.5
Number of hospital days before intubation, mean ± SD		5.39 ± 8.11	3.38 ± 6.37	> 0.5
Number of ICU days before intubation, mean ± SD		0.52 ± 1.94	0.47 ± 2.78	> 0.5
Presence of comorbidities	Diabetes mellitus	19 (41.30)	54 (49.54)	> 0.5
	Hypertension	19 (41.30)	67 (61.47)	> 0.5
	Chronic kidney disease	7 (15.22)	28 (25.69)	> 0.5
	Ischemic heart disease	6 (13.04)	25 (22.94)	> 0.5
	Neurological disorder	5 (10.87)	9 (8.26)	> 0.5
	Malignancy	4 (8.70)	3 (2.75)	> 0.5
	Liver disease	3 (6.52)	8 (7.34)	> 0.5
	Sickle cell disease	3 (6.52)	3 (2.75)	> 0.5
Hospital course	Length of ICU stay, mean ± SD	21.41 ± 11.89	11.01 ± 10.38	< 0.001[a]
	Duration of mechanical ventilation, mean ± SD	16.67 ± 8.70	12.03 ± 10.53	0.009[a]
	Extubation	18 (39.13)	79 (72.48)	< 0.001[a]
	Need of re-intubation	12 (26.09)	11 (10.09)	0.014[a]
	Tracheostomy	14 (30.43)	9 (8.26)	< 0.001[a]
Potential complication	Septic shock	28 (60.87)	31 (28.44)	< 0.001[a]
	ARDS	15 (32.61)	12 (11.01)	0.002[a]
	Acute kidney injury	24 (52.17)	36 (33.03)	0.031[a]
	Pneumothorax	1 (2.17)	2 (1.83)	> 0.5
	Mortality, deaths	14 (30.43)	21 (19.27)	> 0.5

[a]Means significant.

ARDS: Acute respiratory distress syndrome; VAP: Ventilator-associated pneumonia; ICU: Intensive care unit.

DISCUSSION

The Incidence of VAP among intubated patients in the current study was 29.7%; this figure is comparable to the incidence reported by other investigators in the developing region (15%–58%)[16,17]. The calculated VAP rate was 22.14 events per 1000 ventilator days which is high compared to the international standards[18] and to the rate reported by neighboring countries of the Gulf Cooperation Council, which reported a VAP rate of 4.8 per 1000 ventilator days[19]; but our rate was comparable to most data reported by other developing countries[20,21].

Such high incidence should trigger a vital action plan to reinforce healthcare workers' adherence to the recommended preventive VAP bundle.

The current study showed that age and gender were not essential risk factors for VAP development. This agrees with a recently published study by Zubair *et al*[22] in 2018, which demonstrated that age or gender was not a significant risk factor in developing VAP[22]. However, this finding contradicts many previous studies that defined age and gender as important independent risk factors in developing VAP [23-26].

The current study agrees with other previously published studies that VAP development significantly increases the need for re-intubation and tracheostomy and the risk of systemic complications such as septic shock, ARDS, and acute kidney injury, in addition to increasing the duration of mechanical ventilation and length of ICU stay in patients admitted to ICU[27]. Nevertheless, VAP was not a significant risk factor for the increased mortality rate among intubated patients. This finding agreed with other previously published studies, which noted that the mortality risk was not significantly high in VAP presence[27,28]. In the current study, gram-negative bacteria were the most common organisms that cause VAP, whereas *Acinetobacter baumannii* was the most common organism

Table 3 Most common organisms isolated among patients with ventilator-associated pneumonia, *n* (%)

Organism	Total	Early-onset VAP (Number 9)		Late-onset VAP (Number 37)	
		Number (of total)	MDR	Number (of total)	MDR
Total gram negative	38 (82.6)	8 (21)	6 (75)	30 (79)	21 (70)
Acinetobacter baumannii	19 (50)	4 (21)	4 (100)	15 (79)	14 (93)
Klebsiella pneumoniae	8 (21.1)	3 (37.5)	2 (66.6)	5 (62.5)	5 (100)
Pseudomonas aeruginosa	3 (9)	0	0	3 (100)	1 (33.3)
Stenotrophomonas maltophilia	5 (13.1)	0	0	5 (100)	0
Enterobacter asburiae	1 (2.6)	1 (100)	0	0	0
E coli	1 (2.6)	0	0	1	1 ESBL (100)
Hemophilus influenzae	1 (2.6)	0	0	1 (100)	0
Total gram positive	5 (11)	0	0	5 (100)	
Staph aureus	4 (80)	0	0	4 (100)	0
MRSA	1 (20)	0	0	1 (100)	0
	0	0	0	0	0
	0	0	0	0	0
Fungal infection					
Candida species	3 (100)	1 (33.3)	0	2 (66.6)	0
Total microorganisms	46 (100)	9 (19.6)	6 (13)	37 (80.4)	

VAP: Ventilator-associated pneumonia; MDR: Multidrug-resistant; ESBL: Extended spectrum beta-lactamase; MRSA: Methicillin-resistant *staphylococcus aureus*.

Table 4 Antibiotics sensitivity percentage of the common gram-positive causative organisms for patients with ventilator-associated pneumonia in our study, *n* (%)

Antimicrobial agent	MSSA, *n* = 4	MRSA, *n* = 1
Penicillin	0/4 = 0 (0)	0/1 = 0 (0)
Oxacillin	4 (100)	0/1 = 0 (0)
Erythromycin	4 (100)	1 (100)
Clindamycin	4 (100)	1 (100)
Tetracycline	4 (100)	1 (100)
Vancomycin	4 (100)	1 (100)

MSSA: Methicillin-sensitive *staphylococcus aureus*, MRSA: Methicillin-resistant *staphylococcus aureus*.

(50% of all VAP cases). This finding agrees with Ben Lakhal *et al*[29], who had 53% of their cases caused by *Acinetobacter baumannii*[29]. Staph aureus was the causative organism in 11% of all recorded VAP cases in our study, all isolated from late-onset VAP. However, this rate is much lower than in previous studies such as Jones[30] and Chi *et al*[31], who found that *Staphylococcus aureus* was the most common VAP-causing organism, followed by the gram-negative organism[30,31]. The increased prevalence of gram-negative over gram-positive organisms may indicate the changing pattern of the nosocomial infection's microbial profile, including VAP in our region. Unfortunately, we did not have previous studies in our country to compare.

In the current study, *Acinetobacter baumannii* was the most common organism isolated from patients with VAP, with a rate of 44.4% in patients with early-onset VAP (93% MDR) and 40.5% in patients with late-onset VAP (100% MDR). *Acinetobacter baumannii* is an opportunistic pathogen with a high incidence among immunocompromised individuals, particularly those who have experienced a prolonged hospital stay. It is *commonly* associated with high humidity, colonizing the skin, and isolated in high numbers from infected individuals' respiratory and oropharynx secretions[32]. Previous studies showed

Table 5 Antibiotics sensitivity percentage of the common gram-negative causative organisms for ventilator-associated pneumonia in our study, *n* (%)

Antimicrobial agent	*Acinetobacter baumannii*	*Klebsiella pneumoniae*	*Stenotrophomonas maltophilia*	*Pseudomonas aeruginosa*
Number of organisms	19 (50)	8 (42)	5 (26)	3 (16)
Ceftazidime	1 (5.2)	0	1 (20)	3 (100)
Trimethoprim/sulfamethoxazole	7 (37)	4 (50)	5 (100)	-
Levofloxacin	0	1 (12.5)	5 (100)	-
Minocycline	-	-	5 (100)	-
Piperacillin-tazobactam	1 (5.2)	0	-	3 (100)
Cefepime	1 (5.2)	1 (12.5)	-	3 (100)
Meropenem	1 (5.2)	1 (12.5)	-	2 (66.6)
Imipenem	1 (5.2)	1 (12.5)	-	2 (66.6)
Ertapenem	1 (5.2)	1 (12.5)	-	2 (66.6)
Colistin	19 (100)	5 (62.5)	-	3 (100)
Gentamicin	7 (37)	3 (37.5)	-	3 (100)
Amikacin	7 (37)	3 (37.5)	-	3 (100)
Ciprofloxacin	1 (5.2)	1 (12.5)	-	3 (100)
Tigecycline	4 (21)	7 (87.5)	-	-
Ampicillin	-	-	-	-
Amoxiclav	-	1 (12.5)	-	-
Cefuroxime	-	1 (12.5)	-	-
Ceftriaxone	-	1 (12.5)	-	-

that *Acinetobacter baumannii* is prevalent and even endemic in many Middle East and North African countries. A study from Tunisia showed that *Acinetobacter baumannii* caused 45% of ICU-related infections with an MDR-resistance rate of 39% during an epidemic from 2004 to 2005[33]. Another study from Saudi Arabia showed that *Acinetobacter baumannii* was the most common organism isolated from late-onset VAP, causing 26.65% of cases[34]. In our *Acinetobacter baumannii* isolates, the overall MDR rate was 95% (100% and 93% in early-onset and late-onset VAP, respectively). Our institute considers *Acinetobacter baumannii* a "red alert" human pathogen due to the high rate of MDR with almost resistance to all antibiotics except for Colistin. It becomes a cause for serious concern regarding nosocomially acquired infections[35].

Klebsiella pneumoniae was the second most common organism isolated from our patients, with a rate of 17.4% throughout the study with an MDR rate of 87.5%. We detected *Klebsiella pneumoniae* in 33.3% of patients with early-onset VAP (66.6% MDR) and 13.5 % in patients with late-onset VAP (100% MDR). Our results agree with the work from Iran by Bozorgmehr *et al*[36], which showed that *Klebsiella pneumoniae* was the second most common organism isolated from 29.82% of the patients with VAP after *Acinetobacter baumannii*[36]. Our results also agree with the finding observed from a Thailand study that found that *Klebsiella pneumoniae* was the second most common organism isolated from 17.3% of the patients with VAP after *Acinetobacter baumannii*[37]. However, a study from Egypt in 2020 showed that *Klebsiella* spp was the most frequently isolated microorganism, followed by *Pseudomonas aeruginosa* and *Acinetobacter baumannii*[38].

The guidelines for initial empiric antimicrobial therapy for VAP are highly dependent on the type of causative pathogen and the time of diagnosis. Knowing the prevalent organisms helps choose the appropriate antibiotics until culture and sensitivity are available. However, the development of rapid identification technologies and phenotypic methods would significantly help the proper choice to improve the treatment outcomes for VAP. As many hospitals may lack rapid identification technologies, knowing the most common bacterial types causing VAP and their antibiogram may help physicians make quick decisions in VAP management.

Limitations of the study

As the study was a single center-based study in the adult population, this may hinder us from generalizing the data to other public or private hospital settings and the pediatric population. However,

despite the study's limitation, it can provide valuable data concerning the incidence rates and the prevalence of VAP in Bahrain, reflecting the rest of the Arabian Gulf region's status.

CONCLUSION

VAP is a common serious complication among intubated patients in our ICU; our VAP rate is relatively high compared to the international benchmark, which should trigger a vital action plan for reinforcing the implementation of the VAP prevention bundle. Gram-negative bacteria were the most common organisms that cause VAP in the current study, where *Acinetobacter baumannii* was the most common organism, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Knowing the prevalent organisms helps choose the appropriate antibiotics until culture and sensitivity become available.

ARTICLE HIGHLIGHTS

Research background

Ventilator-associated pneumonia (VAP) is the most common infection encountered among intubated patients, occurring in 10%-30% of mechanically ventilated patients.

Research motivations

The lack of data from the Kingdom of Bahrain stimulated us to investigate VAP incidence, risk factors, and microbial profiles in the central hospital in the kingdom.

Research objectives

We aimed to define VAP incidence in the intensive care unit (ICU) at Salmaniya Medical Complex and review the risk factors and the predominant pathogens that cause VAP to choose the appropriate empiric antimicrobial therapy for VAP-related sepsis in adult ICU.

Research methods

The study was a prospective, observational, cross-sectional study done between November 2019 to June 2020 to determine the microbiological profile in adult patients with VAP and evaluate the magnitude of multidrug-resistant (MDR) microbes among those patients. We used patients who needed mechanical ventilation and did not develop VAP as a control group. We included adult and adolescent patients (> 14 years old) who were admitted to the ICU and required intubation and mechanical ventilation.

Research results

The incidence of VAP was 29.7% during the study period, with a calculated VAP rate of 22.14 events per 1000 ventilator days and a mean age of 52 years ± 20. Most VAP cases had late-onset VAP with a mean number of ICU days before the development of VAP of 9.96 ± 6.55. Gram-negative contributed to most VAP cases in our unit, with MDR Acinetobacter being the most identified pathogen.

Research conclusions

The VAP rate in our ICU was relatively high compared to the international benchmark.

Research perspectives

The high VAP rate in our hospital triggered us to initiate a vital action plan to reinforce the implementation of the VAP prevention bundle.

ACKNOWLEDGEMENTS

We thank the anonymous referees for their valuable suggestions.

FOOTNOTES

Author contributions: Hassan ME, Al-Khawaja S, and Radhi SSY designed the study; Hassan ME, Radhi SSY, Al-Awainati M, and Alsaffar M collected and analyzed data; Saeed NK performed microbiological testing, data, and analysis; Hassan ME wrote the manuscript draft; Al-Beltagi M wrote, revised, and edited the final draft; All authors have read and approved the manuscript and take full responsibility for the study.

Institutional review board statement: The study was ethically approved by the Research and Research Ethics Committee for Governmental Hospitals, Salmaniya Medical Complex, Bahrain.

Informed consent statement: Consent was unnecessary as the study was observational without exposure to the patient's data.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at mbelrem@hotmail.com. Participants gave informed consent for data sharing. No additional data are available.

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S-Editor: Li L
L-Editor: A
P-Editor: Li L

REFERENCES

1 **Hunter JD**. Ventilator associated pneumonia. *BMJ* 2012; **344**: e3325 [PMID: 22645207 DOI: 10.1136/bmj.e3325]
2 **Horan TC**, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008; **36**: 309-332 [PMID: 18538699 DOI: 10.1016/j.ajic.2008.03.002]
3 **Horan TC**, Gayness RP. Surveillance of nosocomial infections. In: Mayhall CG, editor. Hospital Epidemiology and Infection Control. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 1659-1702
4 **Magill SS**, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, Lynfield R, Maloney M, McAllister-Hollod L, Nadle J, Ray SM, Thompson DL, Wilson LE, Fridkin SK; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014; **370**: 1198-1208 [PMID: 24670166 DOI: 10.1056/NEJMoa1306801]
5 **American Thoracic Society**; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; **171**: 388-416 [PMID: 15699079 DOI: 10.1164/rccm.200405-644ST]
6 **Indulski JA**, Krajewski JA, Majka JA, Dutkiewicz T. [Chemical safety (III)--its prospects in Poland]. *Med Pr* 1990; **41**: 77-85 [PMID: 2215203 DOI: 10.1186/cc10425]
7 **Kalanuria AA**, Ziai W, Mirski M. Ventilator-associated pneumonia in the ICU. *Crit Care* 2014; **18**: 208 [PMID: 25029020 DOI: 10.1186/cc13775]
8 **Anthony B**, Marin K, Hilary B. A Prospective Analysis of the National Healthcare Safety Network (NHSN) Surveillance Algorithm for Ventilator-Associated Events (VAEs). *Chest* 2013; **144** Suppl: 562A [DOI: 10.1378/chest.1704694]
9 **Klompas M**. Does this patient have ventilator-associated pneumonia? *JAMA* 2007; **297**: 1583-1593 [PMID: 17426278 DOI: 10.1001/jama.297.14.1583]
10 **Zilberberg MD**, Shorr AF. Ventilator-associated pneumonia: the clinical pulmonary infection score as a surrogate for diagnostics and outcome. *Clin Infect Dis* 2010; **51** Suppl 1: S131-S135 [PMID: 20597663 DOI: 10.1086/653062]
11 **Johanson WG Jr**, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with gram-negative bacilli. The significance of colonization of the respiratory tract. *Ann Intern Med* 1972; **77**: 701-706 [PMID: 5081492 DOI: 10.7326/0003-4819-77-5-701]
12 **Pugin J**, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis* 1991; **143**: 1121-1129 [PMID: 2024824 DOI: 10.1164/ajrccm/143.5_Pt_1.1121]
13 **Koenig SM**, Truwit JD. Ventilator-associated pneumonia: diagnosis, treatment, and prevention. *Clin Microbiol Rev* 2006; **19**: 637-657 [PMID: 17041138 DOI: 10.1128/CMR.00051-05]
14 **Clinical and Laboratory Standards Institute**. Performance Standards for Antimicrobial Susceptibility Testing. 28th ed. CLSI supplement M100.Wayne, PA: Clinical and Laboratory Standards Institute; 2018
15 **Center of Disease Prevention & Control**. Pneumonia (Ventilator-associated [VAP] and non-ventilator-associated Pneumonia [PNEU]) Event. Jan, 2023. [cited 23 February 2023]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf
16 **Morehead RS**, Pinto SJ. Ventilator-associated pneumonia. *Arch Intern Med* 2000; **160**: 1926-1936 [PMID: 10888967

DOI: 10.1001/archinte.160.13.1926]

17 **Osman S**, Al Talhi YM, AlDabbagh M, Baksh M, Osman M, Azzam M. The incidence of ventilator-associated pneumonia (VAP) in a tertiary-care center: Comparison between pre- and post-VAP prevention bundle. *J Infect Public Health* 2020; **13**: 552-557 [PMID: 31668986 DOI: 10.1016/j.jiph.2019.09.015]

18 **El-Saed A**, Balkhy HH, Weber DJ. Benchmarking local healthcare-associated infections: available benchmarks and interpretation challenges. *J Infect Public Health* 2013; **6**: 323-330 [PMID: 23999329 DOI: 10.1016/j.jiph.2013.05.001]

19 **El-Saed A**, Al-Jardani A, Althaqafi A, Alansari H, Alsalman J, Al Maskari Z, El Gammal A, Al Nasser W, Al-Abri SS, Balkhy HH. Ventilator-associated pneumonia rates in critical care units in 3 Arabian Gulf countries: A 6-year surveillance study. *Am J Infect Control* 2016; **44**: 794-798 [PMID: 27040565 DOI: 10.1016/j.ajic.2016.01.042]

20 **Rodrigues DO**, Cezário RC, Filho PP. Ventilator-associated pneumonia caused by multidrug- resistant Pseudomonas aeruginosa vs. other microorganisms at an adult clinical-surgical intensive care unit in a Brazilian University Hospital: Risk factors and outcomes. *Int J Med Med Sci***1**: 432-437 [DOI: 10.23959/sfdorj-1000024]

21 **Leblebicioglu H**, Erben N, Rosenthal VD, Atasay B, Erbay A, Unal S, Senol G, Willke A, Özgültekin A, Altin N, Bakir M, Oncul O, Ersöz G, Ozdemir D, Yalcin AN, Özdemir H, Yıldızdaş D, Koksal I, Aygun C, Sirmatel F, Sener A, Tuna N, Akan ÖA, Turgut H, Demiroz AP, Kendirli T, Alp E, Uzun C, Ulusoy S, Arman D. International Nosocomial Infection Control Consortium (INICC) national report on device-associated infection rates in 19 cities of Turkey, data summary for 2003-2012. *Ann Clin Microbiol Antimicrob* 2014; **13**: 51 [PMID: 25403704 DOI: 10.1186/s12941-014-0051-3]

22 **Zubair S**, Ali H, Raza SF, Warind JA, Beg AE, Bushra R. Assessment of Frequency and Transience Rate for Ventilator-Associated Pneumonia (VAP) in Geriatric Patients in Tertiary Care Settings of Karachi, Pakistan. *J Coll Physicians Surg Pak* 2018; **28**: 536-540 [PMID: 29950259 DOI: 10.29271/jcpsp.2018.07.536]

23 **Ding C**, Zhang Y, Yang Z, Wang J, Jin A, Wang W, Chen R, Zhan S. Incidence, temporal trend and factors associated with ventilator-associated pneumonia in mainland China: a systematic review and meta-analysis. *BMC Infect Dis* 2017; **17**: 468 [PMID: 28676087 DOI: 10.1186/s12879-017-2566-7]

24 **Liu Y**, Di Y, Fu S. Risk factors for ventilator-associated pneumonia among patients undergoing major oncological surgery for head and neck cancer. *Front Med* 2017; **11**: 239-246 [PMID: 28493197 DOI: 10.1007/s11684-017-0509-8]

25 **Bornstain C**, Azoulay E, De Lassence A, Cohen Y, Costa MA, Mourvillier B, Descorps-Declere A, Garrouste-Orgeas M, Thuong M, Schlemmer B, Timsit JF; Outcomerea Study Group. Sedation, sucralfate, and antibiotic use are potential means for protection against early-onset ventilator-associated pneumonia. *Clin Infect Dis* 2004; **38**: 1401-1408 [PMID: 15156478 DOI: 10.1086/386321]

26 **Forel JM**, Voillet F, Pulina D, Gacouin A, Perrin G, Barrau K, Jaber S, Arnal JM, Fathallah M, Auquier P, Roch A, Azoulay E, Papazian L. Ventilator-associated pneumonia and ICU mortality in severe ARDS patients ventilated according to a lung-protective strategy. *Crit Care* 2012; **16**: R65 [PMID: 22524447 DOI: 10.1186/cc11312]

27 **Othman AA**, Abdelazim MS. Ventilator–associated pneumonia in adult intensive care unit prevalence and complication. *The Egyptian Journal of critical care medicine* 2017; **5**: 61-63 [DOI: 10.1016/j.ejccm.2017.06.001]

28 **Tejerina E**, Frutos-Vivar F, Restrepo MI, Anzueto A, Abroug F, Palizas F, González M, D'Empaire G, Apezteguía C, Esteban A; Internacional Mechanical Ventilation Study Group. Incidence, risk factors, and outcome of ventilator-associated pneumonia. *J Crit Care* 2006; **21**: 56-65 [PMID: 16616625 DOI: 10.1016/j.jcrc.2005.08.005]

29 **Ben Lakhal H**, M'Rad A, Naas T, Brahmi N. Antimicrobial Susceptibility among Pathogens Isolated in Early- versus Late-Onset Ventilator-Associated Pneumonia. *Infect Dis Rep* 2021; **13**: 401-410 [PMID: 33925385 DOI: 10.3390/idr13020038]

30 **Jones RN**. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis* 2010; **51** Suppl 1: S81-S87 [PMID: 20597676 DOI: 10.1086/653053]

31 **Chi SY**, Kim TO, Park CW, Yu JY, Lee B, Lee HS, Kim YI, Lim SC, Kwon YS. Bacterial pathogens of ventilator associated pneumonia in a tertiary referral hospital. *Tuberc Respir Dis (Seoul)* 2012; **73**: 32-37 [PMID: 23101022 DOI: 10.4046/trd.2012.73.1.32]

32 **Howard A**, O'Donoghue M, Feeney A, Sleator RD. Acinetobacter baumannii: an emerging opportunistic pathogen. *Virulence* 2012; **3**: 243-250 [PMID: 22546906 DOI: 10.4161/viru.19700]

33 **Brahmi N**, Beji O, Abidi N, Kouraichi N, Blel Y, El Ghord H, Thabet H, Amamou M. Epidemiology and risk factors for colonization and infection by Acinetobacter baumannii in an ICU in Tunisia, where this pathogen is endemic. *J Infect Chemother* 2007; **13**: 400-404 [PMID: 18095089 DOI: 10.1007/s10156-007-0557-0]

34 **El-Saed A**, Balkhy HH, Al-Dorzi HM, Khan R, Rishu AH, Arabi YM. Acinetobacter is the most common pathogen associated with late-onset and recurrent ventilator-associated pneumonia in an adult intensive care unit in Saudi Arabia. *Int J Infect Dis* 2013; **17**: e696-e701 [PMID: 23517779 DOI: 10.1016/j.ijid.2013.02.004]

35 **Peleg AY**, Seifert H, Paterson DL. Acinetobacter baumannii: emergence of a successful pathogen. *Clin Microbiol Rev* 2008; **21**: 538-582 [PMID: 18625687 DOI: 10.1128/CMR.00058-07]

36 **Bozorgmehr R**, Bahrani V, Fatemi A. Ventilator-Associated Pneumonia and Its Responsible Germs; an Epidemiological Study. *Emerg (Tehran)* 2017; **5**: e26 [PMID: 28286833]

37 **Chittawatanarat K**, Jaipakdee W, Chotirosniramit N, Chandacham K, Jirapongcharoenlap T. Microbiology, resistance patterns, and risk factors of mortality in ventilator-associated bacterial pneumonia in a Northern Thai tertiary-care university based general surgical intensive care unit. *Infect Drug Resist* 2014; **7**: 203-210 [PMID: 25152627 DOI: 10.2147/IDR.S67267]

38 **Farag AM**, Tawfick MM, Abozeed MY, Shaban EA, Abo-Shadi MA. Microbiological profile of ventilator-associated pneumonia among intensive care unit patients in tertiary Egyptian hospitals. *J Infect Dev Ctries* 2020; **14**: 153-161 [PMID: 32146449 DOI: 10.3855/jidc.12012]

World Journal of Critical Care Medicine

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World J Crit Care Med 2023 June 9; 12(3): 176-187

DOI: 10.5492/wjccm.v12.i3.176

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Observational Study

Knowledge and awareness of infection control practices among nursing professionals: A cross-sectional survey from South Asia and the Middle East

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bittner EA, United States; Marano L, Italy; Roilides E, Greece

Received: April 14, 2023
Peer-review started: April 14, 2023
First decision: May 9, 2023
Revised: May 15, 2023
Accepted: May 31, 2023
Article in press: May 31, 2023
Published online: June 9, 2023

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Abstract

BACKGROUND

The proficiency of nursing professionals in the infection prevention and control (IPC) practices is a core component of the strategy to mitigate the challenge of healthcare associated infections.

AIM

To test knowledge of nurses working in intensive care units (ICU) in South Asia and Middle East countries on IPC practices.

METHODS

An online self-assessment questionnaire based on various aspects of IPC practices was conducted among nurses over three weeks.

RESULTS

A total of 1333 nurses from 13 countries completed the survey. The average score was 72.8% and 36% of nurses were proficient (mean score > 80%). 43% and 68.3% of respondents were from government and teaching hospitals, respectively. 79.2% of respondents worked in < 25 bedded ICUs and 46.5% in closed ICUs. Statistically, a significant association was found between the knowledge and expertise of nurses, the country's per-capita income, type of hospitals, accreditation and teaching status of hospitals and type of ICUs. Working in high- and upper-middle-income countries (β = 4.89, 95%CI: 3.55 to 6.22) was positively associated, and the teaching status of the hospital (β = -4.58, 95%CI: -6.81 to -2.36) was negatively associated with the knowledge score among respondents.

CONCLUSION

There is considerable variation in knowledge among nurses working in ICU. Factors like income status of countries, public *vs* private and teaching status of hospitals and experience are independently associated with nurses' knowledge of IPC practices.

Key Words: Knowledge; Attitude; Policy compliance; Infection control; Infection control practices; Nurses

Core Tip: The knowledge testing on infection prevention and control (IPC) practices among intensive care unit nurses in South Asia and the Middle East showed considerable variation. The higher economic status of the country and working experience were independently associated with better knowledge among respondents. Working in public or teaching hospital were inversely associated with knowledge of IPC practices. There is an urgent need for education and awareness among nurses regarding IPC practices, especially in lower-middle-income countries.

Citation: Sodhi K, Chanchalani G, Arya M, Shrestha GS, Chandwani JN, Kumar M, Kansal MG, Ashrafuzzaman M, Mudalige AD, Al Tayar A, Mansour B, Saeed HM, Hashmi M, Das M, Al Shirawi NN, Mathias R, Ahmed WO, Sharma A, Agarwal D, Nasa P. Knowledge and awareness of infection control practices among nursing professionals: A cross-sectional survey from South Asia and the Middle East. *World J Crit Care Med* 2023; 12(3): 176-187

URL: https://www.wjgnet.com/2220-3141/full/v12/i3/176.htm

DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.176

INTRODUCTION

Healthcare-associated infections (HAI) pose a considerable threat to the patients who are admitted in hospitals, especially in intensive care units (ICU). According to the surveillance report published by the International Nosocomial Infection Control Consortium, despite appreciable efforts on prevention and control of HAI, the Device-Associated (DA)-HAI rates in the ICUs of developing countries are higher compared to the developed nations[1]. Though the device utilization rate is similar, the DA-HAI rates of the ICUs in the developing countries remain higher than the ones belonging to the Center for Disease Control and Prevention- National Healthcare and Safety Network[1,2]. Hence, a robust infection prevention and control (IPC) program involving multi-disciplinary stakeholders is essential to mitigate the threat of HAI[3]. However, the compliance with IPC practices has been a critical implication on the implementation of the IPC program. Nurses have frequent and direct contact with the patients due to which, their knowledge and awareness about the IPC practices are integral[4]. On the other hand, the nurses are also at-risk of self-infection when providing care to critically ill patients[5]. Several factors may affect the compliance with IPC practices, prominent of which are knowledge, education and training, and the experience of nurses[6]. The lack of knowledge among health care workers (HCWs) about the IPC practices or the occurrence of discrepancies when applying this knowledge in bedside has been linked to worsening healthcare delivery outcomes, especially in case of developing countries[6-8]. Recently, the global experts have recommended that the ICU nurses should be a part of the surveillance team that monitor adherence of IPC practices[9].

The countries in South Asia and the Middle East regions constitute one-third of the global population. In spite of such common neighborhoods and centuries of cultural and political exchange, these countries exhibit vast differences in terms of income, availability of the resources and healthcare dynamics[10].

Though studies have been conducted to evaluate the knowledge of the nurses from individual nations, the authors were unable to find any literature that compares the knowledge of the nurses across the South Asian and Middle Eastern nations[8,11,12]. So, the current study is aimed to analyse the knowledge of ICU nurses on various aspects of IPC practices across the countries in South Asia and the Middle East.

MATERIALS AND METHODS

The study was conducted over three weeks, from April 20 to May 10, 2022. An online-based, cross-sectional survey was conducted using a multiple-choice questionnaire to evaluate the knowledge of nurses on various aspects of the IPC program. A 20-member steering committee comprising of critical care physicians, infection control professionals, microbiologist and the nursing administrator was involved in framing the questionnaire and its pilot run. The questionnaire was examined, revised and validated internally among the steering committee. Internal consistency among the questionnaire items using Cronbach's alpha (α) was found to be 0.90, which was considered within the acceptable range. The study was approved by the Ethics Committee (DHEC-2057/2022) of the institute, where the principal investigator (Kanwalpreet Sodhi) is affiliated and is exempted from other participating hospitals.

The final questionnaire has two portions in which the first portion covered the aspects like country name, profile of the hospital such as the type of setup, hospital accreditation and their teaching status, the type, size and the operating model of the ICU, and the nurses' demographic data including their years of clinical experience. The operating model of the ICU had three options such as "Open ICU" in

which the patients are admitted under the care of a non-intensivist physician, with the intensivists providing their expertise consultation when required, "Closed ICU" in which the patients are admitted under an intensivist-led team, and is held responsible for the primary care, and "Semi-closed ICU" in which the intensivist-led team provides direct patient care in collaboration with the non-intensivist physicians with shared decision making[13]. The second portion of the questionnaire consisted of 25 single best response types, *i.e.*, multiple choice questions (MCQ) on different aspects of the IPC practices, categorized under five sections such as the general aspects of infection control, standard precautions, transmission-based precautions, care bundles, and severe acute respiratory syndrome coronavirus 2 transmission (Appendix). Each section had five MCQs, and respondents can score one mark for a correct response. The answers to the MCQs were decided *a priori* by the steering committee members (Kanwalpreet Sodhi, Muktanjali Arya Amandeep Sharma, Prashant Nasa). The knowledge level was categorized based on the mean overall score, secured by the participants, *i.e.*, more than 81% score as proficient, 61%-80% as above average, 41%-60% as average and less than 40% as poor knowledge (Table 1).

The survey was conducted using a web link circulated by the steering committee members of the respective participant countries. The study included around 4-5 tertiary care hospitals from each country. The questionnaire was distributed to the nurses who work full-time in ICUs, and they were asked to fill it anonymously and voluntarily. The nurse trainees were excluded from the study. The consent for participation in the study and the publication of the results was obtained from the respondents at the beginning of the online questionnaire. The STROBE checklist was used for reporting the results of this cross-sectional survey.

Statistical analysis

The data was described in terms of frequencies (number of cases) and relative frequencies (percentages) as appropriate. In order to compare the categorical data, the chi-square (χ^2) test was used. Both univariate and multivariate linear regression analyses were conducted to compare the covariates. A probability value (P value) less than 0.05 was considered to be statistically significant. The outcome variable for the linear regression analysis was the total score secured from the questionnaire and no continuous data sets were present. Collinearity was checked for each predictor variable whereas non-linear regression underwent the same analysis and yielded the same conclusions. (Appendix) Those variables obtaining a P value < 0.05 in the univariate analysis, were included in the multivariate linear regression analyses. The beta coefficient and the confidence intervals were used to present of the multivariate linear regression analysis. All the statistical calculations were done using (Statistical Package for the Social Science) SPSS version 21 (SPSS Inc., Chicago, IL, United States) statistical program for Microsoft Windows.

RESULTS

The questionnaire was filled out by 1376 nurses across 13 countries. Out of the total responses, 43 were excluded from the final analysis (11 with negative consent for participation, and 32 had missing information). The data from 1333 respondents (nurses) was considered for the study (Figure 1).

The demographic profile of the respondents' hospitals and the ICUs is provided in Table 2. For analysis, the countries of the respondents were divided according to the World Bank income classification criteria into high-income countries (HIC) (such as Bahrain, the United Arab Emirates, Oman, Qatar, Saudi Arabia, and Singapore); upper-middle-income countries (UMIC) (*i.e.*, Lebanon); and lower-middle-income countries (LMIC) (such as Bangladesh, Bhutan, India, Sri Lanka, Nepal, and Pakistan). Most of the respondents belong to HIC (608, 45.6%) and LMIC (656, 49.2%). The respondents had varying level of experience, with 232 (17.4%) nurses having less than two years of experience and 396 (29.7%) nurses with more than ten years of experience. Among the responding nurses, 524 (39%) worked in corporate or private hospitals, whereas 570(43%) were in public hospitals. Most of the respondents worked in a hospital, accredited either by an international agency like Joint Commission International (606, 45.5%), or a national level agency (442, 33.2%). Further, majority of the respondents (1056, 79.2%) were working in less than 25-bedded ICUs and 607 (45%) were in mixed medical and surgical ICUs. In terms of the operational model of ICU, 620 (46.5%) respondents were working in closed ICUs and nearly equal proportion (27%) were in open and semi-closed ICUs. Further most of the respondents (911, 68.3%) worked in teaching hospitals.

The average score of the respondents was 72.8% (Figure 2). In terms of knowledge level categories, 480 (36%) respondents were categorized as proficient, and 472 (35.4%) had above-average knowledge. Only 11% of the respondents with less than two years of experience, were found to be proficient, compared to 34% respondents who had 5-10 years of experience. The knowledge of 32% of nurses with > 10 years of experience was above average, compared to 18% nurses with < 2 years of experience (Table 1). A statistically significant difference was found between the respondents on knowledge testing based on the working experience of the nurses (P = 0.001). Further, there was also statistically significant difference in the knowledge of the nurses based on World Bank income status (P = 0.001). The

Table 1 Demographic profile of the respondents and scores achieved by the level of knowledge

	Number of respondents (%)		Number of respondents (%)
World Bank income classification		**Working experience (yr)**	
High-income countries	608 (45.6)	< 2 yr	232 (17.4)
Upper middle-income countries	69 (5.2)	2-5 yr	354 (26.6)
Lower middle-income countries	656 (49.2)	5-10 yr	351 (26.3)
		> 10 yr	396 (29.7)
Score attained by level of knowledge			
Proficient (81%-100%)	480 (36)	**Type of ICU**	
Above average (61%-80%)	472 (35.4)	Medical and Surgical ICU	607 (45.5)
Average (41%-60%)	296 (22.2)	Medical ICU	408 (30.6)
Below average (≤ 40%)	85 (6.4)	Others	318 (23.9)
Type of hospital		**Size of ICU (number of beds)**	
Corporate/private	524 (39)	< 25 bedded	1056 (79.2)
Medical college/university hospital	239 (18)	25-100 bedded	251 (18.8)
Public/government	570 (43)	> 100 bedded	26 (2.0)
Hospital accreditation		**Operating model of ICU**	
International	606 (45.5)	Closed ICU	620 (46.5)
National	442 (33.2)	Open ICU	355 (26.6)
None	285 (21.4)	Semi-closed ICU	358 (26.9)
Teaching status			
Non-teaching	422 (31.7)		
Teaching	911 (68.3)		

ICU: Intensive care unit.

performance of the respondents working in HIC and UMIC was found to be better than the LMIC. Further, 237 (38.9%) and 30 (43.5%) respondents from the HIC and UMIC, respectively, were found to be proficient, compared to 213 (32.4%) respondents from LMIC.

The difference in the knowledge of the respondents, based on the type of hospital was found to be statistically significant (P = 0.001). A more significant proportion of the nurses, working in corporate/private hospitals (231, 44.1%) and medical college/university hospitals (85, 35.6%) was found to be proficient than those working in public hospitals (164, 28.8%). There was also a statistically significant difference found in the knowledge of the nurses based on the accreditation status and teaching status of the hospital (P = 0.001).

In terms of the ICU setup, a difference was found in the knowledge of responding nurses for the type (P = 0.004) and size (P = 0.007) of the ICU. However, no significant difference was found in the knowledge of the respondents based on the operating model of ICU (P = 0.453) (Table 2).

In terms of multivariate analysis, the income status of the country (P < 0.001), type of the hospital (P < 0.001), teaching status (P < 0.001) and the experience of the nurses (P = 0.001) showed an independent association with a difference in knowledge among the nurses. Working in HIC and UMIC was found to be strongly associated with the high knowledge score secured by respondents (β = 4.89, 95%CI: 3.55 to 6.22). The teaching status of the hospital was inversely associated with the knowledge score secured by the respondents (β = -4.58, 95%CI: -6.81 to -2.36) (Table 3).

DISCUSSION

The cross-sectional survey results, on knowledge testing of the nurses working in 13 countries of South Asia and the Middle East, showed a considerable variation. About 3/4th of the respondents secured above average or proficient scores. Some of the factors like the higher economic status of the country and working experience were found to be independently associated with better knowledge among the

Table 2 Comparison of nurses' knowledge based on their experience and the demographic profile of the hospital and intensive care unit, *n* (%)

	Knowledge level categories				χ^2 value	*P* value
	Below average	Average	Above average	Proficient		
Working experience (yr)						
< 2 yr	24 (28.2)	69 (23.3%)	86 (18.2%)	53 (11%)	57.09	0.001[a]
2-5 yr	29 (34.1%)	84 (28.4%)	109 (23.1%)	132 (27.5%)		
5-10 yr	15 (17.6%)	48 (16.2%)	125 (26.5%)	163 (34.0%)		
> 10 yr	17 (20%)	95 (32.1%)	152 (32.2%)	132 (27.5%)		
World bank income classification						
High-income countries	14 (2)	119 (19.6)	238 (39.1)	237 (38.9)	46.47	0.001[a]
Lower-middle-income countries	68 (10.4)	164 (25)	211 (32.2)	213 (32.4)		
Upper-middle-income countries	3 (4.3)	13 (18.8)	23 (33.3)	30 (43.5)		
Type of hospital						
Corporate/private	42 (8)	98 (18.7)	153 (29.2)	231 (44.1)	60.53	0.001[a]
Medical college/university hospital	26 (10.9)	56 (23.4)	72 (30.1)	85 (35.6)		
Public/government	17 (2.9)	142 (24.9)	247 (43.3)	164 (28.8)		
Hospital accreditation						
International	30 (4.9)	120 (19.8)	220 (36.3)	236 (38.9)	30.56	0.001[a]
National	42 (9.5)	122 (27.6)	153 (34.6)	125 (28.3)		
None	13 (4.6)	54 (18.9)	99 (34.7)	119 (41.7)		
Teaching status						
Non-teaching	18 (4.2)	70 (16.6)	149 (35.3)	185 (43.8)	23.61	0.001[a]
Teaching	67 (7.3)	226 (24.8)	323 (35.5)	295 (32.4)		
Operating model of ICU						
Closed ICU	46 (7.4)	146 (23.5)	215 (34.7)	213 (34.4)	5.74	0.45
Open ICU	18 (5.1)	81 (22.8)	122 (34.4)	134 (37.7)		
Semi-closed ICU	21 (5.9)	69 (19.3)	135 (37.7)	133 (37.1)		
Type of ICU						
Medical-surgical ICU	30 (4.9)	113 (18.6)	221 (36.4)	243 (40)	19.39	0.004[a]
Medical ICU	30 (7.4)	98 (24)	134 (32.8)	146 (35.8)		
Other	25 (7.9)	85 (26.7)	117 (36.8)	91 (28.3)		
Size of ICU (number of beds)						
< 25	61 (5.8)	231 (21.9)	390 (36.9)	374 (35.4)	17.27	0.008[a]
25-100	18 (7.2)	59 (23.5)	77 (30.7)	97 (38.6)		
> 100	6 (23.1)	6 (23.1)	5 (19.2)	9 (34.6)		

[a]*P* value < 0.05 is significant.
ICU: Intensive care unit.

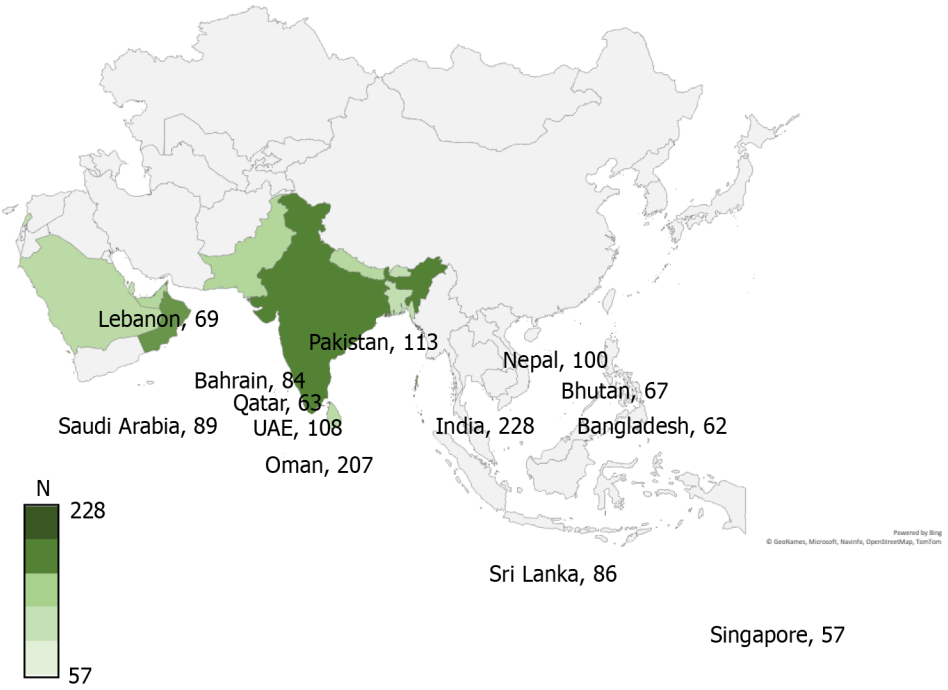
respondents. On the other hand, working in teaching or public hospitals was inversely associated with the knowledge level of IPC practices than the private and university hospitals.

In general, the ICUs show the highest prevalence of HAIs in a hospital setting. This may adversely affect the patients' clinical outcomes like length of stay in the hospital and ICU, quality of life after discharge, and mortality[14,15]. Nurses are the first and the foremost formidable line of defense against the HAIs. Hence their training, and awareness levels, knowledge, and compliance for the IPC practices are crucial in preventing the HAIs. The regional studies conducted earlier found gaps in the knowledge

Table 3 Multivariate analysis of demographic variables of respondents

Variables	Beta coefficient	*P* value	95%CI	
			Lower bound	Upper bound
Type of hospital	-3.76	< 0.001[a]	-5.03	-2.49
Hospital accreditation	0.89	0.24	-0.59	2.36
Teaching status	-4.58	< 0.001[a]	-6.81	-2.36
World bank income classification	4.89	< 0.001[a]	3.55	6.22
Type of ICU	-1.04	0.13	-2.40	0.32
Size of ICU	-2.01	0.07	-4.21	0.19
Working experience	1.71	0.001[a]	0.70	2.71

[a]$P < 0.05$ is significant.
CI: Confidence Interval, ICU: Intensive care unit.



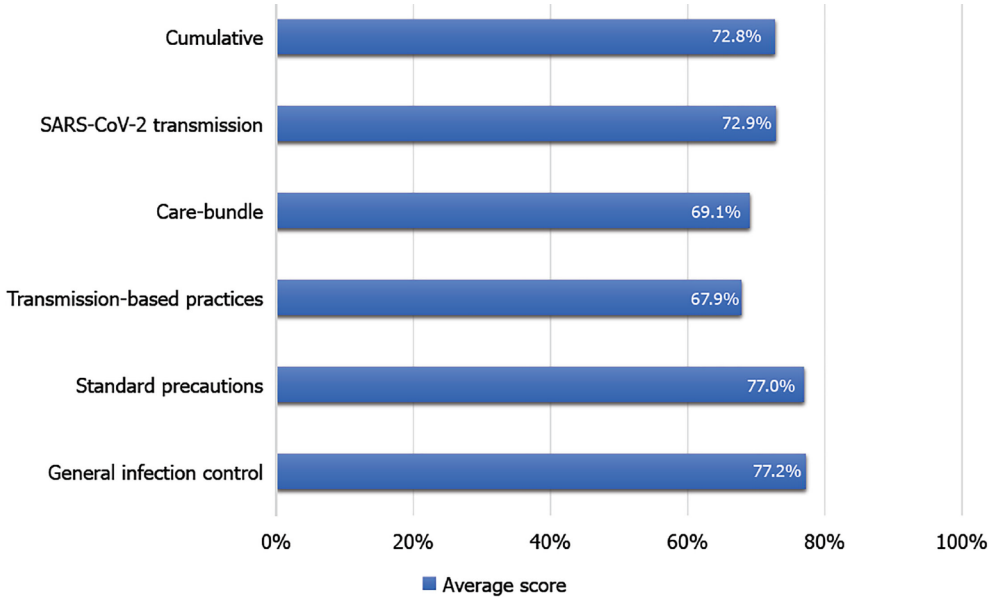
DOI: 10.5492/wjccm.v12.i3.176

Figure 1 Country-wise representation of the respondents of the survey. N: Number of respondents.

of HCWs upon the IPC practices, whereas training was found to be independently associated with better knowledge[16,17]. The literature showed a positive correlation between knowledge and better compliance with IPC practices among the HCWs[18,19].

Among five sections, the performance of the respondents was found to be worst in the section in transmission-based precautions. This reflects the knowledge deficiency of the nurses in understanding the microbiology aspect of IPC among nurses, which can be a focal point for future training programs. A systematic review of 30 studies also identified few gaps in the knowledge of HCWs among different IPC areas, such as vaccinations for HCWs, modes of transmission of infectious diseases, and the risk of infection from needle-stick and sharps injuries[6].

A recent review found that the structure and the skills of the ICU nurses vary according to the patient population, and availability of the resources, and treatments[20]. The current study found a strong association between the economic status of the countries (either UMIC or HIC *vs* LMIC) and better knowledge among the nurses. This finding infers about the impact caused by better resources, training, and surveillance opportunities on IPC practices in HIC or UMIC compared to LMIC. However, this finding is worrisome since the burden of HAIs is considerably higher in LMICs[21]. A recent global survey conducted by the World Health Organization on core components of the IPC programme and its



DOI: 10.5492/wjccm.v12.i3.176

Figure 2 Section-wise average score of the respondents in the questionnaire. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

implementation in healthcare facilities also highlighted the existence of critical gaps in LMIC and low-income countries[22]. The core components involving the workload, staffing, bed occupancy, education and training were scored the lowest in the survey.

The respondents working in private hospitals had significantly better knowledge about the IPC compared to their counterparts working in public hospitals. Though no direct studies compare different hospital settings on IPC practices, a few single-center studies have shown sound knowledge of the nurses working in private hospitals[23]. This can be attributed to resource constraints in terms of equipment, medications and the availability of the trained HCWs in public hospitals compared to private hospitals[24]. The current study finding with regards to teaching status of the hospital being negatively associated with knowledge of the nurses, is surprising. However, this can be explained by the fact that most of the teaching hospitals are public hospitals in UMIC and LMIC countries. Few studies conducted with the small number of samples in these countries from the region also found a deficiency in the knowledge among nurses working in teaching hospitals[25-27]. This suggests that education and training on IPC should be incorporated into medical teaching.

In the current study, a statistically significant difference was found in the knowledge of respondents based on their hospital accreditation status. Patient safety remains the centerpiece of hospital quality accreditation programs. Periodic training of the HCWs on various hospital-based policies, including IPC, is a core component of patient safety. In the current study, it is surprising to find the deficiency in knowledge of among the respondents working in hospitals with a national-level accreditation compared to their counterparts in international accreditation. However, the accreditation status was found to be not independently associated with better knowledge. This may reflect a difference in the standards of accreditation among the participating hospitals.

The working experience of the nurses was another factor, independently associated with a better knowledge. Since experience is the best teacher, it is expected that the knowledge of the nurses gets enhanced with increasing number of years of practice along with periodic trainings. In our previous multi-center study conducted in India, the working experience had a significant association with better knowledge among nurses[28]. Another single-center study from Saudi Arabia also found that the age (> 34 years), training and experience (> 6 years) were a predictor of good knowledge[17].

Strengths and limitations

The current study is a first-of-its-kind in this domain since the study conducted simultaneous knowledge testing of more than 1300 critical care nurses on IPC practices from 13 Asian countries. The survey intends to provide a snapshot of the knowledge of nursing professionals in terms of IPC practices, working in countries with a close cultural, social, and economic exchange. Besides testing the knowledge of the nurses on different aspects of IPC practices, the current study also tried to compare the knowledge based on a few factors such as the economic status of the country, working experience of the respondents; the type, accreditation, and the teaching status of the hospital, in which the respondents are working; and the type, size, and the operating model of ICUs by the respondents. The survey was participated by ICU nurses from large public and private hospitals with varying levels of accreditation and ICU setup.

The current study has a few limitations. Non-random convenience sampling method was followed for the study to obtain the data from only a set of selected hospitals from each participating nation. So, this data may not represent any individual country on the whole. We did make an effort to make the study population representative of nurses within respective countries with inclusion of public, corporate or university hospitals; teaching and non-teaching hospitals; and accredited as well as non-accredited hospitals, but still, this might not be an absolute representation. The number of entries received from each country varied from 57 to 228 which may have caused some statistical bias. The questionnaire did not include all the components of IPC as the intention was to evaluate only the knowledge of nurses working in the ICU. The questionnaire was made available to the study participants only in English and was not translated in their local language, due to concerns regarding accuracy and the misinterpretation of the questions. There is a potential for bias because of the gap in understanding the questions by the nurses due to language barrier. The knowledge testing of the IPC practices does not reflect the actual compliance with IPC practices and might not correlate with this self-answered knowledge evaluation. We did not capture the age, gender, qualification, and method of training rendered to the respondents, as these factors may have explained the variation in knowledge. Since the survey was an open-book and without any time restriction, the respondents might have answered the questions after taking external help, thus bringing a possible bias.

CONCLUSION

The current cross-sectional survey on testing the knowledge of nursing professionals on IPC practices from 13 Asian countries found a considerable variation. The higher economic status of the country and working experience were found to be independently associated with a better knowledge among the respondents. Working in public or teaching hospitals were found to be inversely associated with better knowledge about the IPC practices. There is an urgent need for periodic training and audits on the IPC practices of HCWs working in ICUs, especially in LMICs.

ARTICLE HIGHLIGHTS

Research background

Healthcare-associated infections (HAI) pose a significant threat to patients in hospitals, particularly in intensive care units (ICU). Despite efforts to prevent and control HAI, rates of device-associated (DA)-HAI in ICUs of developing countries remain higher than those in developed nations. Compliance with infection prevention and control (IPC) practices is crucial, and nurses play a key role due to their frequent contact with patients.

Research motivation

The lack of knowledge and awareness among healthcare workers about IPC practices, as well as discrepancies in applying this knowledge, have been linked to poor healthcare outcomes, especially in developing countries. ICU nurses' knowledge and awareness are integral to an effective IPC program. However, there is a lack of literature comparing the knowledge of ICU nurses across South Asian and Middle Eastern countries.

Research objectives

The current study aims to analyse the knowledge of ICU nurses regarding various aspects of IPC practices across countries in South Asia and the Middle East.

Research methods

The study conducted an online-based, cross-sectional survey using a multiple-choice questionnaire. The questionnaire was developed and validated by a 20-member steering committee comprising critical care physicians, infection control professionals, microbiologists, and nursing administrators. The survey was distributed to full-time ICU nurses in participating hospitals. The data were analysed using descriptive statistics, chi-square tests, and linear regression.

Research results

A total of 1333 nurses from 13 countries participated in the study. The average knowledge score was 72.8%, with 71.4% of respondents categorized as having above-average or proficient knowledge. Factors such as higher country income status, private hospital setting, and greater nursing experience were associated with better knowledge. Teaching hospitals and public hospitals showed lower knowledge levels.

Research conclusions

The study revealed significant variation in knowledge levels among ICU nurses across South Asian and Middle Eastern countries. Factors such as country income status, hospital type, teaching status, and nursing experience were associated with knowledge differences. These findings highlight the need for targeted interventions and training programs to improve IPC knowledge and practices, particularly in public and teaching hospitals.

Research perspectives

Future research should focus on developing comprehensive training programs and policies to enhance IPC knowledge and compliance among ICU nurses in South Asian and Middle Eastern countries. Comparative studies between different hospital settings and income groups can provide valuable insights into the factors influencing IPC practices and outcomes. Additionally, exploring the impact of improved IPC knowledge on healthcare delivery outcomes can further strengthen the evidence base for effective infection control strategies.

FOOTNOTES

Author contributions: Nasa P, Sodhi K, Arya M, Chanchalani G participated in the acquisition, and interpretation of the data and contributed equally to this work; Sodhi K designed the research and drafted the initial manuscript; Sodhi K and Nasa P, analyzed the data; Nasa P, Arya M, Chanchalani G, Shrestha G, Chandwani J, Kumar M, Kansal MG, Ashrafuzzaman M, Mudalige AD, Al Tayar A, Mansour B, Saeed HM, Hashmi M, Das M, Al Shirawi NN, Mathias R, Ahmed WO, Sharma A, Agarwal D performed the research, were involved in the recruitment of participants from their respective countries, revised the article critically for important intellectual content.

Institutional review board statement: The study was approved by the Ethics Committee (DHEC-2057/2022) of the institute of the principal investigator (KS) and exempted from other participating hospitals, as only healthcare professionals participated in the survey.

Informed consent statement: All study participants, provided informed written consent prior to study enrolment.

Conflict-of-interest statement: GPC reports receiving honorarium for advisory and consultancy services from Pneumocare Health Pvt Ltd. PN reports speaker honorarium from Tabuk Pharmaceuticals and MSD Pharmaceuticals. All other authors declare no competing interest in relation to the contents of this manuscript.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: United Arab Emirates

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

REFERENCES

1 **Rosenthal VD**, Bat-Erdene I, Gupta D, Belkebir S, Rajhans P, Zand F, Myatra SN, Afeef M, Tanzi VL, Muralidharan S, Gurskis V, Al-Abdely HM, El-Kholy A, AlKhawaja SAA, Sen S, Mehta Y, Rai V, Hung NV, Sayed AF, Guerrero-Toapanta FM, Elahi N, Morfin-Otero MDR, Somabutr S, De-Carvalho BM, Magdarao MS, Velinova VA, Quesada-Mora

AM, Anguseva T, Ikram A, Aguilar-de-Moros D, Duszynska W, Mejia N, Horhat FG, Belskiy V, Mioljevic V, Di-Silvestre G, Furova K, Gamar-Elanbya MO, Gupta U, Abidi K, Raka L, Guo X, Luque-Torres MT, Jayatilleke K, Ben-Jaballah N, Gikas A, Sandoval-Castillo HR, Trotter A, Valderrama-Beltrán SL, Leblebicioglu H; International Nosocomial Infection Control Consortium. International Nosocomial Infection Control Consortium (INICC) report, data summary of 45 countries for 2012-2017: Device-associated module. *Am J Infect Control* 2020; **48**: 423-432 [PMID: 31676155 DOI: 10.1016/j.ajic.2019.08.023]

2 **Jahani-Sherafat S**, Razaghi M, Rosenthal VD, Tajeddin E, Seyedjavadi S, Rashidan M, Alebouyeh M, Rostampour M, Haghi A, Sayarbayat M, Farazmandian S, Yarmohammadi T, Arshadi FK, Mansouri N, Sarbazi MR, Vilar M, Zali MR. Device-associated infection rates and bacterial resistance in six academic teaching hospitals of Iran: Findings from the International Nocosomial Infection Control Consortium (INICC). *J Infect Public Health* 2015; **8**: 553-561 [PMID: 26027477 DOI: 10.1016/j.jiph.2015.04.028]

3 **Marano L**, Carbone L, Poto GE, Calomino N, Neri A, Piagnerelli R, Fontani A, Verre L, Savelli V, Roviello F, Marrelli D. Antimicrobial Prophylaxis Reduces the Rate of Surgical Site Infection in Upper Gastrointestinal Surgery: A Systematic Review. *Antibiotics (Basel)* 2022; **11** [PMID: 35203832 DOI: 10.3390/antibiotics11020230]

4 **Stewart S**, Robertson C, Pan J, Kennedy S, Dancer S, Haahr L, Manoukian S, Mason H, Kavanagh K, Cook B, Reilly J. Epidemiology of healthcare-associated infection reported from a hospital-wide incidence study: considerations for infection prevention and control planning. *J Hosp Infect* 2021; **114**: 10-22 [PMID: 34301392 DOI: 10.1016/j.jhin.2021.03.031]

5 **Nasa P**, Modi P, Setubal G, Puspha A, Upadhyay S, Talal SH. Demographic and risk characteristics of healthcare workers infected with SARS-CoV-2 from two tertiary care hospitals in the United Arab Emirates. *World J Virol* 2023; **12**: 122-131 [PMID: 37033144 DOI: 10.5501/wjv.v12.i2.122]

6 **Alhumaid S**, Al Mutair A, Al Alawi Z, Alsuliman M, Ahmed GY, Rabaan AA, Al-Tawfiq JA, Al-Omari A. Knowledge of infection prevention and control among healthcare workers and factors influencing compliance: a systematic review. *Antimicrob Resist Infect Control* 2021; **10**: 86 [PMID: 34082822 DOI: 10.1186/s13756-021-00957-0]

7 **Allegranzi B**, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, Pittet D. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011; **377**: 228-241 [PMID: 21146207 DOI: 10.1016/S0140-6736(10)61458-4]

8 **Das R**, Saha AK, Barua PK, Borua JP, Akhter N, Hossain A. Knowledge and practices regarding infection control among nurses in secondary level hospital. *Asian J Med Biol Res* 2020; **6**: 731-737 [DOI: 10.3329/ajmbr.v6i4.51240]

9 **Nasa P**, Azoulay E, Chakrabarti A, Divatia JV, Jain R, Rodrigues C, Rosenthal VD, Alhazzani W, Arabi YM, Bakker J, Bassetti M, De Waele J, Dimopoulos G, Du B, Einav S, Evans L, Finfer S, Guérin C, Hammond NE, Jaber S, Kleinpell RM, Koh Y, Kollef M, Levy MM, Machado FR, Mancebo J, Martin-Loeches I, Mer M, Niederman MS, Pelosi P, Perner A, Peter JV, Phua J, Piquilloud L, Pletz MW, Rhodes A, Schultz MJ, Singer M, Timsit JF, Venkatesh B, Vincent JL, Welte T, Myatra SN. Infection control in the intensive care unit: expert consensus statements for SARS-CoV-2 using a Delphi method. *Lancet Infect Dis* 2022; **22**: e74-e87 [PMID: 34774188 DOI: 10.1016/S1473-3099(21)00626-5]

10 **Chanchalani G**, Arora N, Nasa P, Sodhi K, Bahrani MJA, Tayar AA, Hashmi M, Jaiswal V, Kantor S, Lopa AJ, Mansour B, Mudalige AD, Nadeem R, Shrestha GS, Taha AR, Türkoğlu M, Weeratunga D. Visiting and Communication Policy in Intensive Care Units during COVID-19 Pandemic: A Cross-sectional Survey from South Asia and the Middle East. *Indian J Crit Care Med* 2022; **26**: 268-275 [PMID: 35519910 DOI: 10.5005/jp-journals-10071-24091]

11 **Alojaimy RS**, Nakamura K, Al-Sobaihi S, Tashiro Y, Watanabe N, Seino K. Infection prevention and control standards and associated factors: Case study of the level of knowledge and practices among nurses in a Saudi Arabian hospital. *J Prev Med Hyg* 2021; 62: E501-E507 [PMID: 34604592 DOI: 10.15167/2421-4248/jpmh2021.62.2.1957]

12 **Abed Alah M**, Abdeen S, Selim N, Hamdani D, Radwan E, Sharaf N, Al-Katheeri H, Bougmiza I. Knowledge and Perceived Effectiveness of Infection Prevention and Control Measures Among Health Care Workers During the COVID-19 Pandemic: A National Survey. *J Nurs Care Qual* 2022; **37**: E23-E30 [PMID: 34935733 DOI: 10.1097/NCQ.0000000000000615]

13 **Chowdhury D**, Duggal AK. Intensive care unit models: Do you want them to be open or closed? A critical review. *Neurol India* 2017; **65**: 39-45 [PMID: 28084236 DOI: 10.4103/0028-3886.198205]

14 **European Centre for Disease Prevention and Control**. Healthcare-associated infections in intensive care units - Annual Epidemiological Report for 2017. [accessed 10 January 2023]. Available from: https://www.ecdc.europa.eu/en/publications-data/healthcare-associated-infections-intensive-care-units-annual-epidemiological-1/

15 **World Health Organization**. Report on the burden of endemic health care-associated infection worldwide. 2011. [cited 2016 May 04]. Available from: https://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf/

16 **Tamang N**, Rai P, Dhungana S, Sherchan B, Shah B, Pyakurel P, Rai S. COVID-19: a National Survey on perceived level of knowledge, attitude and practice among frontline healthcare Workers in Nepal. *BMC Public Health* 2020; **20**: 1905 [PMID: 33317486 DOI: 10.1186/s12889-020-10025-8]

17 **Abalkhail A**, Al Imam MH, Elmosaad YM, Jaber MF, Hosis KA, Alhumaydhi FA, Alslamah T, Alamer A, Mahmud I. Knowledge, Attitude and Practice of Standard Infection Control Precautions among Health-Care Workers in a University Hospital in Qassim, Saudi Arabia: A Cross-Sectional Survey. *Int J Environ Res Public Health* 2021; **18**: 11831 [PMID: 34831585 DOI: 10.3390/ijerph182211831]

18 **Thu T**, Anh N, Chau N, Hung N. Knowledge, attitude and practices regarding standard and isolation precautions among Vietnamese health care workers: a multicenter cross-sectional survey. *Intern Med* 2012; **2**: 115 [DOI: 10.4172/2165-8048.1000115]

19 **Wisniewski MF**, Kim S, Trick WE, Welbel SF, Weinstein RA; Chicago Antimicrobial Resistance Project. Effect of education on hand hygiene beliefs and practices: a 5-year program. *Infect Control Hosp Epidemiol* 2007; **28**: 88-91 [PMID: 17230394 DOI: 10.1086/510792]

20 **Macey A**, O'Reilly G, Williams G, Cameron P. Critical care nursing role in low and lower middle-income settings: a scoping review. *BMJ Open* 2022; **12**: e055585 [PMID: 34983772 DOI: 10.1136/bmjopen-2021-055585]

21 **World Health Organization**. Report on the Burden of Endemic Health Care-Associated Infection Worldwide. 2011.

Available from: https://www.who.int/publications/i/item/report-on-the-burden-of-endemic-health-care-associated-infection-worldwide

22 **Tomczyk S**, Twyman A, de Kraker MEA, Coutinho Rehse AP, Tartari E, Toledo JP, Cassini A, Pittet D, Allegranzi B. The first WHO global survey on infection prevention and control in health-care facilities. *Lancet Infect Dis* 2022; **22**: 845-856 [PMID: 35202599 DOI: 10.1016/S1473-3099(21)00809-4]

23 **Sodhi K**, Shrivastava A, Arya M, Kumar M. Knowledge of infection control practices among intensive care nurses in a tertiary care hospital. *J Infect Public Health* 2013; 6: 269-275 [PMID: 23806701 DOI: 10.1016/j.jiph.2013.02.004]

24 **Basu S**, Andrews J, Kishore S, Panjabi R, Stuckler D. Comparative performance of private and public healthcare systems in low- and middle-income countries: a systematic review. *PLoS Med* 2012; **9**: e1001244 [PMID: 22723748 DOI: 10.1371/journal.pmed.1001244]

25 **Al-Rawajfah OM**. Infection control practices among intensive care unit registered nurses: a Jordanian national study. *Nurs Crit Care* 2016; **21**: e20-e27 [PMID: 24450751 DOI: 10.1111/nicc.12078]

26 **Acharya AS**, Khandekar J, Sharma A, Tilak HR, Kataria A. Awareness and practices of standard precautions for infection control among nurses in a tertiary care hospital. *Nurs J India* 2013; **104**: 275-279 [PMID: 24974532]

27 **Dhedhi NA**, Ashraf H, Jiwani A. Knowledge of standard precautions among healthcare professionals at a Teaching Hospital in Karachi, Pakistan. *J Family Med Prim Care* 2021; 10: 249-253 [PMID: 34017735 DOI: 10.4103/jfmpc.jfmpc_1622_20]

28 **Sodhi K**, Arya M, Chanchalani G, Sinha V, Dominic Savio R, Ak AK, Ahmed A, Jagiasi B, Agarwal D, Jagathkar G, Khasne R, Sahasrabudhe SS, Jha SK, Sahoo TK, Mittal V, Hr H, Bansal S, Agarwal C, Kumar M. Comparison of knowledge and awareness of infection control practices among nurses in India: A cross-sectional survey. *Am J Infect Control* 2022; **50**: 1368-1373 [PMID: 35181374 DOI: 10.1016/j.ajic.2022.02.014]

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