Circadian disruption of ICU patients: a review of pathways, expression and interventions

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Abstract

ICU patients typically exhibit pathologic wakefulness, poor quality of daytime sleep, nocturnal sleep fragmentation, and sleep patterns that feature the absence of SWS and REM. This paper offers a review of the existing literature examining circadian desynchronization in critically ill patients, highlighting contributing factors identified by scholars, and circadian abnormalities observed in these patients. It discusses potential implications for clinical practice and suggests avenues of future research. Elucidating the role of circadian rhythms in the management of critical illness can guide future chronotherapeutic approaches and optimise patient outcomes.

Introduction

The pathway between endogenous circadian clocks and behaviour is perhaps the best understood of the mysteries of gene expression [1] but the relationship between these internal clocks and the external ones controlling social and organisational behaviour, including in hospitals, is still relatively poorly illuminated. The endogenous nature of circadian rhythms was first experimentally demonstrated through observations of leaf movements in botanical laboratories in the 19th century. The internal locus of circadian control was pinpointed in the 20th century, while the central and independent role of the bilateral hypothalamic suprachiasmatic nucleus (SCN) cells was demonstrated when circadian oscillation was noted to persist in SCN cells removed from their host and placed in culture [2]. In humans, circadian pacemakers in the SCN of the anterior hypothalamus [3] appear to be part of a hierarchical network [4] and control not just sleep-wake cycles but also have much wider health implications, including direct linkages with the immune system [5] and the human autonomic nervous system [6]. Molecular 'clocks' are controlled by a number of genes forming primary and auxiliary transcriptional and translational feedback loops that express themselves in both a positive and negative manner [7,8].

This review looks at the interaction between these endogenous patterns and exogenous variables, in circumstances where rhythmic light/dark cycles are *forced to alter*, namely the intensive care unit (ICU) environment. The mismatch between internal states and external cycles is a significant issue that has been associated with disturbances of physiological homeostasis and critical illness [9], and it may well be that the very intensity of treatment given to ICU patients results in diminution of their health status.

In this review, we aim to systematically review factors that contribute to circadian disruption in general, while examine how abnormalities in circadian rhythms are expressed in ICU patients in particular. In addition, we present recommendations both for clinical practice and research.

Method

The PubMed database was accessed in May 2016. In the literature, there are a number of overlapping terms used to describe the disturbance of circadian rhythms, notably circadian abnormalities, circadian dysrhythmias, arrhythmias, circadian misalignment, circadian disruption or chronodisruption (CD), all of which are well established terms [4]. In the light of the varied nomenclature, in order to exhaustively capture the literature within PubMed, the following strategies were performed: "circadian rhythm" [MeSH Terms] OR "circadian" [All Fields] AND "rhythm" [All Fields] OR "circadian rhythm" [All Fields] OR "circadian" [All Fields] AND "rhythms" [All Fields]) OR "circadian rhythms" [All Fields] AND ICU [All Fields] AND "patients" [MeSH Terms] OR "patients" [All Fields]. No restrictions as to time of publication were applied, however, only articles with abstracts written in English were included. If the title or the abstract included the key words, the paper was identified as relevant and included in the study. A total of 70 articles were retrieved using this process with 36 selected as directly dealing with the scope of this study. Only one additional article was retrieved using the terms "circadian dysrhythmias"[All Fields] AND "ICU"[All Fields]. The 37 selected papers were scrutinized carefully and further key words and phrases identified, including *light*, *noise*, *patients care activities*, *sleep*, *mechanical ventilation*, and *medication*. Using these additional terms in combination with the circadian search terms noted earlier, a supplementary search identified an additional 51 articles were identified as relevant, and in rare cases where the literature suggested key research outside the scope of the PubMed database, these rules were extended to the broader literature. A reading of the total set identified three key themes in relation to the literature on circadian disruption to ICU patients: factors that contribute to circadian disruption; how these disruptions translate into clinical problems, and finally,

implications for practice and research. The review will be structured around these three themes.

Findings

Factors that contribute to circadian disruption

Light: ICU patients are exposed to some degree of artificial light over a 24 hour cycle. Nightingale in the early 20th century identified light and day-night rhythms as two important factors in supporting and restoring patient health [10]. Artificial light in the night is a known causal factor in circadian disruption, producing a number of direct effects, including alterations to melatonin secretion,elevation of cortisol production and normal and neoplastic tissue growth, as well as indirect effects mediated through its impact on sleep [11]. Daylight is often obscured or eliminated in ICUs, and substituted or supplemented with artificial lighting [12]. Artificial lighting is particularly common at high levels during night-time, as an aid to conducting examination, treatment and other nursing activities. Nocturnal light levels as low as 100–500 lux are known to affect melatonin secretion, and nocturnal levels between 300 and 500 lux may triggerthe circadian pacemaker [13,14]. Considering this, mean illumination levels measured in ICUs at night ranging from 2.4 to 145 lux and ranging by day from 55.3 to 165 lux [3] pose a significant threat to normal circadian rhythms, with even short term exposure to lighting with blue-spectral components influencing melatonin excretion and alertness [15]. These measurements indicate a pattern of relatively low (and less variable) illumination levels by day and high (and distinctly more variable) levels by night [3]. Thus, lack of diurnal cues caused by absence of daylight and the presence of artificial lighting during night (lighting practices) is almost certainly a parameter contributing significantly to circadian disruption of ICU patients. Most patients report that sleep in ICU is inferior to that experienced at home and light is one of five most frequently-cited reasons for sleep deprivation [16]. Table 1 summarizes papers examining the role of light in ICUs.

Auditory disruption: ICUs present a complex auditory environment. Monitor alarms, mechanical ventilation, operating and moving equipment, telephones, televisions, conversations between nursing/medical personnel, nursing activities (e.g. endotracheal suction, lab draws, radiographs) and even the footsteps of medical staff have been implicated in circadian disruption and sleep abnormalities [17,18]. The World Health Organization (WHO) suggests patient care zones should suppress sound levels below 35 dB peaking at no more than 40 dB overnight [17]. The reality in the wards stands in contrast to these standards. Studies measuring ambient noise levels in ICUs established that

means are exceeding Environmental Protection Agency (and WHO) recommendations for both day and night [12] with peak noise levels in excess of those recommended, that is approximately 45 dB during the day and 35 dB at night [14]. Mean noise levels in ICU environments have in fact been documented as high as 55–65 dB over a full-day cycle, peaking as high as 80 dB [14]. Table 2 summarizes papers studying auditory issues in ICUs, and it is worth noting that while there are numerous studies with a descriptive focus, ascertaining auditory pollution in ICUs, few aim to determine impact on circadian rhythmicity of ICU patients, by measuring sleep fragmentation and deprivation [19].

Respiratory support. Respiratory support and mechanical ventilation (MV) is a common component of the treatment regimen of critically ill patients. Assisted ventilation determines the type of breathing, the tidal volume and the respiratory rate, reducing the patient 'work' of breathing, but also requiring synchronicity with the ventilator. When asynchrony arises between the patient and the ventilator, alarms are activated regardless of the time of the day, causing sleep disruption, with inevitable circadian implications. Several studies have investigated the relationship between sleep patterns and respiratory support in critically ill patients [13,20,21]. Pressure Support (PS) appears to be associated with greater sleep fragmentation compared with other ventilation modes [20]. A recent study of 10 patients showed reduced sleep efficiency, reduced REM sleep, and reduced percentage of Slow Wave Sleep (SWS) amongst patients experiencing artificial assistance with ventilation [22]. Frisk et al. have found that mechanical ventilation was associated with a markedly lower 6-sulfatoxymelatonin (6-SMT) excretion compared with periods without support [23]. However, there are also tracheostomy patients at the weaning stage, no longer dependent on the ventilator. In these cases, the normal cycle of day and night, exposure to light, the timing of meals, and other diurnal cues play their important role as zeitgebers, contributing to normalized sleep cycles and the reset of circadian rhythms.

Medication.The degree to which the impairment in sleep quality and quantity found in ICU patients can be attributed to medication is particularly difficult to determine [24]. Pharmacologic agents such as vasoactive drugs, antibiotics and especially analgesics and sedatives alter sleep architecture [25]. Vasopressors, positive inotropes and b-agonists tend to increase melatonin levels, while b-blockers may suppress melatonin production, one of the most important determinants of circadian rhythms [23]. More specifically, benzodiazepines increase sleep efficiency (SE), shorten sleep latency, and suppress Rapid Eye Movement (REM) and Slow Wave Sleep (SWS). The use of midazolam can result in the total absence of SWS or REM sleep patterns in patients undergoing constant sedation [24]. Conversely, propofol administration may cause a decrease in REM sleep, but Frisk et al found no differences in SE, sleep fragmentation, or NREM sleep distribution [24]. Opioids (e.g. morphine)

similarly are associated with decreased REM, total sleep time and SWS [24]. Finally, corticosteroids have been proven to decrease REM, SWS and increase wakefulness and stage 2 NREM sleep [26]. Finally, reviews have also identified antibiotics, beta-lactams and quinolones, as candidates for sleep disturbance [9,14].

Nutritional support. Time of feeding tends to be a dominant zeitgeber for peripheral mammalian clocks [27], with food acting to trigger circadian cues that control rest cycles and, in turn, metabolism [28]. Evidence suggests that the peripheral organs' coordination with circadian rhythms is critical. For example, the molecular liver clock regulates the expression of enzymes pivotal to gluconeogenesis such as phosphoenolpyruvate carboxykinase and glucose-6-phophatase [29]. Collectively, evidence suggests that a "major function of peripheral clocks is to prepare the human body for…alternating periods of food intake… and fasting" [30]. Thus parenteral and enteral feeding may result in the disruption of further cues to rhythmicity [28]. Continuous tube feeds may further diminish circadian rhythmicity [31]. Disruption of these rhythms can lead to systemic inflammatory response syndrome, which in turn can evolve into multiple organ dysfunction syndrome [32].

Hormonal rhythms also have a close relationship with the digestive system and their relationships with circadian regulation have, in general, been under-estimated. Challet, in a recent review, noted adrenal glucocorticoids, pineal melatonin and adipocyte-derived leptin are key in controlling or being controlled by circadian clocks [33]. Furthermore, "pancreatic insulin is involved in the food synchronization of peripheral clocks, while stomach ghrelin sends temporal signals that modulate the individual's anticipation of mealtimes" [33]. It seems logical, thus, that treatment with endocrinal implications—for example the timing of endocrine therapies—needs to be considered particularly sensitively from a circadian perspective [33].

Illness characteristics: As noted in the previous section, illness characteristics can themselves also result in deregulated circadian homeostasis [34]. In critical illness acute inflammatory response or prolonged systemic inflammation can lead to desynchronisation of circadian cues and consequently to organ failure and death [35,36]. Patients with severe sepsis, the most demanding of the immune responses [36] also exhibit loss of circadian melatonin rhythms, whereas non-septic patients in the ICU are relatively more able to maintain circadian rhythms that track similarly to non-hospitalized controls [23,37,38]. Hormonal changes may be a component of protective mechanisms triggered by disease (e.g., cortisol elevation may assist in the resolution of inflammation), a dysfunctional response to the disease process, or may even contribute to its etiology. A number of reviews have addressed the relationship between immune

function and hormonal fluctuations [39], illuminating the bi-directional relationship between the two systems - disrupted rhythms and immune function [28,40].

How rhythm abnormalities are expressed in the ICU patients

Sleep: Considering the nature of circadian rhythms, not surprisingly the domain of impact most commonly discussed in the literature is that of sleep abnormality. Once sleep is disturbed the clinical implications cascade to multiple wellbeing outcomes: the literature notes effects on respiratory, cardiovascular, immunological, metabolic and neurocognitive systems [19,20,41–43], and in the following sections we will deal with specific categories of change. Mortality statistics also show a link with sleep disruption. In a large population of 14,705 ICU patients, rhythms were preserved in significant portion of septic patients who survived the critical illness, whereas, there was a loss of circadian rhythm in non-survivors [44]. A number of review articles have summarized the role of the ICU environment in sleep impairment [9,13,21,42,45–50], which collectively suggest (as we have done) that the clinical environment itself has a significant role in disrupting sleep. Not surprisingly, sleep deprivation and the inability to sleep are described by survivors as major sources of anxiety and stress during stays in the ICU [4].

Studies with patients in particular categories, such as pregnant patients as well as 'normal' populations [51] support the view that interrupted sleep means sleep reduced in quality, not just quantity. Sleep abnormalities include both quantity (total sleep time and time spent in each stage of sleep) and quality (fragmentation and abnormal sleep architecture) [52]. Total Sleep Time (TST) for ICU patients is often observed to be the same duration as for the 'normal' population, but is disrupted with around 50% of sleep occurring during daytime. Other polysomnography parameters are also altered: sleep efficiency, a marker of sleep quality, is decreased; Stages 1 and 2 of NREM sleep are increased, while Stage 3 NREM and REM are decreased. In summary, ICU patients spend more time in non-consolidated ''light sleep'' and less time in deep restorative sleep [4] when examined in the light of the influential criteria established by Rechtschaffen and Kales [53].

Melatonin changes: Melatonin is considered to be one of the primary markers of circadian rhythm [54], normally increasing in the evenings, and remaining elevated until early morning. In the ICU environment, this pattern is almost invariably interrupted. Abnormal melatonin patterns have been noted in multiple ICU studies [12]. Most demonstrate that the acrophase (i.e. the peak of a cycle) in melatonin levels is shifted away from the night, and indeed largely

abolished [55]. Bagci et al. comparing 23 septic and 13 non-septic pediatric ICU patients, found no difference for nocturnal and total 6-SMT excretion between septic patients and non-septic patients [56]. A recent study from Verceles et al. found that the circadian rhythm was disrupted in 7 patients with severe sepsis, as reflected by disordered diurnal variation of urinary 6-SMT excretion [57]. Mundigler et al. compared 17 septic patients versus 7 non-septic in an ICU and found altered urinary 6-SMT in septic patients [58]. These findings hold despite controlling for illumination in the ward [23].

Apart from manifesting flattened or shifted diurnal rhythms in melatonin secretion, ICU patients under certain circumstances also show overall increased or decreased levels of melatonin. Hyposecretion of melatonin has serious clinical corollaries, considering that melatonin has been implicated in a broad range of clinical outcomes, notably immunity [59] preventing acute gastric lesions induced by stress [60], inflammation and decreased lung function [61]. More generally, it is associated with impaired mitochrondial oxidative phosphorylation [62] and the body's ability to cope with endotoxemia [63]. There are also longer term implications of elevated melatonin output such as eye [64] and skin [65] pathology. Retinal damage can be reduced by artificially depressing melatonin levels in laboratory conditions, for example [66].

Reduced melatonin levels have also been associated with a number of pathological processes, principally central nervous system diseases [67,68], but from a shorter-term ICU perspective, the relationship with delirium is perhaps the most immediately relevant. ICU delirium has been associated with decreased levels of melatonin, although causality has not been firmly established [69,70]. Delirium may plausibly lead to sleep deprivation, and sleep deprivation similarly may lead to delirium [42,69]. There are strong associations between critical illness, sleep deprivation and delirium however, with the plausible pathway being that a combination of ICU factors identified in this study—light, noise, critical illness and its treatment—contribute to pineal dysregulation, which is translated to reduction of melatonin and cortisol levels.

Other physiological parameters: Blood pressure, heart rate, temperature, plasma electrolytes and blood glucose are monitored and evaluated continuously in ICU patients [71,72], enabling the longitudinal impact of the ICU environment on a range of physiological outcomes to be tracked over a 24 hour cycle. These studies have identified that Core Body Temperature (CBT) is one of the three biomarkers along with cortisol and melatonin, which exhibits strong diurnal rhythmicity. Outside the ICU environment, CBT reaches its nadir in the early morning, followed by an increase during afternoon and evening hours with an estimated variation up to 0.8°C. In contrast to melatonin, CBT is *not* impacted by light exposure. The low point of CBT can be used to identify the end of the

circadian night, and in ICU patients the degree of CBT displacement from its customary early morning locus correlates with illness severity [73,74].

Circadian variation has also been noted in febrile seizures, with a significant peak in the evening between 4 and 8 PM [75]. As far cardiovascular parameters are concerned, there is a paucity of clinical data for ICU patients. Lazreg et al found that for both comatose and non-comatose populations, blood pressure and heart rate showed circadian fluctuation and disturbed profiles in 22 ICU patients [76]. The presence of coma also did not affect the rhythmicity of chemistry variables in ICU patients [77]. Paul and Lemmer in an earlier study showed that the 24 hour profiles of cortisol, blood pressure, heart rate, body temperature, and spontaneous motor activity were remarkably distorted amongst 24 critically ill analgosedated patients compared with the rhythmic 24-hr patterns in healthy control subjects [78]. These distortions of usual patterns were more pronounced in patients with brain injury [4]. In critically ill patients, blood glucose values and the incidence of hyperglycemia also demonstrate circadian rhythmicity [4]. This has obvious clinical practice implications. Egi et al have shown that morning blood glucose may not be an accurate surrogate of overall daily blood glucose control with glucose levels observed to be lowest in the morning [79]. Glucose fluctuates with an ultradian pattern (i.e. shorter than a day, but longer than an hour) in ICU patients on an insulin infusion protocol (IIP) [80].

Immune system: Apart from the abovementioned parameters, the functioning of the T cells, part of adaptive immunity response, appears to be vulnerable to disruption through sleep disturbance [81]. This may form part of the mechanism for immunosuppression observed in sepsis [82] and in patients with disturbed sleep patterns. Extensive research on healthy individuals has revealed that sleep provides an important role in the effective functioning of the immune system. Several studies have reported a circadian rhythm in the activity of the immune system and the inflammatory mediators in blood (leukocytes, cytokines, and hormones) [83–85]. Inflammation mediators exhibit a circadian rhythm associated with molecular clock components, as demonstrated in knockout mice (mice where researchers have experimentally muted or 'knocked out' a DNA sequence), where inflammatory cytokines are associated with the presence of proteins that regulate the rhythms of natural killer cells, critical to the human immune system [86]. Moreover, ICU patients particularly patients with sepsis, experience mitochondrial and endothelial dysfunction as well as alterations to nitric oxide synthesis processes and pyruvate dehydrogenase activity. These functions are all regulated by circadian proteins, thus it is not surprising that observing that the pathophysiology and symptoms of sepsis, as well death itself in the ICU, possesses circadian rhythmicity [36,87,88]. It is worth noting that evidence of a link between circadian rhythms and sepsis is generally more

reliably confirmed in animal studies, possibly due to the bi-direction nature of the relationship in humans.

Neurocognitive changes: Short-term sleep deprivation such as that observed in ICUs compromises an array of cognitive functions, notably attention, short-term memory, and working memory [89]. Sleep deprived individuals, who enjoy less than seven hours night-time sleep, perform relatively poorly on task-switching activities compared to the non-sleep deprived, demonstrating a link between sleep deprivation and executive cognitive functioning [90]. Sleep deprivation has also been linked to emotional reactivity manifested in increased amygdala reactivity to aversive stimuli [91], exaggerated reactivity in mesolimbic reward brain networks to pleasant stimuli [92], and, at a level more easily observable in an ICU setting, heightened negative evaluation of neutral stimuli [93]. The greater lability of emotional reaction has implications for patient care.

Again at an observable clinical level, the neurocognitive changes may be exacerbated under conditions of delirium. Delirium, as noted earlier, is a key symptom. It has a severe effect on disease prognosis and mortality [86] and is common in an ICU environment. It occurs, for example, in 60-80% of patients under mechanical ventilation and 20-50% of non-MV patients [42]. There is a reciprocal relationship between delirium and sleep deprivation, and the research is not yet settled on whether sleep deprivation is causal in delirium or delirium contributes to sleep deprivation, or indeed whether *both* represent drivers of 'ICU syndrome' [69]. Delirium symptoms are expressed both cognitively and behaviourally. The most common cognitive symptoms are disorientation, inability to sustain attention, impaired short-term memory, impaired visuospatial ability, and reduced levels of both consciousnesses. The cognitive changes have obvious spillover implications for behaviour. The most common behavioural symptoms are sleep-wake cycle disturbance [94], irritability, hallucinations and delusions [70], and reduced perseveration. However, the adverse clinical outcomes of delirium independent of the underlying pathophysiology include prolonged length of stay, increased risk of dementia and other complications (such as pneumonia) and death [95]. A recent study reported that delirium frequently arises at initiation of ventilator weaning and it is associated with a prolongation of weaning and, not surprisingly, an alteration in the circadian rhythm of melatonin excretion [96], contradicting an earlier study by Nuttall et al. who found no alteration in the circadian rhythms between ICU patients with or without delirium [97].

Implications for practice and research

Although much is known about the impact of circadian rhythms on the development of a broad range of human diseases, relatively little attention has been paid to how circadian rhythms interact with conditions experienced by

critically ill patients in the ICU. This is partly because of the difficulties of untangling the effects of the illness on circadian rhythms from the impacts of the ICU environment itself. As Chan et al note, it remains uncertain if circadian rhythm alterations observed in the critically ill "represent[s] a compensatory response or whether they are in and of themselves pathologic" [4].

Understanding the mechanisms that regulate circadian clocks and the ways in which the resultant rhythms influence how the patient responds to challenges, is thus complex. Studies are required to examine whether restoring circadian rhythms in the critically ill should be shifted in order of priorities, or whether the status quo in circadian rhythms needs to be sacrificed in favour of higher therapeutic goals. Some interventions to improve rhythm are relatively easy to implement. A number of studies have revealed that focusing on noise and light reduction can result in significant sleep improvements [98], although this review shows that more work needs to be done to establish relationships between auditory pollution and circadian rhythmicity. Selected interventional studies, conducted in ICU patients in order to improve sleep and circadian rhythmicity, are listed on Table 3. In addition, the logic of the literature presented suggests that circadian realignment may be progressed by introducing measures such as time-restricted feeding that parallels meal times outside the hospital environment, and by turning to the emerging field of chronopharmacology in order to refine drug-administration times to enhance outcomes.

Intervention studies have shown that altering the cycle of lighting in ICUs can have a number of ancillary benefits beyond partial restoration of normalcy in circadian rhythms. For example, Engwall et al found that a cycled lighting intervention led to improved patient satisfaction and greater calmness amongst medical staff [3]. Patient needs are primary, but the nurse-sensitive indicator literature reminds us that the effect of the ICU on nursing staff in itself has patient wellbeing implications. Bright light in ICUs undoubtedly assists in the maintenance of alertness in medical staff, something that has not been independently addressed in primary research, but nevertheless should be taken into account. Returning to a direct patient perspective, however, cycled light has also stimulated the immune system by improving regulation of melatonin [99], assisted in the absorption of vitamin D [100] and reduced the number of days in hospital for patients with bipolar depression [101]. More generally, improved lighting regimes were found in a case control study to result in experimental group patients returning to ambulatory status two days ahead of controls [102]. Some studies have looked merely at increasing exposure of patients to daylight, rather than regulating levels of night light, finding that exposure to morning bright light (at least 4,000 Lux, similar to a sunny day outside) for example leads to reductions in delirium and sleep improvements [24].

The effect of noise reduction in ICUs on sleep quality is not unequivocally positive, with some studies showing that while quantity of sleep improves, quality remains suboptimal [103]. Interventions include the use of ear plugs [103], which in one case was found to decrease incidence of delirium [104], but there have also been suggestions to reduce the production rather than the reception of noise pollution. Auditory alarms have a level of immediacy and convenience that mean they are unlikely to be soon superseded, however, Salandin et al. suggest that standardising the sounds, as well as the volume of sounds in an ICU might reduce the impact [18], and studies looking at altering the materials used to construct ICUs, to maximize the use of sound-absorbing materials, has promising impacts [105,106]. Finally, the use of white noise, and implementing altered work practices to ensure the quarantining of key 'quiet' periods had some success in improving sleep [107].

Finally, turning to the key issue of melatonin, Hatta et al. report a randomised controlled trial of elderly patients examining the use of ramelteon, a synthetic melatonin agonist, in reducing delirium [108]. Despite a relatively small sample size, the results highly significantly indicate a benefit, and these have been supported both outside the ICU context by a number of recent studies [109,110]. Thus melatonin or melatonin agonists may be underutilized in promoting healthy circadian rhythms in the ICU. Intervention studies in animal models suggest that melatonin may have beneficial implications on immune function and thus outcomes, such as sepsis and trauma-hemorrhage. For example, Wichmann et al. report on a study of mice exposed to a sepsis challenge, thereafter receiving either a saline-alcohol solution or melatonin (10mg/kg body weight), with significant improvements in survival [111]. The results were not uniformly positive, with continuous melatonin treatment worsening the prognosis for sham-operated animals, thus suggesting the mechanisms require significant further study.

Conclusions

This review has provided a summary of factors that contribute to circadian disruption in an ICU environment, the consequences of those disruptions, and opportunities for improvement (Figure 1). The potential health benefit of re-synchronizing of the circadian rhythm to a natural cycle—what Garaulet et al. call *chronoenhancement* ("resetting of the circadian system" [112]), a term that is starting to appear in the literature—is substantial.. For example, the economic costs of the treatment of sepsis in the US alone have been estimated in 2001 at $16.7 billion [113], and the evidence is clear that circadian disruption has a significant role in amplifying the severity—and chronoenhancement correspondingly a significant role in mitigating it.

While the body of research is extensive, there are key gaps—and clearly further studies are required of lighting, and melatoninergic interventions deserve to be tested in full-scale trials.In the latter case, there is enough evidence to suggest that the promise of melatonin interventions is tempered by real risks. Sufficiently powered studies are required to identify optimal timing of interventions, for example in the field of chronopharmacology, as well as the role of medications in general in disturbing sleep, and thus acting in an iatrogenic manner that clinicians may still remain unaware of. Additional education is required to ensure clinicians are aware of both the risks, as well as the opportunities offered by the growing field of chronobiology. Notably, circadian outputs can act as useful biomarkers for immune and inflammatory disease and are probably underutilised in this regard. More generally, while the body of research is growing demonstrating that circadian dysrhythmias in ICUs exist—expressed primarily as sleep deprivation, delirium incidence, and immunosuppression—there has been relatively little applied response in hospitals to overcome factors that lead to sleep disturbance. The evidence suggests that with relatively modest expense, zeitgebers, or naturally occurring phenomena that cue circadian rhythms, can be harnessed in the cause of chronoenhancement. Alterations to noise and lighting patterns, in particular, show significant promise.

In addition, we suggest that focus also needs to be addressed to the impact of the ICU environment on the circadian rhythms of nurses and other medical staff. The lighting and auditory environment of the ICU is partly set up to ensure that nurses are alert to patient status and needs, and are able to address those requirements professionally. However, the environment also alters the circadian rhythms and, for example, alertness, of medical staff. There is clearly a need for further primary research within the context of the nurse-sensitive outcomes or indicators field [114]. The nurse, for example, may have different circadian requirements to the patient, meaning the optimal state of the ICU may need to be a compromise.

The nature of the ICU environment, which is characterized by evolving crises, militates against the easy evaluation of sleep and circadian alignment, unless in a specific research setting. Unobtrusive, accurate and efficient measures of circadian variables, notably sleep, are thus required to enable clinicians to respond to the knowledge being generated by the research community. Such advances will enable those working in ICUs to individualise cues to circadian rhythm, such as lighting and feeding protocols without disturbing the efficient operation of ICUs. Finally, due to the nature of the ICU patient, an often-forgotten aspect in circadian research in this setting is the subjective responses of patients to changes. Global, subjective ratings by patients, in relation to sleep and rest cycles, can be difficult to obtain in the crisis environment of the ICU, but may well

form an important part of the patient experience in the ICU and may, in itself, offer key insights to both clinicians and researchers.

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Table 1. Methodological characteristics of studies measuring light in ICU

Type and aim of study	Sample	Method	Results	Reference
Observational study to assess the relationship between ambient light and circadian rhythms	7 septic ICU patients	Actigraph/luxmeter	No relationship between light levels and 6-SMT excretion in ICU septic patients	56
Observational study to determine the association of light duration and intensity with mortality	9,534 ICU patients	Photoperiod and insolation data from USNO and NASA	No association between ICU photoperiod or insolation and mortality	115
Interventional study to determine the effect of light levels reduction on sleep efficinency	50 neuro-ICU patients	Light meter	Association of lower light levels with significantly higher proportion of patients sleeping	37
Observational study to measure light intensity in the ICU	4 ICU patients	Luxmeter	Light intensity from 120 to 770 lux	38
Observational study to determine the hour with the lengthiest and shortest light exposure	12 surgical ICU patients	Light-Activity Time Evaluation (LATE) Sheet	Establishing the lengthiest cumulative light exposure at 10pm and the shortest light exposure at 1am	116
Study to test the physiological response of the pineal gland to light and darkness in critical illness	20 ICU patients	Luxmeter	Abolishment of melatonin secretion regulation by darkness and light in severely ill patients	117
Observational study to measure melatonin and cortisol excretion during ICU stay	16 ICU patients	Photometer	Disturbed diurnal rhythm of cortisol and melatonin in most ICU patients	23

Table 2. Methodological characteristics of studies measuring noise in ICU

Type and aim of study	Sample	Method	Results	Reference
Observational study to measure noise levels in the ICU	Five adult ICUs	Portable sound level monitors	All time recordings above 45 dB and between 52 and 59 dB for more than 50% of the time	17
Observational study to measure noise levels in an intermediate care unit (IMCU)	A two-bed and a four-bed room in IMCU	Acoustic level analyzer	Sound levels between 36 dB and 104 dB	18
Interventional study to determine the effect of noise reduction on sleep efficiency	50 neuro-ICU patients	Digital sound meter	Association of lower noise levels with significantly higher proportion of patients sleeping	37
Observational study to record noise levels in the ICU	4 ICU patients	Decibel meter	Sound levels between 48 dB and 81 dB	38
Observational study to determine the effect of environmental noise on sleep efficiency	22 ICU patients	Portable integrating/logging sound level meter	Association of environmental noise with sleep–wake abnormalities, but not with sleep fragmentation	19

Table 3. Interventional studies for the improvement/ prevention of circadian rhythm desynchronization in ICU patients

Type and aim of study	Sample	Method for circadian rhythm assessment	Melatonin intervention	Noise intervention	Light intervention	Results	Reference
Intervention study to evaluate and compare experiences of lighting environments in two ICU rooms with different lighting environments	95 patients (50 in the ordinary group and 45 in the intervention group)	Written questionnaire			Intervention room: cycled lighting system	Different perception of daytime brightness and lower lighting variation in nighttime	3
Randomised controlled single-center pilot study for the feasibility of sleep improvement using light and noise interventions	12 neurologic ICU patients (6 with standard care vs 6 intervention care)	Continuous electroencephalography (EEG)		Noise-cancelling headphones	Eye mask	Unable to provide evidence of benefit using noise-cancelling headphones or eye masks	118
Randomised controlled study to investigate the effectiveness of oral melatonin, earplugs and eye masks on sleep quality	40 healthy subjects exposed to an ICU simulated situation	Polysomnography (PSG)	1 mg oral dose	Earplugs	Eye mask	Improvement of sleep quality by oral administration of melatonin and use of earplugs and eye masks	119
Randomised controlled trial to verify the usefulness of bright light therapy	22 ICU patients (10 study vs 12 control)	NEECHAM Confusion Scale			bright light exposure device for four days	Lower level of arrhythmia and lower delirium	120
Quasi-experimental design to test the efficacy of the sleep care guidelines for controlling night-time noise and care-related	55 ICU surgical patients (27 with standard care vs 28 intervention care)	Sleep in the Intensive Care Unit questionnaire (SICUQ), Richards Campbell Sleep Questionnaire (RCSQ)		(1) close door at 11:00 p.m., (2) dim lights to 40 lux, (3) decrease telephone ring volume to 40 dB (4) lower the volume of the monitor and its alarm to 50 dB at 11:00 p.m. (5) prevent the alarm of tube feeding from sounding (6) respond to an alarm within one minute (7) rearrange the time for		Lower perceived noise and sleep interruptions from care-related activities and noises, better sleep quality and sleep efficiency	121

activities on sleep quality				taking a chest X-ray from midnight to between 7:00 p.m.–10:00 p.m. (8) rearrange the time for morning care and drawing blood from 5:00 a.m.–6:30 a.m. (9) lower the volume of staff conversation after 11 p.m.			
Pilot study to evaluate the effect of bright light therapy on circadian rhythm adjustment and postoperative delirium	15 ICU surgical patients (7 with standard care vs 8 intervention care)	Accelerometer and NEECHAM Confusion Scale			Bright light therapy 5000 lux	Reduced postoperative delirium upon bright light therapy	102
Randomised double-blind placebo controlled trial to evaluate the effect of exogenous melatonin on nocturnal sleep quantity	24 ICU patients (12 intervention vs 12 placebo)	Bispectral Index (BIS)	10 mg melatonin			Association of melatonin with increased noctrurnal sleep efficiency	122
Double-blind, randomised, placebo-controlled pilot study to test the effect of nocturnal melatonin on the improvement of nightly sleep	32 ICU patients (14 intervention vs 18 placebo)	Observed sleep hours (bedside nurse) and Riker Sedation–Agitation Scale (SAS)	3 mg melatonin			Similar nocturnal sleep	123
Double-blind, placebo-controlled study to examine the role of melatonin administration on sleep quality	8 pulmonary ICU vs 8 controls	Wrist actigraphy	3 mg melatonin			Improvement of duration and quality of sleep upon melatonin administration	124

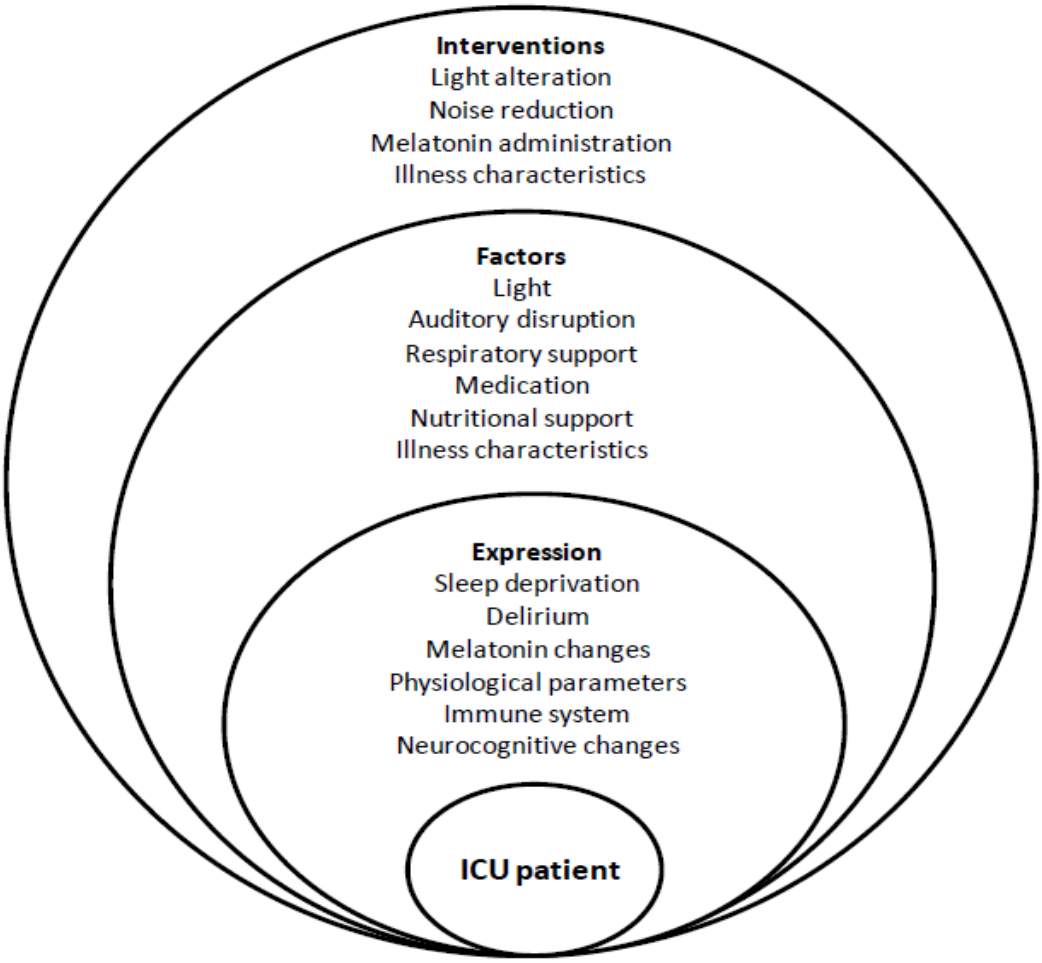

Figure 1 Circadian disruption in the ICU patients: concept chart of factors, expression and interventions.

Highlights

- *Light, noise, medication and illness contribute to circadian disruption in the ICU*
- *Circadian dysrhythmias affect sleep, melatonin levels, immunity and neurocognition*
- *Lighting, noise reducing and melatoninergic interventions aim at chronoenhancement*