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Nonpharmacological Interventions in Delirium: The Law of the Handicap of a Head Start

Numerous patients who have been admitted to an ICU show a disturbance of consciousness and cognition. Usually this is compatible with delirium, a clinical expression of acute encephalopathy (1). Important sequelae of delirium may include long-term cognitive impairment, discharge to a nursing home, and low quality of life (2, 3). Delirium also has an impact on society due to increased duration of ICU and hospital admission, which results in decreased medical capacity and increased costs (2, 4).

It is generally assumed that nonpharmacological measures may decrease the burden of delirium, both by prevention and by treatment. The current Society of Critical Care Medicine guideline for pain, agitation/sedation, delirium, immobility, and sleep disruption suggests application of multicomponent nonpharmacologic intervention programs to optimize modifiable delirium risk factors (5). However, evidence is limited, particularly in ICU patients. A meta-analysis on multicomponent nonpharmacological interventions in non-ICU patients showed that these could decrease the odds of delirium by 53% (6). These components included "improvement of cognition or orientation," "early mobility," "stimulation of the use of hearing aids and glasses," "sleep–wake cycle preservation," and "treatment of dehydration" (6). It is important that these measures are studied in ICU patients for at least two reasons. First, although delirium features are similar in patients across different settings, findings in non-ICU patients may not be generalizable to ICU patients, as these may differ from non-ICU patients with regard to risk factors as well as treatment. Second, application of nonpharmacological interventions is not for free, as successful implementation requires time and effort to change the work culture of healthcare professionals. The application of nonpharmacological interventions in the ICU should therefore be supported by solid scientific evidence.

The UNDERPIN-ICU (Nursing Delirium Preventive Interventions in the Intensive Care Unit) study, described in this issue of the *Journal* (pp. 682–691), is an important contribution (7). UNDERPIN-ICU investigated the impact of a multicomponent nursing intervention program with a multicenter stepped-wedge cluster-randomized clinical trial in 1,749 patients who were admitted to one of 10 participating ICUs and who were at high risk of developing delirium (7). A program targeting modifiable risk factors was implemented as standard of care, focusing on visual and hearing impairment, orientation loss, sleep deprivation, cognitive impairment, and immobility. These domains were customized for

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ICU patients by expert consensus and pilot testing. Nurses were allowed to tailor the program to patient needs, starting within 24 hours after ICU admission until ICU discharge. However, the intervention program was not associated with a beneficial effect on the primary outcome, the number of delirium-free and coma-free days alive 28 days after ICU admission, or any of the secondary outcomes (7).

The UNDERPIN-ICU study has several strengths as it was large and well designed. Conventional randomization of patients to either intervention or control procedures would have been labor-intensive with a risk of decreased external validity due to refusals of informed consent (8). Furthermore, randomization of patients would likely have led to contamination of intervention and control procedures as patients from both trial arms would have been treated by the same nurses. Instead, in this trial, ICUs (i.e., clusters) were randomized for the order to change standard of care. As the intervention was harmless and the study evaluated a change of standard practice, explicit patient consent was not required, and all eligible patients could participate in this study without concerns about selective inclusion (8). Another strength of this study was that there were extensive implementation efforts that included education, motivational strategies, outreach visits, and a comprehensive process evaluation. As in 9/10 hospitals, over 70% of the nursing/medical staff received a training presentation, these efforts seem to have been reasonably adequate. As a consequence, the time spent on improving cognitive function increased, and light levels during nighttime and noise levels during daytime decreased significantly after implementation of the program (7).

There are also some limitations. A before–after study aiming to improve daily practice is essentially a quality-of-care study, and results are completely dependent on the amount of care at baseline. Findings in UNDERPIN-ICU were obtained in ICUs where the intervention had to a large extent already been applied and where the duration of delirium at baseline was quite low (median 2 days, interquartile range 1–4). Time spent on interventions slightly increased (median 32–38 minutes per nursing shift, $P = 0.44$) (7). Of note is that participating ICUs were selected based on interest in delirium (i.e., membership to the Dutch ICU Delirium Consortium). The intervention could therefore have been beneficial in ICUs with lower baseline quality of delirium care.

Findings from this study suggest several areas for future research. First, future studies on nursing delirium preventive interventions should be performed in ICUs where these measures have not been implemented yet. Second, the components of the intervention program may be adjusted, cognitive training in particular. There are currently very few pilot studies on cognitive exercise during ICU admission, and it is unknown how this should be applied. As an alternative to conventional cognitive training, serious games could be used to entertain, encourage, and optimize compliance (9). Third, as our knowledge on delirium pathophysiology is limited (2) and adequately powered randomized clinical trials on patient-centered outcomes are expensive and time-consuming, there is a need for mechanistic studies on intermediate outcomes. Unfortunately, it is currently not completely clear which intermediate outcome could be used. EEG is promising for biomarker studies as it typically shows profound alterations during delirium, such as increased delta activity and spectral variability as well as decreased complexity, connectivity strength, and network integration (10–13). Future studies should indicate which EEG characteristic should be used as a delirium biomarker to investigate whether application of a nonpharmacological measure would result in EEG improvement under otherwise stable physiological conditions.

In conclusion, as delirium is a serious condition, every intervention that could decrease its burden should be applied. As nonpharmacological measures have been shown to be beneficial in non-ICU patients, we should not discard these in the ICU based on a study in which these measures were to a large extent already implemented at baseline. ■

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Early Antibiotics in Cystic Fibrosis: Lessons from the Cystic Fibrosis Pig Model

Cystic fibrosis (CF) is caused by mutations in CFTR (cystic fibrosis transmembrane conductance regulator), which results in defects in ion transport. The leading causes of morbidity and mortality are respiratory symptoms and progressive pulmonary failure. Three hallmarks of this pathogenesis identified to date are abnormal mucus accumulation, mucus tethering, chronic sinopulmonary inflammation, and recurrent infections (1). However, there has been continued debate about what comes first: infection or inflammation, akin to the chicken or the egg argument.

Evidence of intrinsic airway inflammation has been described in fetal lungs homozygous for the ΔF508del-CFTR mutation. This study found that even in fetal lung tissue, which was presumably sterile, there was overexpression of proinflammatory proteins and evidence of nuclear factor-κB activation in the airway (2). Meanwhile, studies from AREST-CF (the Australian Respiratory Early Surveillance Team for Cystic Fibrosis) showed that bacterial infections can exacerbate airway inflammation and worsen other clinical outcomes in early CF lung disease as well (3, 4). Newborn screening allows us to diagnose CF and apply early interventions before clinical presentation. Early childhood may represent a critical time point to delay or prevent the onset of lung damage and may impact the future clinical trajectory (5). In this issue of the *Journal*, Bouzek and colleagues (pp. 692–702) used the CF pig model to study bacterial-dependent and -independent inflammatory responses and mucus accumulation in newborn pigs (6).

The authors chose the CF pig model because this model develops spontaneous lung disease. Commonly used rodent models are not ideal in the CF lung field as they fail to develop spontaneous lung disease as observed in humans (7). Investigators have developed newer animal models for CF, including pigs (8), ferrets (9), and rabbits (10), that to some extent overcome this limitation. The newborn pigs in this paper have similar anatomical, physiological, and biochemical features to those of early events in humans with CF compared with other models, such as *1*) pigs contain submucosal glands throughout the cartilaginous airways, whereas those in rodents are limited in trachea; *2*) the major type of secretory cell is the goblet cell instead of the club cell in mice; and *3*) newborn pigs with the *CFTR* mutation have acidic airway surface liquid pH (11) and mucous tethering (12), leading to lower bacterial killing efficiency and abnormal mucociliary clearance. Within months, they develop spontaneous sinopulmonary diseases with hallmarks of CF such as infection, inflammation, mucus accumulation, airway remodeling, and lobar pathological heterogeneity (13).

To determine the effects on airway bacterial burden as well as airway inflammation, the authors applied early-onset continuous broad-spectrum antibiotics to newborn CF pigs. Before the initiation of antibiotics, CF pigs at 3 weeks of age had a greater absolute number of bacteria as well as a greater number of bacterial species in lung tissue than non-CF pigs. Continuous antibiotic treatment (a combination of ceftiofur hydrochloride intramuscularly from birth as well as oral cephalexin, ciprofloxacin, and trimethoprim-sulfamethoxazole till study completion) reduced the bacterial burden as well as the bacterial species abundance in lung tissue. Furthermore, antibiotic treatment reduced certain aspects of CF lung pathology, including less mucus accumulation, measured by periodic acid–Schiff staining, and less lung parenchymal heterogeneity, measured by computed tomography (CT) lung scanning, compared with control CF pigs. However, some lung abnormalities persisted. Antibiotic-treated CF pigs still showed similar inflammatory histopathologic scores in hematoxylin and eosin staining and air trapping abnormalities on CT imaging.

Notably, this extensive antibiotic regimen did not affect sinusitis, with no reduction in bacterial burdens in this anatomic niche. However, the authors did find that antibiotics altered the dominant bacterial species from *Streptococcus* spp. to *Enterococcus* spp. and *Pseudomonas* spp., which may suggest an active selection mechanism. This shift in bacterial species induced by antibiotics was also observed in the lungs and had a strong correlation with lung heterogeneity on CT imaging. This raises concerns for the use of routine clinical antibiotics as the main option in treating or preventing frequent infections in CF (14), given the potential risks of antibiotic resistance, disruption of gastrointestinal tract microbiome, and bacterial selection. In turn, this shift in bacterial populations may further contribute to the persistent sinopulmonary disease. Stutman and colleagues demonstrated higher colonization of *P. aeruginosa* and no improvement on the major health outcomes after continuous antistaphylococcal antibiotics prophylaxis (15).

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