Early detection of ICU-acquired weakness in septic shock patients ventilated longer than 72 hours

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Research Article

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Abstract

Purpose: *ICU acquired weakness*, comprising Critical Illness Polyneuropathy (CIP) and Myopathy (CIM) is associated with immobilization and prolonged mechanical ventilation. This study aims to assess feasibility of early detection of CIP and CIM by peroneal nerve test (PENT) and sensory sural nerve action potential (SNAP) screening in patients with septic shock invasively ventilated for more than 72 hours and to investigate risk factors associated with CIP and CIM.

Methods: We performed repetitive PENT screening from 72 hours after intubation until detecting a pathological response. We tested SNAPs in pathological PENT to differentiate CIP from CIM. Muscle strength examination was performed in awake patients and time from intubation to first in-bed and out-of-bed mobilization were recorded.

Results: Eighteen patients were screened with PENT and 88.9% had abnormal responses. Mean time between intubation and first screening was 94.38 (± 22.41) hours. Seven patients (38.9%) had CIP, 2 (11.1%) had CIM, 1 (5.6%) had CIP and CIM, 6 (33.3%) had a pathological response at PENT associated with ICU acquired weakness but no SNAP could be performed to differentiate between CIP and CIM and 2 patients had (11.1%) had no peripheral deficit. In the patients where it could be performed, muscle strength testing concorded with electrophysiological findings. Twelve patients (66.7%) had out-of-bed mobilization 10.8 (± 7.4) days after admission.

Conclusion: CIP and CIM are frequent in septic patients and can be detected before becoming symptomatic with simple bedside tools. Early detection of CIP and CIM opens new possibilities for timely management of CIP and CIM through preventive measures such as passive and active mobilization.

Introduction

Critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) are part of a clinical entity called *intensive care unit* (*ICU) acquired weakness*, a frequent complication of critical illnesses, [1] which has been shown to delay ventilator weaning and discharge from the ICU, prolong the rehabilitation period and general hospitalization stay and increase risk of death [2–4]. Identified risk factors for CIP and CIM are multiple organ failure (MOF), sepsis and prolonged mechanical ventilation. Prevalence of ICU acquired weakness in septic patients was shown to vary from 50 to 70% depending on the studied population [5–6].

In clinical practice, ICU acquired weakness is usually diagnosed by muscle strength testing. Clinical muscle strength testing is only possible after reducing sedation on awake patients; therefore, screening takes place after the acute phase of hospitalization, which can extend to long durations, [7] delaying any possible preventive measures to avoid development of ICU acquired weakness. Many studies used accurate and extensive electrophysiological testing to diagnose CIP and CIM after patients showed signs of muscle weakness [1–3]. However, earlier identification of persons at risk for ICU acquired weakness would allow timely preventive interventions, [8] such as treating conditions leading to multi organ failure, avoiding unnecessary deep sedation, controlling excessive blood glucose levels and corticosteroid administration, and promoting early mobilization as preventive strategy.[9] A recent study proposed possible earlier diagnosis using a full range electrophysiological testing at 10 days after intubation, and showed that CIP is associated with increased duration of mechanical ventilation and in-hospital mortality. [4, 10]

Complete electrophysiological screening is too fastidious for screening critically ill patients.[11] Latronico et al. proposed therefore, a simplified screening method using motor peroneal nerve test (PENT) to identify motor conduction loss, [12] allowing early testing on particularly at-risk populations. This opens new perspectives for earlier management of CIP and CIM through preventive measures, like passive and active early mobilization.

Early mobilization methods are constantly progressing through the introduction and improvement of robotic devices such as cycloergomatry, MOTOmed-letto® and Erigo®, for example facilitating coma patient rehabilitation in an upright position. [13–14] Very early rehabilitation improves muscle force, endogenous catecholamine production and prevention of complications by bed rest. [13–16]

The aim of this study is to assess the feasibility of the simplified screening method of Latronico et al. for early detection of CIP and CIM in a population known to be at high risk of developing these two conditions: patients admitted to the ICU with septic shock and mechanically ventilated for more than 72 hours. This research also aims to confirm described risk factors for developing CIP and CIM during acute ICU stay and to reinforce the necessity of prevention by very early neurorehabilitation.

Methodology

Study site and population:

This study took place in the adult ICU of the Lausanne university hospital. We recruited patients over a six-month period from January 1st to June 31st, 2019. Patients admitted to the ICU who either had septic shock or who developed septic shock during ICU stay and who had invasive ventilation for ≥ 72 hours were eligible for the study. Septic shock was defined according to the Surviving Sepsis Campaign guidelines 2017. [17] Exclusion criteria were pregnancy, aged below 18 years, patients with previously known nerve or muscle disorders to eliminate potential confounding conditions and patients with lower-limb disorders precluding nerve and muscle conduction study, such as massive edema, fractures, lower-limb amputation, and lower-limb

immobilization from a plaster. We also excluded patients hospitalized for more than 14 days before intubation, patients with a known functional disability of four or more on the Modified Rankin Scale, [18] and patients admitted to the ICU for severe burns.

Clinical assessment

Included patients were evaluated on the day following 72 hours of intubation (day 3, Fig. 1). Patients were then examined each week according to the investigation plan (Fig. 1). We used the following clinical scores: Simplified Acute Physiology Score II (SAPS II) [19] to monitor illness severity at ICU admission and predict patient outcome, Sepsis-Related Organ Failure Assessment (SOFA) [20] to grade organ failure severity, Kidney Disease Improving Global Outcomes (KDIGO)[21] to grade acute kidney injury and Richmond agitation-sedation scale (RASS) [22] to grade state of sedation.

For each patient, we noted the cumulated doses of opiates, propofol and midazolam and recorded mobilization onset and schedule, focusing on time between intubation and first passive and active mobilizations in-bed, sitting in the bed or out-of-bed. Passive in-bed mobilization consisted of two methods, a passive mobilization of the patient's articulations by a physiotherapist in daily 15-minute sessions and motorized mechanical mobilization with the Motomed® cyclo-ergometer.

We assessed factors associated with CIP and CIM, such as length of mechanical ventilation and extubation failure. [23–24] We considered extubation failure as any case of endotracheal tube removal and re-intubation before 72 hours. Regarding weaning difficulties, we classified patients according to the categories proposed by the WIND study: no weaning (WIND 0), no extubation or attempt, short weaning (WIND 1), successful weaning process in less than one day, difficult weaning (WIND 2), weaning within one day to one week and prolonged weaning (WIND 3), weaning taking more than one week. [24] We also recorded length of stay in the ICU, patient destination after the ICU and re-admission rate to the ICU.

Clinical assessment:

Patients underwent neurological examination at inclusion (day 3), then weekly and finally, on their last day in the ICU. We assessed reflexes (brachial biceps, quadriceps, and Babinski's sign) before electrophysiological examination. We tested muscle strength of three muscle groups of the four limbs using the Medical Research Council (MRC) scale (from 0 to 5) with a cutoff value defining muscle weakness below 48/60 points. [25–26] The clinical investigator was not the physician in charge of the therapeutic decisions.

Neurophysiological studies:

Motor nerve conduction was recorded using peroneal nerve test (PENT), [12] which we performed on the day of inclusion (day 3) or as soon as the patient's condition would allow performing a test without artefacts caused by agitation or severe edema hindering the nerve conduction study. Patients under muscle-blocking drugs were tested only after their complete interruption and assessment of a positive train-of-four muscle response. [27] PENT measures compound muscle action potentials (CMAPs) with surface electrodes after electrical stimulation of the peroneal nerve at the patient's ankle. We placed the active electrode on the belly of the extensor digitorum brevis muscle and the indifferent electrode on the distal tendon of the recorded muscle. The stimulus intensity was gradually increased until the maximal CMAP was obtained. The CMAP negative peak amplitude was measured, and an abnormal amplitude was defined as < 2.5 mV. When the test showed a normal response, we repeated it on the contralateral limb. Normal responses on both sides defined a normal condition. We considered an unpaired response on one side as abnormal condition, indicating further testing.

Further testing involved wider investigation in a second session where we measured other CMAPs (distal stimulation of the median nerve at the wrist to the abductor pollicis brevis muscle and stimulation of the musculocutaneous nerve at the arm to biceps brachialis muscle). In addition, sensory nerve action potentials (SNAPs) following stimulation of the sural nerve at the ankle [28] (stimulation to the lower third of the leg with SNAP recording bilaterally on the lateral malleolus with surface electrodes). The normal sural SNAP had peak-to-peak amplitude ≥ 5 μV.

We considered CIP diagnosis when CMAPs and SNAPs were of low amplitude. We defined CIM when CMAPs were of low amplitude together with an increased duration, with a normal sural SNAP. [29–30]

Statistical methods and follow-up

We did a descriptive statistical analysis. Results are reported as mean (SD) or median (IQR) as appropriate for continuous values. Numbers and percentages are used to describe proportions.

Results

Patient screening and demographics:

Over the six months of investigation, we screened 574 potentially eligible patients (see Fig. 2, Patient inclusion flow chart). Of the 21 eligible patients with septic shock and more than 72 hours of intubation, we missed one and two withdrew their consent resulting in 18 included patients. The patients were mainly male (77.8%) with an average age of 63.6 ± 11.7 years and a body-mass-index of 28.0 ± 5.2 kg/m^2. (Table 1). Twelve patients (66.7%) were directly hospitalized in the ICU and the six others (33.3%) were admitted to the ICU after hospitalization in another department.

Outcomes and risk factors:

As shown in Table 1 and supplementary Table 1, the overall length of stay in the ICU was 14.9 ± 9.1 days, with 10 patients (55.5%) staying less than 10 days, 4 (22.2%) between 10 and 24 days and 4 (22.2%) between 24 and 31 days.

The average SAPS II score for the population was 41.8 ± 11.1 points (Table 1), meaning an average predicted mortality of 31.8 + 19,5%. Three patients (16.7%) had a predicted mortality above 50% at ICU admission.

At admission, seven patients (38.9%) had continuous noradrenaline administration and seven (38.9%) had a PaO_2/FiO_2 ratio inferior to 200. Mechanical ventilation modality was Pressure Support Ventilation (PSV) in thirteen patients (72.2%) and Volume Assisted Control Ventilation (VAC) in the five others (27.7%). The most frequent sepsis etiologies were pneumonia and peritonitis (Fig. 3A). Detailed items of the SOFA score are showed in Fig. 3B and the SOFA scores of each patient are recorded in supplementary table 1.

Concerning risk factors, five patients (27.7%) presented a malignancy, five (27.7%) had diabetes and four (22.2%) had COPD. Fourteen patients (77.8%) presented either high creatinine levels or required dialysis. At admission, five patients (27.7%) already presented KDIGO III criteria. Four additional patients had a deteriorated kidney condition during their stay, leading to a total of nine patients (50%) with KDIGO III acute kidney injury during their ICU stay (See Table 1 and supplementary Table 1).

SOFA score reevaluation in the ICU stay showed improvement of the septic condition in nine patients (50%), of whom seven showed remission and were transferred from the ICU after 8.6 (± 1.6) days, 1 died and 1 remained hospitalized for 24 days for severe refractory arrhythmia, ventilator associated pneumonia, prolonged weaning and ICU acquired weakness. The other nine had worsening sepsis and organ failure, six stayed in the ICU for 23.8 (± 8.3) days and three died (See Table 1 and supplementary Table 1).

We recorded failed extubation attempts in five patients (27.8%). Of these, four (22.2%) had prolonged weaning (WIND 3), and one (5.6%) had difficult weaning (WIND 2). Of the whole cohort, five patients (27.8%) had prolonged weaning (WIND 3) taking an average time of 18.8 + 5.9 days, five (27.8%) had difficult weaning (WIND 2), five (27.8%) had short weaning (WIND 1), and three patients (16.7%) died before attempted separation (WIND 0).

Neurophysiological studies:

First neurophysiological study took place after an average time of 5.7 ± 3.4 days after intubation. All patients, except one were sedated and none were paralyzed or alternatively received NMDA blockers. We performed between one and three PENTs (1.67 ± 0.75) for each patient.

Seventeen of the eighteen patients (94.4%) had abnormal PENT and twelve (66.7%) were tested further by SNAP (see Table 2). Among these twelve, we confirmed CIP, CIM or both in ten (83.3%) and the two others showed no signs of nerve conduction impairment (16.7%). Specifically, six (33.3%) showed evidence of CIP on CMAPs of median or musculocutaneous nerves and on SNAPs, three (16.7%) showed evidence of CIM with positive CMAP and lengthened conduction time. One patient (5.6%) had evidence of both CIP and CIM and one had unilateral pathological PENT but no amplitude loss in either motor or sensory responses in other parts of the body and was therefore considered a false positive. The final patient showed normal bilateral PENT. The six patients tested only by PENT (33.3% of our population of eighteen) showed bilateral amplitude loss on one (n = 4, 22.2%) or two (n = 2, 11.1%) tests.

MRC strength assessment:

To validate muscle weakness in early detected CIP and CIM patients, we performed MRC on 8 of the 18 patients (44.4%), possible after an average time of 17.0 (± 9.0) days after intubation (Table 2). The eight patients obtained an average score of 39.75 (+ 13.7) points (Table 2). Six showed insufficient muscle contraction and two showed normal muscle strength, one of whom had normal ENMG findings and the other bilateral loss of amplitude at PENT.

One of the two patients with normal nerve conduction (patient 5, see Tables 2 and 3) had the longest ICU stay of our cohort (36 days). The patient showed isolated abnormal PENT without loss of amplitude elsewhere on motor upper limb or on sensory stimulation. The patient was also tested by MRC muscle strength test at the end of stay that showed preserved muscle strength. The patient recovered with satisfactory muscle contraction and fine motility 8 days after ICU discharge.

Sedation:

Patients were moderately to deeply sedated (RASS <-2) for 59.4% (± 20.9%) of their stay and mechanically ventilated for 77.0% (± 17.7%) of the ICU stay, corresponding to an average time of 11 (± 7.3) days of mechanical ventilation. They received two types of opiates: fentanyl or morphine. Cumulated administered doses of opiates over the whole ICU stay were equivalent to 1067.0 (± 699.2) milligrams of morphine on average. The average cumulated doses of propofol and benzodiazepines were 19247.9 (± 22133.5) milligrams of propofol and 215.4 (± 241.0) milligrams of midazolam, respectively.

Mobilization rehabilitation:

All patients benefited from either passive mobilization during sedation and/or active mobilization after awakening. The different mobilization programs accomplished are shown in Table 3 along with the time from admission to first mobilization. All patients, except one, benefited from passive mobilization at an average time of 77.6 (± 39,1) hours after intubation.

Active mobilization by physiotherapists took place after an average time of 75 (± 41) hours on 16 patients (88.9%). Motorized passive mobilization was performed on 10 patients after 9 (± 4.8) days.

Seven patients (38.9%) were mobilized passively in the sitting position after an average time of 11.9 (± 9.4) days.

Eight patients (44.4%) benefited from active mobilization in the sitting position after 11.3 (± 4.1) days after intubation, of whom four (22.2%) also underwent out-of-bed mobilization in the upright position after 22.3 (± 5.5) days.

Out-of-bed passive or active mobilization was performed on twelve patients (66.7%) after an average time of 10.8 (± 7.4) days after intubation. Six patients (33.3%) neither received sitting nor upright mobilization. Four of them had critical organ failure and died in the ICU. The two others were discharged 8 and 9 days after ICU admission, respectively; one of whom was re-admitted to the unit 16 days after discharge for ICU-acquired polyneuropathy. It took 3 months from the first ICU discharge for this patient to recover fine motility and muscle strength.

Discussion

Our patients with septic shock and mechanically ventilated for more than 72 hours were moderately to deeply sedated for more than half of their time in the ICU and the average ICU stay length was 14.9 ± 9.1 days. We explored screening for CIP and CIM in this acute phase of sepsis before apparition of muscle weakness. Indeed, using the simplified screening test proposed by Latronico et al, [7] this is the first study to evaluate septic patients systematically with PENT, around 72 hours after intubation. Our results revealed early abnormal changes in PENT in short-term critical care patients, which is unprecedented as previous studies only made precise symptomatic diagnosis of CIP and CIM at days to weeks after ICU admission.

The results of this study confirm the likelihood of developing CIP and CIM in patients with MOF, sepsis, and mechanical ventilation [31–32] and add new information on early nerve conduction disorder in critically ill patients.

The incidence of CIP and CIM varies in the literature, depending on the studied population. A study considering a population of patients similar to ours, showed an incidence of up to 70% in septic patients with long-term intubation. [4] The main difference in this study was the time-to-first electrophysiological investigation; Garnacho-Montero evaluated patients at days 10 and 21 after intubation. Using such a late interval, only eight (44.4%) of our patients would have been enrolled in this recruitment method because the others would have been deceased or discharged from the ICU before the MRC could be assessed. A systematic review found an association of about 50% between CIP/CIM and sepsis.[5] Recruitment was once again different; most of the studies treated in the review concerned patients tested for polyneuropathy after appearance of muscle weakness and absent deep-tendon reflexes. Testing patients in the early phase of ICU stay allowed us to include a more diversified population of septic patients, including those with early sepsis recovery and therefore shorter ICU stay. Of note, even a fast recovery from sepsis does not protect against eventually contracting critical care illness from ICU stay as seen in the three patients hospitalized for less than 10 days, with critical care illness revealing itself after ICU discharge. Indeed, early testing provided evidence that this patient population is at risk of developing CIP or CIM later as seen in the case of one patient who was dismissed from the ICU on day 9 without benefiting from out-of-bed mobilization, and later re-admitted to the ICU for CIP-induced respiratory failure. This patient only recovered muscle strength and fine motility at 3 months after the first ICU discharge and experienced a very stressful hospitalization.

Systematic acute phase nerve conduction studies on short stay patients offers new diagnostic horizons but is also an organizational challenge, which represents the major limitation of our study. As the study design foresaw a first screening session with PENT and a second for further testing, the second session was not possible for some patients who had either died, left the ICU before further investigation was possible, received muscle relaxants or who were in a state of stress and refused investigation. In addition, the unavailability of nerve conduction studies on some occasions prevented further investigation. Consequently, six patients were only tested with PENT and defined as possible CIP or CIM, without a SNAP analysis allowing differentiating between the CIP and CIM subgroups of ICU acquired weakness patients. This inconvenience hindered the assessment of possible associations between sedation times and CIP and CIM subgroups. Essentially, positive PENT screening should be followed by further electrophysiological testing to allow a more accurate diagnosis of CIP from CIM. Systematic early testing in the ICU is already challenging, and full neurophysiological diagnosis on acute septic patients is remarkably complex in the first acute hospitalization phase. However, as prognosis of CIM is better than CIP, [26] systematic positive PENT coupled to SNAPs, muscle conduction time and at least one CMAP on another limb can already be considered an appropriate systematic testing regime. [33]

MRC testing of our patients was difficult as most patients were transferred quickly to the intermediate care unit after awakening and extubation and were either sedated or unable to follow orders before ICU discharge. Advantages of PENT for early screening again crystallize; this method is independent of patient awareness. Six patients presenting loss of amplitude on motor stimulation with PENT also had muscle contraction impairment in the MRC test, corroborating the PENT results. One, however, had an important loss of amplitude in PENT but no contraction deficit on the MRC test, raising the question of a possible focal neuropathy of the peroneal nerve. This patient had the shortest stay of the whole cohort and remission. MRC testing also allowed confirming the presence of muscle weakness in one patient who had not been examined by other electrophysiological investigation than PENT. Even though MRC muscle strength testing was not systematic and was only performed on eight (44.4%) of the 18 patients, it confirmed the presence of muscle weakness.

Exploring polyneuropathy at an early stage also gave a new perspective on risk factors of developing CIP and CIM. Association between the two conditions and COPD, cancer, diabetes and acute kidney injury (AKI) is possible but should be explored further in studies with higher numbers of patients. As COPD impairs ventilation weaning, it would be interesting to compare weaning failure in COPD patients with and without ICU acquired weakness. [31–32, 34] Regarding diabetes, a case report showed a 27-year-old female diabetic patient who developed acute polyneuropathy at day 2 of ICU admission. [35] Our patient population had 5 diabetic patients out of 18 (27.8%), not significantly higher than the 20% expected in a population of similar average age of 63.6 ± 11.6 years according to worldwide diabetes prevalence in 2019 from the International Diabetes Federation.[36–37] Furthermore, diabetes does not seem to impair prognosis of septic patients but rather increases the incidence of acute kidney injury (AKI). [38] Concerning the latter risk factor, renal failure is associated with higher mortality and the population we studied showed a particularly high incidence of AKI.[35–36]AKI shows approximately 50% association with septic shock, [39] which is inferior to the overall incidence of 13 out of 14 patients (92.9%) with AKI in our study. In addition, 8 out of 9 with renal replacement therapy (88.9%) had peripheral nerve conduction impairment, so association between AKI and sepsis severity, as well as ICU acquired weakness warrants further investigation to allow better prediction of its occurrence in early-stage septic shock patients. Furthermore, investigating peripheral nerve conduction impairment in AKI patients could furnish new information on the well-known association between CIP/CIM and MOF. Cancer is also known to worsen prognosis of septic patients. [40–41] All five patients of our cohort with an ongoing malignancy showed nerve conduction impairment, of whom four were clearly diagnosed with CIP and three died. Exploring an association between this risk factor and CIP/CIM would offset the lack of data in the current literature.

Early mobilization techniques have been proven beneficial in shortening ICU stay and improving rehabilitation. [42] Specific treatment of CIP and CIM include limb and respiratory muscle stimulation, but these techniques are still lacking in current practice. [6] A recent review stated that acute pharmacological treatment of inflammation has been explored but that mobilization was poorly investigated[41]. Beginning mobilization in the first days after onset of critical illness and intubation was reported to be safe and offer a real improvement in rehabilitation and in shortening the length of hospital stay in critically ill patients[42–44]. Coupled with efficient sepsis treatment, [45] early mobilization offers better chances of recovery from many complications associated with critical illness. Indeed, early mobilization, especially verticalization associated with cyclic movement, maintains the neuro-vegetative system by stimulating the endogenous adrenergic system and preventing complications from immobilization such as CIP and CIM.[46] This passive mobilization method has been proven not to increase the need of using catecholamine for intensive and intermediate care patients with severe brain injuries. As we have shown that CIP and CIM may be detected in the early phase of ICU stay [12] and prompt mobilization improves prognosis, [47] we can expect benefit from new mobilization techniques such as cyclical movement by MOTOmed-letto®. Early mobilization, however, should always be coupled with diaphragm stimulation as the incidence of diaphragm muscle weakness may be twice that of skeletal muscle weakness [32].

Passive robotized verticalization and mobilization techniques are still unexplored, but their use with comatose patients offers a potential treatment of CIP and CIM as they improve passive physiotherapy.

Our study emphasizes the need for early screening of CIP/CIM for three reasons. First, although severe sepsis with MOF and lengthened hospitalization are risk factors, it seems impossible to predict whether a patient is more likely to develop these conditions as we found one patient with severe sepsis and the longest stay, who did not show evidence of polyneuropathy. Second, the average state of consciousness of these patients and average time to awakening makes it impossible to diagnose the CIP/CIM by following symptoms. Early neurophysiological screening is therefore necessary to allow early recognition of the disease and to avoid misdiagnosis of a disorder of consciousness and absence of motor response[48]. Third, benefit can be expected from early specific passive muscle stimulation since active mobilization techniques are impossible on sedated patients. Early diagnosis would enable a tailored therapy for these at-risk patients. However, specific benefits need to be evaluated in a larger study with the same inclusion criteria and a protocol focusing on the mobilization procedure.

Conclusion

CIP, CIM and other peripheral deficits can be detected early by electrophysiological screening with motor and sensory testing in 55.6 to 88.8% of patients with septic shock undergoing mechanical ventilation. Association of CIP/CIM with cancer, acute kidney injury and diabetes is possible and should be explored in future research. The expected benefit from early screening of CIP and CIM is to allow early active mobilization by physiotherapists if the patient is awake or passive mobilization if still sedated to improve patient outcome. Cyclic movement by MOTOmed-letto® or verticalization could potentially improve these patients' outcomes.

This study brings new knowledge on CIP and CIM in ICU patients with mechanical ventilation and septic shock by having systematically screened for them at an early stage of the disease and before symptoms are apparent. It furnishes information concerning early weaned and short stay patients that have not been explored in previous studies not testing CIP and CIM systematically. It further opens perspective for use of emerging mobilization techniques on this category of patients.

Abbreviations

Nerve conduction study :

CIP Critical Illness Polyneuropathy

CIM Critical Illness Myopathy

PENT Peroneal Nerve Test

SNAP Sensory Nerve Action potential

Scores and scales :

SAPS II Symplified Acute Physiology Score II

SOFA Sequential Organ Failure Assessment

KDIGO Kidney Disease Improving Global Outcome

RASS Richmond Agitation-Sedation Scale

MRC Medical Research Council

Declarations

Ethics approval and patient consent

The clinical study protocol n° 2018-01233 was approved by the local ethics committee CER-VD.

Consent for publication

After providing written and detailed information on the study aims and safety of electrophysiological investigations, we obtained written informed consent from all surviving patients or from legal representatives of deceased patients. We conducted clinical investigations according to the principles expressed in the Declaration of Helsinki.

Availability of data and materials

Most of the data that support the findings of this study are included in the article for publication and its supplementary information file. Restrictions apply to availability of additional data such as patient screening, which requires authorization from the Lausanne ICU for sensitive data. Other data are available from the authors upon reasonable request and with permission from PD-MER Lise Piquilloud Imboden.

Competing interests

The authors declare no conflicts of interest.

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Author contributions

CA was responsible for the screening, initial inclusion, PENT tests, neurological and MRC examinations of the patients. TK performed the nerve conduction studies in case of abnormal PENT findings. LPI gave access to the ICU for all investigators, gave valuable advice on ethical and organizational issues, inclusion and exclusion criteria and coordinated the investigations in the ICU. LS recorded patient data and was a major contributor to writing the manuscript. JJ gave helpful advice about neurological rehabilitation concerning the state of coma and sedation and for writing the article. KD led the research work, ensured cohesion of the team and participated in the neurological examinations. All authors read and approved the final manuscript.

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Tables

Table 1: Included population's general data, risk factors and outcomes. Detailed patient characteristics are available in supplementary table 1 in the electronic supplementary material.

Population	n=18		
Age (years)	**63.6** ± 11.6		
Sex	14 M (77.8%) ; 4 F (22.2%)		
BMI	**28.0** ± 5.2		
Length of stay (days)	**14.9** ± 9.1		
SOFA Score	**12.8** ±3.1		
SAPS II – Score			
Points	**41.8** ±11.1		
% predicted mortality	**31.8** ±19,5%		
Risk factors	CIP/CIM	Normal	Died
COPD (n=4)	4 (100%)	-	-
Cancer (n=5)	5 (100%)	-	3 (60%)
Diabetes (n=5)	3 (60%)	2 (40%)	-
AKI KDIGO ≥ 1 (n=14)	13 (92.9%)	1 (7.1%)	3 (21.4%)
AKI KDIGO ≥ 3 (n=9)	8 (88.9%)	1 (1.1%)	2 (2.2%)
Overall	16 (88.9%)	2 (1.1%)	4 (2.2%)

Table 2: Detailed results nerve conduction study and MRC scale.

N°	First nerve conduction study			**PENT** (mV) evolution R / L (day from intubation)	**Muscle strenght** according to **MRC** Pathological below 48/60 points (day from intubation)	**Clinical result**
	PENT (mV) R / L (day from intubation)	Sural SNAP (µV) R / L	Sural SNAP velocity in m/s			
1	**1.1** / - (day 3)	7.9 / -	56.3	- / -	-	**CIM**
2	**1.3** / - (day 3)	7.5 / -	55.9	- / -	-	**CIP**
3	**0.0** / - (day 4)	4.0 / -	-	- / -	-	**CIP**
4	**1.1** / - (day 5)	13.0 / -	44.8	0,6 / - (day 19)	**38** (day 26)	**CIM**
5	**1.7** / - (day 17)	7.0 / -	50.4	1.3 / 1.7 (day 24)	60 (day 34)	Normal
6	**0.8** / **0.3** (day 9)	- / -	-	- / -	-	Possible CIP/CIM but no SNAP
7	**0.9** / **0.9** (day 5)	0.0 / 0.0	-	- / -	**45** (day 17)	**CIP, CIM**
8	**0.2** / **0.5** (day 7)	0.0 / -	-	0.4 / - (day 14)	-	**CIP**
9	**2.2** / - (day 4)	0.0 / -	-	1.4 / 0.7 (day 7)	**27** (day 20)	**CIP**
10	**3.0** / **2.5** (day 3)	- / -	-	1.4 / 1.2 (day 7)	-	Possible CIP/CIM but no SNAP
11	**0.7** / **0.6** (day 9)	- / -	-	0.6 / 1.7 (day 16)	**33** (day 13)	Possible CIP/CIM but no SNAP
12	**0.5** / **0.6** (day 4)	- / -	-	- / -	59 (day 4)	Possible CIP/CIM but no SNAP
13	**2.1** / **2.4** (day 7)	- / -	-	- / -	-	Normal
14	**1.3** / **1.4** (day 4)	3.8 / 0.0	61.4	- / -	-	**CIP**
15	**0.3** / - (day 4)	0.0 / 1.5	-	0.1 / 0.4 (day 8)	**18** (day 14)	**CIP**
16	1. **0.0** (day 4)	- / -	-	- / -	-	Possible CIP/CIM but no SNAP
17	**0.7** / **2.6** (day 7)	7.3 / -	74.1	- / -	**38** (day 8)	**CIM**
18	**1.1** / **1.7** (day 3)	- / -	-	2.2 / 1.8 (day 7)	-	Possible CIP/CIM but no SNAP

Table 3: Ventilation, Sedation and mobilization

N°	ICU stay length in days	Mechanical ventilation in days	% of stay with RASS <-2	Cumulated doses of sedatives			Days from admission to first mobilization				
				Morphine equivalent mg	Propofol mg	Midazolam mg	Passive muscle stimulation	Cyclo-ergometer	Out of bed		
									Passive sitting	Active Sitting	Active Upright
1	4	4	**100**	196.15	0	106	3	-	-	-	-
2	8	7	**62.5**	620.90	7426	334	4	-	-	-	-
3	9	7	**77.8**	631.50	878	90	1	-	-	-	-
4	**32**	20	37.5	**1250.92**	15585	591	6	10	11	12	31
5	**36**	34	**80**	**1792.70**	35011	564	2	-	34	-	-
6	12	9	**58.3**	539.00	1102	271	4	-	-	10	-
7	**24**	20	**58.3**	**2124.50**	83987	34	2	18	5	21	22
8	**14**	14	**100**	**1456.60**	24733	138	7	11	-	-	-
9	**25**	15	44	**1487.70**	13829	325	4	-	12	-	-
10	9	5	**55.6**	**1286.00**	13672	116	4	14	-	8	-
11	**17**	8	35.2	702.30	23343	0	2	4	9	11	16
12	5	5	20	118.00	5721	0	1	3	5	-	-
13	9	7	**66.7**	193.02	5062	157	2	4	-	7	-
14	**19**	11	47.3	**2147.80**	62050	0	-	-	-	-	-
15	**21**	12	47.6	**1244.60**	12164	908	5	12	-	12	20
16	5	5	**100**	**1056.90**	3096	66	4	-	-	-	-
17	10	6	40	106.80	2767	99	-	4	7	-	-
18	10	9	**70**	**2249.70**	36036	79	2	10	-	9	-

Figures

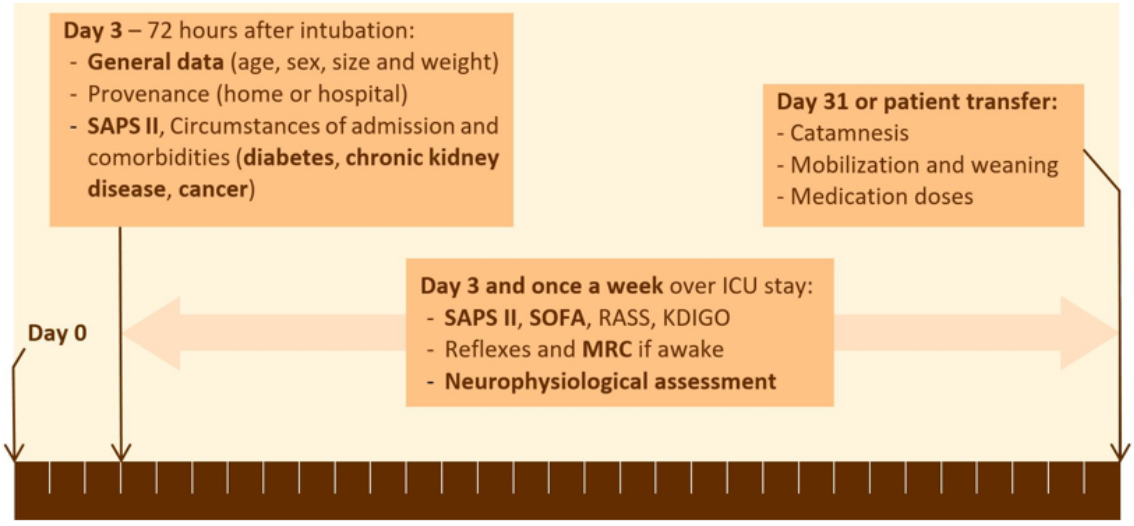

Figure 1

Course of investigation and measures during the ICU stay.

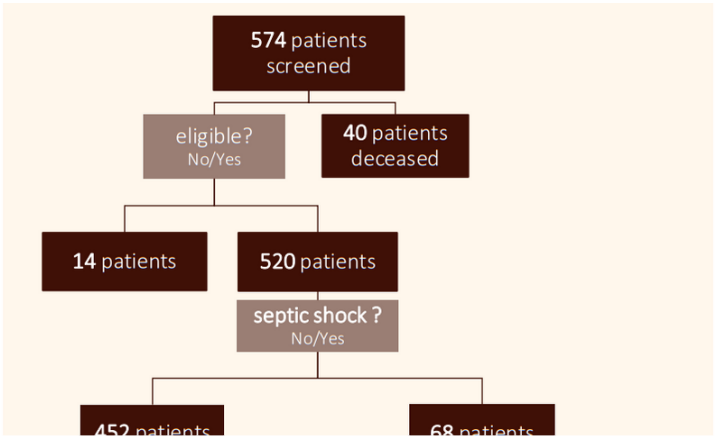

Figure 2

Flow diagram of patient screening and inclusion

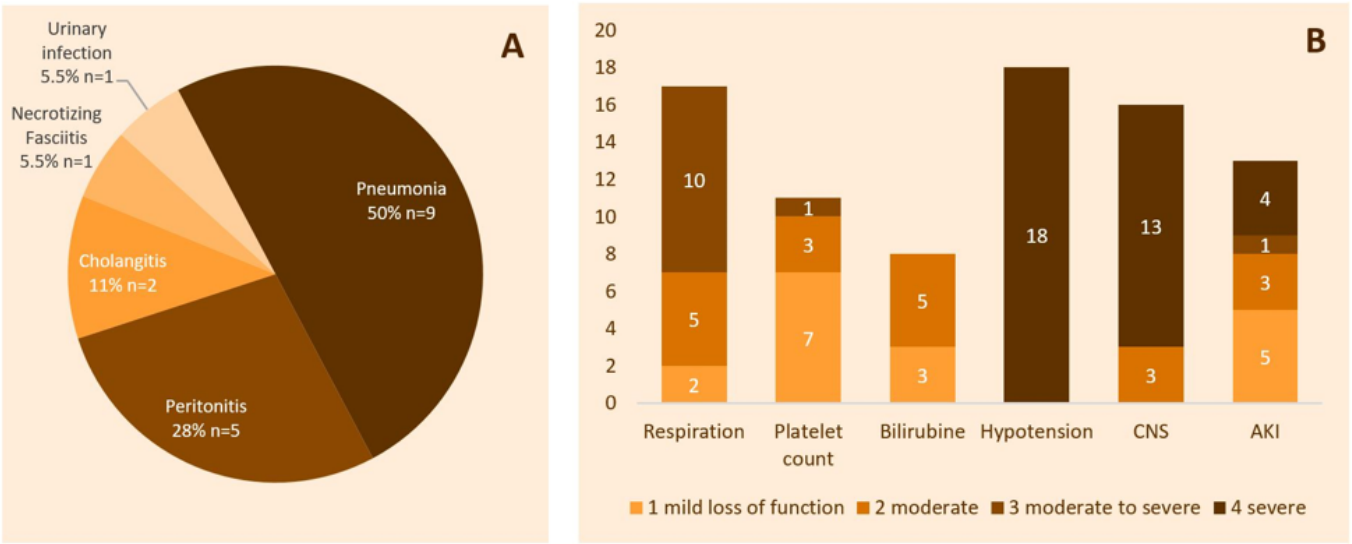

Figure 3

Sepsis etiology and severity on ICU admission. **A** shows the number and percentage of patients per presumed sepsis origin. **B** shows organ failure extent with the number of patients per level of gravity for each item of the SOFA score.

Supplementary Files

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- Populationgeneraldatariskfactorssepsisandoutcomeindetailforeachpatient.docx