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Title: Could neuromuscular electrical stimulation improve the recovery of people with Covid-19 who require care in the intensive care unit? A narrative review

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Short title: NMES in Covid-19 patients admitted to the ICU

33 **Abstract**

34 The rehabilitation of Covid-19 patients after prolonged intensive care unit treatment is often
35 complex and challenging. Patients may suffer a myriad of long-term multi-organ impairments
36 affecting the respiratory, cardiac, neurological, digestive and musculoskeletal systems. Skeletal
37 muscle dysfunction of respiratory and limb muscles, commonly referred to as intensive care
38 unit acquired weakness, occurs in around 40% of all patients admitted to intensive care. The
39 impact on mobility and return to activities of daily living is severe. Furthermore, many patients
40 suffer ongoing symptoms of fatigue, weakness and shortness of breath in what is being
41 described as “Long Covid”. Neuromuscular electrical stimulation is a technique in which small
42 electrical impulses are applied to skeletal muscle to cause contractions when voluntary muscle
43 contraction is difficult or impossible. Neuromuscular electrical stimulation can prevent muscle
44 atrophy, improve muscle strength and function, maintain blood flow and reduce oedema. This
45 review examines the evidence, current guidelines, and proposed benefits of using
46 neuromuscular electrical stimulation with patients admitted to the intensive care unit. Practical
47 recommendations for using electrical muscle stimulation with Covid-19 patients are provided
48 and suggestions for further research are proposed.

49

50 **Keywords:** critical care; rehabilitation; neuromuscular electrical stimulation; muscular
51 atrophy; coronavirus infections; Covid-19

52

53 **Lay Abstract**

54 Many patients with Covid-19 who are admitted to the intensive care unit suffer ongoing
55 symptoms of fatigue, weakness and shortness of breath. Neuromuscular electrical stimulation
56 is a technique in which small electrical impulses are applied to skeletal muscle to cause
57 contractions when voluntary muscle contraction is difficult or impossible. It can prevent
58 muscle atrophy, improve muscle strength and function, maintain blood flow and reduce
59 oedema. This review examines the evidence, current guidelines, and proposed benefits of
60 using neuromuscular electrical stimulation with patients admitted to the intensive care unit.
61 Practical recommendations for using electrical muscle stimulation with Covid-19 patients are
62 provided and suggestions for further research are proposed.

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67 **Background**

68 The COVID-19 (C-19) pandemic has seen unprecedented numbers of people being treated in
69 Intensive Care Units (ICUs) throughout the world. Many patients have received artificial
70 ventilation, and some have been ventilated for many weeks. Those that survive are often left
71 with long term disabilities as a result of the effects of both the disease and of the treatments
72 necessary to keep them alive. A myriad of multi-organ impairments is associated with C-19
73 including respiratory, cardiac, neurological, bowel and kidney dysfunction (1). The
74 unexpectedly large number of C-19 patients requiring a prolonged ICU stay additionally
75 increases the risk of dysfunction of both respiratory and skeletal muscle, commonly referred to
76 as ICU acquired weakness (ICUAW). A conspicuous feature of C-19 is the persistence of
77 symptoms, which may appear to resolve but then recur. As a result, many survivors are left
78 needing significant rehabilitation at a time when such services are under great stress. This has
79 led to the blanket term “Long Covid”, which describes ongoing fatigue, weakness and delayed
80 recovery (2).

81

82 Strikingly, in the first seven months of 2020, there were more than 10,000 C-19 admissions to
83 critical care in the United Kingdom (UK) National Health Service (NHS), which is four times
84 greater than historic annual viral pneumonia cases (3). Our experience of C-19 in the UK is
85 that critically unwell patients generally require a longer course of respiratory support,
86 exacerbating other risk factors for ICUAW (Table 1) (3). At present, ICUAW is seen in around
87 20-50% of C-19 patients admitted to the ICU (4). General deconditioning, muscle atrophy,
88 inflammation, and functional disability often necessitates transfer from the ICU to a long-term
89 care facility. Exacerbations of chronic comorbidities and the cycle of prolonged bed rest,
90 ongoing inflammation and malnutrition can lead to continued functional disability, immobility
91 and continued ventilation support. Data from the UK Intensive Care National Audit and
92 Research Centre (ICNARC) database indicates that older age, obesity, multiple deprivation,
93 and the requirement for assistance in the activities of daily living are predictors for severe
94 disease requiring admission to Critical Care (3). These risk factors are associated with a
95 reduced level of background fitness, malnutrition and neuropathy. Infection with C-19
96 characteristically causes myalgia, lethargy and a loss of appetite likely to exacerbate this pre-
97 morbid condition. Further deconditioning may result from constrained normal daily activities.
98 This may be due to the disease itself, causing shortness of breath on exertion or delirium (5),
99 or may be the result of supportive interventions and infection control measures. It is also

100 noteworthy that proximal myopathy is associated with the use of therapeutic dexamethasone,
101 a drug that has been shown to reduce 28 day mortality in C-19 (6).

102

103 After leaving hospital, almost 90% of survivors experience ongoing symptoms for more than
104 two months, such as fatigue and shortness of breath, which are likely to limit rehabilitation and
105 potentiate deconditioning (7). ICUAW is associated with worse outcomes, including a nearly
106 two-fold increase in one-year mortality, and decreased quality of life (8, 9). A major challenge
107 within current practice is how to ameliorate profound physical and functional deficits in C-19
108 survivors at a time where traditional services are stretched. Innovations that reduce the duration
109 and improve the outcome of rehabilitation will alleviate the burden of suffering and economic
110 damage caused by C-19.

111

112 Neuromuscular electrical stimulation (NMES) is the application of small electrical impulses to
113 nerves supplying muscles using electrodes applied to the skin and has long been used as a
114 treatment for muscle weakness (10). NMES can be used to induce a muscle contraction when
115 it is difficult or impossible for the person to achieve this voluntarily thereby allowing effective
116 exercise and the strengthening of muscles. NMES has been proposed as an intervention to
117 address immobilisation and ICUAW in severe C-19 patients (11), however details on when and
118 how to utilise NMES are lacking. As post-acute rehabilitation services respond to the
119 increasing demand on services; recommendations are required to guide the delivery of
120 rehabilitation models. This narrative review critically examines the evidence for using NMES
121 in the ICU and offers suggestions for clinical practice among C-19 patients. This article
122 provides practical recommendations using a continuum of care model for clinicians interested
123 in using electrical stimulation for patients during and after prolonged ICU treatment.

124

125 **Methodology**

126 This narrative review was informed by the findings of a web-based literature search, completed
127 in October 2020. The search aimed to identify studies that have investigated the role of
128 electrical stimulation in the recovery of patients admitted to the ICU and published in the last
129 ten years (January 2010-October 2020). A search strategy (supplementary material 1) was
130 developed to capture randomised controlled trials or non-randomised clinical trials that have
131 evaluated an intervention of electrical stimulation (FES or NMES) in patients admitted to the
132 ICU. Specifically, we sought studies of adults (aged over 18 years), admitted to the ICU due to
133 chronic illness or following non-elective surgery, who received an intervention of electrical

134 stimulation, either i) during their stay in the ICU, ii) during the acute recovery phase in hospital,
135 or iii) following discharge from hospital. The databases searched included: PubMed,
136 EMBASE, Medline, CINAHL Complete, and The Cochrane Library. Articles were
137 systematically reviewed by the research team to ensure they met the eligibility criteria
138 (supplementary material 2) and were subsequently used to inform this critical analysis and
139 recommendations for future practice. Studies were only included if they reported a replicable
140 NMES protocol. In addition, recently published guidelines recommending the use of home
141 based NMES for chronic respiratory conditions such as chronic obstructive pulmonary disease
142 (COPD) from the National Institute of Clinical Excellent (NICE) were used to inform
143 recommendations (12). A narrative review was considered the most appropriate methodology
144 so that the research team could use a broad survey of the literature, in combination with expert
145 opinion, to inform clinical recommendations. The research team is a multinational,
146 multidisciplinary group of experts with many years clinical experience of NMES. The group
147 includes biomedical engineers; physiotherapists; intensive care clinicians; physiologists and
148 haematologists.

149

150 **Recommendations**

151 **Physiological considerations**

152 Fundamental to the treatment with NMES is an understanding of the electrophysiological
153 mechanisms associated with skeletal muscle function. Skeletal muscles, including diaphragm
154 and accessory respiratory muscles, are made up of long, multinucleate, approximately
155 cylindrical cells containing sarcomeres in which the contractile proteins actin and myosin
156 interact to generate force and shortening. Skeletal muscle powers voluntary movement,
157 including speech and breathing, buffers circulating glucose, and is surprisingly labile. Disuse
158 during bedrest causes loss of muscle mass by active cellular mechanisms. This presents a severe
159 problem in ventilated patients. The domed diaphragm muscle normally flattens by shortening
160 to generate a lower than atmospheric pressure in the pleural space, so the lungs inflate. During
161 mechanical ventilation it quickly loses mass so that after ventilatory assistance, diaphragm
162 function is reduced (13). The extreme reduction in activity from contraction during every
163 breath, to zero, may explain why the diaphragm loses mass more quickly than, say, the pectoral
164 muscles. In healthy persons, growth of muscle is often considered to be slower than the loss of
165 muscle with disuse; to gain 1kg of leg muscle might take 12 weeks of resistance training,
166 whereas 1kg of mass is lost in one week with complete disuse (14). The magnitude of the
167 difference in activity before and after is very different in these scenarios, so prevention of

168 atrophy with early activity-based methods may reduce the human and financial cost of
169 rehabilitation after critical illness.

170

171 To activate muscle contractions from outside the body, action potentials must be generated in
172 the muscle membrane. Stimulation is usually applied where the nerve that contains the target
173 motor neurones is most accessible. Muscles respond to single action potentials with a brief
174 period of activation then relaxation. The force response to a single stimulus is a very brief
175 twitch with a low force. To produce stronger contractions, successive activations must be
176 applied before the relaxation of the prior stimulus, and so frequencies in humans of 20-50
177 impulses per second are used (20-50Hz). Muscles require a continuous supply of oxygen and
178 glucose to generate sustained work, and therefore contractions must be intermittent, because
179 blood flow is excluded during strong contractions. The activity/rest cycle and the number of
180 contractions in a session provides a huge number of possible combinations. Exercise is often
181 prescribed in terms of a number of sets of repetitions (single contractions), with a rest period
182 between sets. As a result, unless otherwise stated, cyclic electrical stimulation was used in the articles
183 considered in this review, rather than any other NMES (for example, EMG-triggered stimulation).

184

185 **Neuromuscular electrical stimulation and intensive care unit acquired weakness**

186 The application of NMES to treat ICUAW is well documented within the evidence-base (15-
187 18). The primary objective of interventions has been to induce intermittent muscle contractions
188 with electrical stimulation to minimize the loss of muscle mass and excitability, to strengthen
189 these muscles and to enhance the recovery of mobility during and after discharge from the ICU
190 (19). The findings from pre-clinical work on underlying electrophysiological mechanisms from
191 healthy participants and data from critical care patients suggest that to prevent ICUAW, an
192 NMES program should begin in the ICU as soon as medically feasible. This is particularly
193 relevant to people with C-19, as early intervention is advised due to the often-prolonged stay
194 and risk for subsequent long-term ICUAW. Reducing initial muscle atrophy is preferable to
195 extending rehabilitation due to the extended amount of time it takes to recover pre-ICU muscle
196 strength (20). Those with risk factors for ICUAW should be prioritised because there is a small amount
197 of evidence that NMES can reduce the prevalence of ICUAW (21).

198

199 Many studies have activated the quadriceps (Figure 1) along with another muscle group such
200 as the hamstrings, whereas others have targeted the abdominal musculature. Stimulation
201 parameters commonly used are a frequency between 30-50Hz, pulse duration of 250-400 μ s

202 and an intensity adjusted up to maximum sensory tolerance so that contractions are easily
203 visible and palpable. Most studies have included one hour-long session or two 30 minutes
204 sessions per day. There has been enough commonality to conduct systematic reviews and a
205 meta-analysis using the Medical Research Council's (MRC) score for muscle strength as an
206 outcome measure. Liu et al. (15) found a significant improvement in muscle strength for NMES
207 over control (mean difference (MD)=1.78, 95% CI 0.44, 3.12 ($p = 0.009$)). All studies included
208 in the review used the MRC scale to evaluate the strength of the surrounding muscles, with a
209 score of <48 to diagnose ICUAW (22-26). Several previously conducted systematic reviews in
210 the area are largely consistent with these findings (16-18).

211

212 The current most commonly protocols on the ICU, suggest that NMES at this stage for a limited
213 amount of time might be sufficient to maintain muscle volume but not increase it. In one of the
214 larger studies conducted, Dall'Acqua et al. (27) did not find a significant improvement in
215 abdominal muscle thickness for NMES but interestingly found a significant decline in the
216 control. Further support for this hypothesis is suggested in a recent study from Nakamura et al,
217 (28) who examined the effects of a 20-minute daily dose of NMES (171 contractions per day)
218 on femoral muscle volume. Researchers found a significant decrease in muscle volume for both
219 the control and intervention group; however, the mean rate of muscle volume reduction was
220 significantly less for the NMES group (NMES (standard deviation (SD))=10.4% (SD 10.1%),
221 control=17.7% (SD 10.8%) ($p=0.04$)). The data from these studies and longer-term treatment,
222 for example, up to nine weeks (29) suggests that NMES can be used in the ICU to slow down
223 muscle wasting but it is necessary for participants to then use home based NMES to maintain
224 and strengthen muscles post-ICU. Interestingly, recent research by Nakashini et al. (30)
225 suggests that identifying the motor-point to elicit the strongest contraction, as well as increasing
226 the number of contractions in a session, may maintain muscle strength more effectively.
227 Researchers included a 30-minute daily session (180 contractions) for five days to the NMES
228 group while the control had usual care. A significant difference in muscle volume and strength
229 was found but no difference in ICUAW was found. This suggests that further research should
230 be conducted into optimal dosing for ICU patients and is supportive of a period of post ICU
231 NMES treatment for maintenance and recovery of strength.

232

233 **Neuromuscular electrical stimulation in chronic obstructive pulmonary disease**

234 As Covid-19 is a chronic respiratory condition, patients may share some similarities with
235 COPD patients in terms of symptoms and complications (for example, shortness of breath,

236 respiratory infection, heart problems and peripheral muscle weakness) and thus it is beneficial
237 to review the evidence for NMES within COPD patient groups. Recently published NICE
238 guidelines for the use of NMES to strengthen muscles in patients with chronic respiratory
239 disease recommend that for those who are unable to exercise, evidence supports the use of
240 electrical muscle stimulation. However, standard arrangements must be in place for clinical
241 governance, consent and audit (12). A meta-analysis of nine studies including 276 patients with
242 moderate-to-severe COPD found improvement in quadriceps muscle strength (standardised
243 mean difference (SMD)=1.12, 95% CI 0.64 to 1.59 ($p<0.001$); 6 studies of 207 patients) with
244 NMES (31). In a recent Cochrane review, improvements were found for peripheral muscle
245 endurance (SMD=1.36, 95% CI 0.59 to 2.12, ($p<0.001$); 2 studies of 35 patients) and these
246 improvements translated into improved 6-minute walking distance (MD=39.26m, 95% CI
247 16.31 to 62.22, ($p<0.001$); 2 studies of 72 patients) (32). An improvement in exercise endurance
248 was also found (MD=3.62 minutes, 95% CI 2.33 to 4.91, ($p<0.001$); 3 studies of 55 patients)
249 and days to first transfer out of bed was decreased for the NMES group (MD=-4.98 days, 95%
250 CI -8.55 to -1.41, ($p=0.006$); 2 studies of 44 patients) (32). However, NMES was not associated
251 with improvements to health-related quality of life (32), and thus the actual value of NMES for
252 improved quality of life remains uncertain (31).

253
254 NMES stimulation parameters for COPD vary considerably among studies, with stimulation
255 frequency set to a median value of 50Hz (range 15-75 Hz), pulse duration 400 μ s (200-700),
256 target duty cycle 33% (13-75), session length 30 minutes (18-240), session frequency 5 times
257 (2-7) each week, and programme duration 6 weeks (4-11) (31). All studies set stimulation
258 amplitude to elicit a visible muscle contraction within the participant's tolerance and most
259 found that the amplitude could be increased over the course of the programme. However, the
260 high variability in length of time, parameters and different type of outcome measures used in
261 the studies made comparison difficult.

262
263 **Neuromuscular electrical stimulation to wean critically ill patients off ventilators**
264 Neuromuscular electrical stimulation may be considered to help wean critically ill patients off
265 ventilators and is advantageous when the patient cannot participate in voluntary exercise.
266 Preliminary work supporting the added value of an NMES program to wean patients from
267 dependence on ventilators is supportive of further research in this area. McCaughey et al. (33)
268 provided the most credible, albeit preliminary data, that earlier weaning is possible. They
269 applied NMES over the posterior-lateral abdominal wall to activate the transversus abdominis

270 and internal and external oblique muscles during exhalation, automatically synchronized with
271 the participant's breathing pattern. Stimulation was applied for 30 minutes, twice per day, five
272 days per week, until discharge from the ICU. The study compared an active group receiving
273 stimulation that caused a strong visible muscle contraction (30Hz frequency and a pulse-width
274 of 350 μ sec) to a control group that received sensory level stimulation (10 Hz frequency and
275 350 μ sec pulse-width, but with an amplitude sufficient to be felt on the skin but not to cause
276 muscle contraction). A survival analysis found ICU length of stay (median 11 versus not
277 estimable days, ($p=0.011$)) and ventilation duration (median 6.5 versus 34 days, ($p=0.039$))
278 were shorter in the intervention compared to the control group. Dall'Acqua and colleagues (27)
279 stimulated the pectoral and rectus abdominis muscles bilaterally for 30 min daily, using 300
280 μ sec phase duration, 50 Hz pulse rate to induce a 3 second contraction followed by 10 seconds
281 of relaxation and compared it to a sensory threshold stimulation group. Time to weaning off
282 the ventilator was not recorded but the length of ICU stay was shorter in the NMES group
283 (mean: 10 ± 4 days) compared to the control group (mean: 16 ± 9) ($p=0.045$). Other
284 investigators used NMES to activate the deltoid and quadriceps muscles bilaterally, applied
285 concurrently with active exercises or without exercises or exercise only and found no difference
286 between groups in terms of time to discharge from the ICU (34). None of these three groups of
287 investigators reported any adverse response or interference with the recovery of and discharge
288 from the ICU.

289

290 **Neuromuscular electrical stimulation and venous thromboembolism prevention**

291 Venous thromboembolism (VTE), encompassing pulmonary embolism (PE) and deep venous
292 thrombosis (DVT), is a common and severe complication of critical illness (35, 36). Many
293 critically ill patients have multiple risk factors that predate ICU admission; including, recent
294 surgery or trauma, sepsis, malignancy, immobilisation, increased age and cardiac or respiratory
295 failure (37). Once admitted, patients that need treatment on the ICU are exposed to additional
296 VTE risk factors, including prolonged immobilisation, pharmacological paralysis, central
297 venous catheterisation, haemodialysis and treatment with vasopressors (37-39). In four recent
298 meta-analyses of hospitalised C-19 patients, incidence of thrombotic complications was
299 reported between 22.7%-31%, and risk persisted even in those receiving anticoagulation (40-
300 43).

301

302 Prophylaxis aims to combat the three predisposing factors to VTE; venous stasis,
303 hypercoagulability and endothelial injury (44). Traditional prevention strategies include

304 pharmacological agents such as unfractionated heparin, low molecular weight heparin
305 (LMWH) direct oral anticoagulants, and mechanical devices such as graduated compression
306 stockings or intermittent pneumatic compression of the limbs (45). Interim guidance for C-19
307 recommends treatment with LMWH administered at prophylaxis doses pending the emergence
308 of additional data and guidance (46). Despite receiving anticoagulation for
309 thromboprophylaxis, a high rate of VTE has been observed among C-19 patients admitted to
310 the ICU (43). NMES has been approved by NICE as an alternative prophylaxis when other
311 mechanical and pharmacological methods of prophylaxis are impractical or contraindicated
312 (47, 48). The transcutaneous application of electrical impulses stimulates the common peroneal
313 nerve to generate dorsiflexion in the lower limb, which in turn activates the calf muscle pump
314 emulating the normal physiological response achieved by walking, without the patient having
315 to mobilise. NMES has been shown to be effective in reducing fibrinogen, D-Dimer and tPA
316 levels, and increasing venous, arterial and microcirculatory flow, thus preventing venous stasis
317 and oedema (49-58). Moreover, clinical evidence has shown effectiveness of NMES for
318 reducing the incidence of DVT in hospitalised patients (59-66).

319

320 In line with recommendations from NICE, NMES should be considered as an alternative or
321 adjunct prophylaxis in C-19 patients where other mechanical and pharmacological prophylaxis
322 are impractical (47). It may be most effective when used prior to the formation of oedema, to
323 prevent venous stasis and reduce VTE risk. Devices should be used in accordance with
324 guidance (47) and the individual instructions for use of specific devices. If NMES is used for
325 other treatment aims (such as muscle strengthening), it should be acknowledged that a
326 circulatory effect will be delivered simultaneously, and so competing treatment aims may be
327 balanced by preferentially aiming NMES settings for muscle strengthening parameters.
328 Furthermore, NMES may provide the most benefit to patients who are immobilised or
329 positioned where the leg is lower than the body.

330

331 **Neuromuscular electrical stimulation and the continuum of care model**

332 Neuromuscular electrical stimulation may be advantageous in C-19 as it can be used throughout
333 the patient's recovery to address a number of physiological and clinical deficits (Figure 3) in a
334 continuum of care model. Example applications of NMES for patients admitted to the ICU with
335 C-19 are illustrated in Figure 4.

336 While minimising the amount of stimulation is pragmatic on the ICU unit, following discharge,
337 similarly to any exercise programme, NMES can be progressively increased subject to patient

338 tolerance and measurable benefits. As the patients begin to mobilize out of bed, a structured
339 mobility program has been recommended (67). Adding the NMES to a structured physical
340 exercise program appears advisable compared to applying the NMES in isolation (68). From a
341 practical perspective, as long as the patient is non-responsive to verbal commands the NMES
342 can be combined with passive range of motion (PROM) exercises. Once responsive, the patient
343 should be encouraged to add volitional contraction and active range of motion (AROM)
344 combined with the NMES. In studies with neurological patients, volitional contraction has been
345 found to be more effective at inducing useful therapeutic improvements (69).

346

347 Following discharge from hospital, ongoing use of NMES may also be considered to address
348 persistent symptoms and functional limitations. NMES can be applied independently in the
349 home environment and is considered an attractive adjunct to enhance the hypertrophic effect
350 of traditional exercise (10). Likewise, following discharge it may be appropriate to consider
351 the ongoing use of NMES to increase blood flow and prevent oedema or DVT. Nonetheless,
352 one of the main shortcomings of current research on NMES in the ICU is the lack of long-term
353 follow-up because most studies only use NMES for the duration of hospital stay (5-14 days).
354 This may be reflective of the lack of long-term rehabilitation and follow-up for these patients
355 once they leave the ICU and hospital. Further research including long term follow-up should
356 be conducted as currently it is unknown whether patients who appear to benefit during their
357 stay in ICU continue to benefit after a relatively short period of treatment. Further research
358 should also examine the potential benefits of home based NMES post-ICU as part of a
359 continuum of care. Using NMES for a period of nine weeks such as in previous investigations
360 (29) or for a minimum of six weeks as in many of the COPD studies may lead to sustained
361 longer-term benefits (31).

362

363 **Practical considerations**

364 Early rehabilitation has been generally accepted as a safe and effective intervention in Critical
365 Care (70-74). However, there are several practical issues that make the implementation of these
366 interventions challenging, especially in those with C-19. Such issues include deep sedation for
367 facilitating mechanical ventilation; delirium; prone positioning; access to appropriate number
368 or type of personnel; physiological stability and obesity. An observation study in France
369 demonstrated that 65% of those with C-19 admitted to Critical Care experienced delirium and
370 therefore a significant number of patients presumably would have been unable to
371 safely/successfully participate in active physiotherapy regimes while affected (75).

372 Furthermore, even passive interventions such as in-bed cycle ergometry are restricted to those
373 in the supine position, rendering them unsuitable for C-19 patients for whom prone positioning
374 for more than 12 hours per day is a widely accepted strategy for improving oxygenation (76).
375 In addition, in-bed cycling is purely passive and although it will help maintain range of
376 movement it will not increase muscle bulk or strength. Another consideration is weight
377 restrictions on rehabilitation equipment, which may preclude the 7.9% of morbidly obese
378 patients (3) admitted to Critical Care with C-19 from receiving a number of interventions.
379 Finally, accepting that C-19 has resulted in an increase in intensive care admissions and
380 physiotherapy demand, more efficient rehabilitation interventions and use of staff is required.

381

382 **Safety considerations**

383 Common equipment in an ICU includes mechanical ventilators to assist breathing through an
384 endotracheal tube or a tracheostomy tube; monitors of cardiac functions; equipment for the
385 constant monitoring of bodily functions; a web of intravenous lines, feeding tubes, nasogastric
386 tubes, suction pumps, drains, and catheters; syringe pumps; and a wide array of drugs to treat
387 the primary condition(s) of hospitalization. Accordingly, the clinical team must verify the
388 compatibility of the stimulation system to ensure there is no interference with the electronic
389 systems such as ECG and EEG monitors, pacemakers, defibrillators, or other implanted
390 stimulators. Iwatsu et al. (77) provided evidence assuring the safety of stimulation in the ICU.
391 Furthermore, none of the other published clinical trials that used non-invasive electrical
392 stimulation in the ICU reported interference with the ICU equipment (27, 28, 30, 33, 34, 78).
393 Interference with pacemakers and implantable cardioverter defibrillators appears to depend on
394 the proximity of the electrodes to the implanted device; lower limb stimulation in particular
395 appears safe in this group, but clinicians must be aware of, and monitor for, such an interaction
396 (79) especially if stimulation of respiratory muscles is indicated. In addition, the stimulation
397 system must meet all hygiene, disinfection and sterilization standards required by the hospital.
398 When applying the electrical stimulation, clinicians must not apply the electrode over open
399 wounds and should avoid any contact of the electrodes with external fixation hardware. In
400 contrast, applying NMES over internal hardware appears safe (80, 81). Electrical stimulation
401 is known to increase muscle perfusion and oxygen consumption in a similar way to light
402 intensity exercise. Given that changes are small and reversible, it is likely to be safe in those
403 receiving cardiovascular support, and studies in this cohort have not reported any adverse
404 effects (78). Finally, when applying electrical stimulation to those with reduced consciousness,
405 special care must be taken over skin integrity as the patient will not be able to report pain.

406

407 **Summary**

408 Innovations that save time and improve the outcome of rehabilitation will alleviate the burden
409 of suffering and economic damage caused by C-19. Current evidence suggests that NMES can
410 reduce the rate of muscle atrophy for patients admitted to the ICU. Whilst the evidence for
411 increasing muscle mass is less clear, reduction of atrophy is a worthwhile goal in the pursuit of
412 expedited recovery and return to independence. For the immobilised patient, NMES increases
413 blood flow, reduces oedema and can be used as an alternative prophylaxis in cases where
414 traditional methods are contraindicated. Evidence suggests NMES may play a role in the
415 weaning of patients from ventilators and should be continued in the post-acute and longer-term
416 phases of recovery. As such, NMES may be a suitable treatment modality to implement within
417 rehabilitation pathways for C-19, with consideration of the practical and safety issues
418 highlighted within this review. Future research endeavours should aim to evaluate the specific
419 application of NMES to C-19 patients, the longer-term effect of NMES and the most effective
420 parameters to influence underlying electrophysiological mechanisms.

421

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425

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Table I. Risk factors for deconditioning and ICU associated weakness in C-19 in comparison to viral pneumonia(3)

Risk Factor for deconditioning/ICU associated weakness	C-19 (N=10,557)	Viral Pneumonia, 2017-19 (N=5,782)
Duration of advanced respiratory support, median days (IQR)	13 (7,23)	9 (4,17)
Multi-organ failure, %	40.8	26.3
Age, mean (SD)	58.8 (12.7)	58 (17.4)
Very severe comorbidities, %	13.6	24
Dependency prior to hospital admission, %	10.3	26.4

ICU=intensive care unit; C-19=Covid-19

Figure legends

Figure 1. Electrode positioning for electrical stimulation of the quadriceps (mannequin)



Figure 2. Electrode position for electrical stimulation of the peroneal stimulation for increased blood flow to the lower limb (mannequin)



Figure 3. Characteristics of a patient admitted to intensive care unit with Covid-19

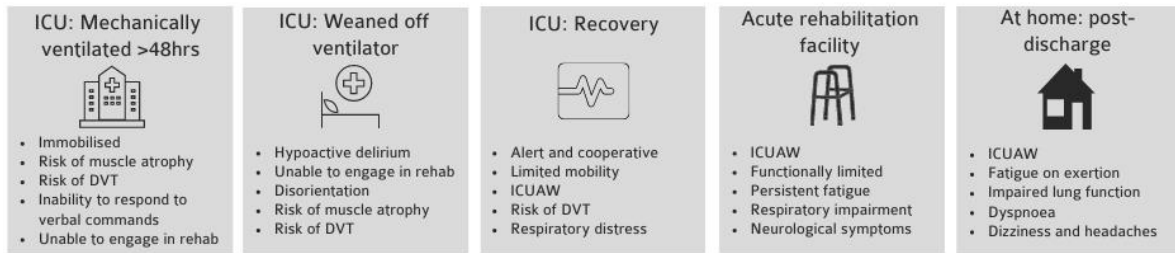
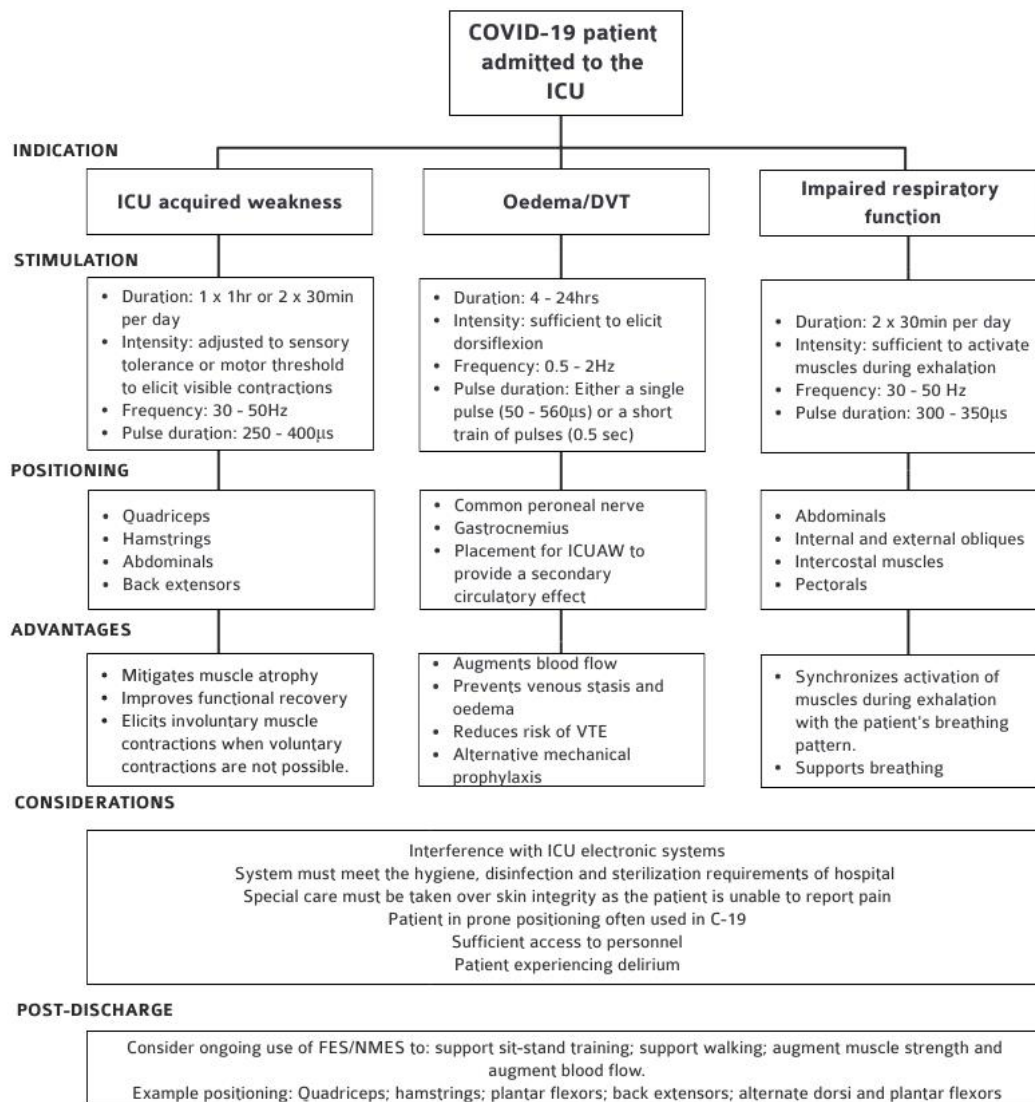


Figure 4. Example neuromuscular electrical stimulation application for patients admitted to intensive care unit with Covid-19 by indication



669 **Supplementary material 1 – Search strategy**

670

671 ((heart failure) OR (chronic kidney disease) OR (critically ill) OR (critical illness) OR (multiple
672 organ failure) OR (intensive care unit) OR (critical care) OR (ICU) OR (CCU) OR (intensive
673 therapy unit) OR (ITU) OR (acute respiratory failure) OR (acute respiratory distress) OR
674 (ARDS) OR (multiorgan failure) OR (mechanical ventilat*) OR (mobili*) OR (sepsis) OR
675 (septic) OR (deep vein thrombosis) OR (DVT) OR (COPD) OR (COAD) OR (chronic
676 obstruct* pulmonary disease) OR (chronic obstruct* airway disease) OR (chronic obstruct*
677 airflow disease) OR (chronic obstruct* pulmonary disorder) OR (chronic obstruct* airway
678 disorder) OR (chronic obstruct* airflow disorder) AND ((muscle strength) OR (muscle
679 dysfunction) or (muscle atrophy) or (muscle degeneration) or (muscle deteriorate*) OR
680 (intensive care unit acquired weakness) OR (ICUAW)) AND ((electrical stimulation) OR
681 (neuromusc* stimulation) OR (function* stimulation))

682

Supplementary material 2 – Inclusion/exclusion criteria

Inclusion Criteria	Exclusion Criteria
Patient Population	
<ul style="list-style-type: none">• Patients being treated for ICU-acquired weakness with NMES• Patients with Chronic Illness such as COPD, heart failure, and CKD that were being treated using NMES/FES to improve muscle mass and prevent muscle atrophy• Patients that were being treated using NMES/FES to improve blood flow and oedema.	<ul style="list-style-type: none">• Patients with ICU-acquired weakness after an elective surgery.• Patients with stroke, multiple sclerosis, and spinal cord injuries.
Intervention	
<ul style="list-style-type: none">• Functional Electrical Stimulation or Neuromuscular Electrical Stimulation	<ul style="list-style-type: none">• Transcutaneous electrical nerve stimulation
Outcome	
<ul style="list-style-type: none">• Stimulation parameters and the protocol used for the therapy	<ul style="list-style-type: none">• Studies that did not clearly specify the protocol or the FES/NMES intervention
Methodology	
<ul style="list-style-type: none">• Randomised controlled trials, systematic reviews and meta-analyses, and clinical studies that used NMES for the intended patient group.• Studies reporting a replicable NMES protocol	
Publication	
<ul style="list-style-type: none">• Published in the last 10 years• Published in the English language• Studies with human participants• Access to full texts	<ul style="list-style-type: none">• Animal studies• Conference abstracts• Protocols and non-clinical studies