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► **To cite this version:**

Samir Jaber, Audrey de Jong. Weaning from mechanical ventilation in intensive care units: a call for new international consensus guidelines. *The Lancet Respiratory Medicine*, 2023, 10.1016/S2213-2600(22)00502-1 . hal-03955471

HAL Id: hal-03955471

<https://hal.science/hal-03955471v1>

Submitted on 25 Jan 2023

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Weaning from mechanical ventilation in intensive care units: a call for new international consensus guidelines

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No funding source was used. ADJ reports receiving remunerations for presentations from Medtronic, Drager, and Fisher & Paykel. SJ reports receiving consulting fees from Drager, Medtronic, Mindray, Fresenius, Baxter, and Fisher & Paykel.

In *The Lancet Respiratory Medicine*, Tàì Pham and colleagues¹ report the results of the WEAN SAFE study, aiming to describe the epidemiology, management, timings, risk for failure, and outcomes of weaning in patients requiring at least 2 days of invasive mechanical ventilation. WEAN SAFE was an international, multicentre, prospective, observational study including 5869 critically ill adult patients, conducted in 481 intensive care units in 50 countries.¹ The authors can be congratulated for this large convenience sample reporting novel and important findings. The main result was that only 3817 (65·0%) patients were successfully weaned at day 90—ie, without reintubation within 7 days of extubation. WEAN SAFE is the first study reporting data relating long-term weaning practices to outcomes from invasive mechanical ventilation in a global cohort of patients at risk for weaning failure. Pham and colleagues¹ reported that higher sedation levels and increased time intervals from meeting weaning criteria to their first separation attempt were potentially modifiable factors independently associated with weaning failure. Weaning eligibility criteria were defined as follows (modified from Boles et al²): positive end-expiratory pressure less than 10 cm H₂O, fractional concentration of oxygen in inspired air less than 0·5, not receiving paralyzing agents, and receiving no or low doses of vasopressors (<0·2 µg/kg per min of norepinephrine or equivalent). It is worth noting that extubation on high-dose vasopressors, defined as more than 0·1 µg/kg per min, has been found to be a risk factor of reintubation,³ making the threshold of 0·2 µg/kg per min questionable. Moreover, the level of consciousness was excluded from the weaning criteria.² The results might have been affected by the absence of identification of consciousness as a risk factor for delayed weaning and weaning failure. To better discriminate the influence of level of consciousness, sedation, or both, on weaning failure, Pham and colleagues¹ conducted a noteworthy sensitivity analysis restricting the

sample to patients without neurological impairment (post cardiac arrest, neurosurgery, or non-traumatic neurological event), excluding approximately 25% of patients. Sedation at the time of weaning readiness remained strongly associated with weaning failure.¹ Randomised controlled trials have shown that reduction in sedation might improve weaning and outcomes;^{4–6} however, the cohort analysed by Pham and colleagues was substantially larger in terms of the number of patients enrolled, the number of participating centres, and the geographical spread than any previous weaning study. Patients were followed-up for longer timeframes than previous studies, with outcomes recorded up to day 90, and the population, invasively ventilated for more than 2 days, was at high-risk of weaning difficulties

Main results of the WEAN SAFE study	Proposed research agenda
65% of patients who required invasive ventilation for at least 2 days successfully weaned from invasive ventilation at day 90	Multicentre, randomised controlled trial focusing on preventing airway and weaning failure according to respective known risk factors and personalised selection of patients
Increased time intervals from meeting weaning criteria to their first separation attempt independently related to weaning failure	Clustered, randomised controlled trial with an interventional group implementing a rapid separation attempt after meeting weaning criteria
Strong association between moderate and deep sedation levels and the risk of delayed weaning, and of weaning failure for deep sedation	Clustered, randomised controlled trial implementing a bundle with early stopping of sedation at the time of fulfilling weaning eligibility criteria
Strong association between moderate and deep sedation levels and the risk of delayed weaning, and of weaning failure for deep sedation	Redefining weaning personalisation eligibility criteria in a development cohort with an external validation cohort
Substantial variations in weaning practices, particularly in defining weaning readiness and in the use of spontaneous breathing trials	Qualitative study across centres aiming to understand the variations in weaning practices, such as organisational, contextual, and individual preferences
Distinct patterns of weaning with very different outcomes	Early identification of patients with intermediate, prolonged, or absence of weaning with specific interventions aiming to improve weaning success and outcomes of these patients through a before-after study or a randomised controlled trial

Table: Proposed research agenda following the results of the WEAN SAFE study

Despite well conducted statistical analyses, some limitations must be considered with the interpretation of findings. The observational design without blinded assessment of the main outcome can only infer association and not causation. All the adjustment methods are imperfect, and large, multicentre, observational studies are subject to residual confounding, such as the sickness of patients assessed by clinicians at bedside, and imprecision of the data recorded.⁷ Temporal biases are also likely—for example, between sedation management and outcomes, because stopping sedation will precede weaning failure—but weaning failure can also lead to prolonged sedation. Furthermore, one could say that the beginning of the weaning phase was subjectively assessed by on-site clinicians. A patient was considered to be formally in the weaning phase when a first attempt at separating a patient from the ventilator was performed, whereas the real weaning phase could have started earlier. Moreover, among extubation failures, airway failure was not differentiated from weaning failure, although risk factors of airway and weaning failure are known to be different.⁸ However, the limitations of

the study were accurately described and no overinterpretation or inferences of causation were made.

We commend Pham and colleagues¹ for exploring a complex topic with a large, multicentre, observational study. The results confirmed those from previous studies showing the higher rate of weaning failure in patients undergoing a longer period of mechanical ventilation⁹ as well as the negative effect of sedation and delayed weaning.⁶ Following the results of this study, and those by Jaber and colleagues⁸ and Burns and colleagues,⁹ a research agenda for better preventing weaning failure can be proposed (table).¹⁰

The WEAN SAFE study confirms the results of previous studies^{8,9} showing great heterogeneity in the clinical practices of weaning mechanical ventilation in intensive care units and their respective effects on the outcome. This is a call for the realisation of new international consensus guidelines for weaning from mechanical ventilation after the SARS-CoV-2 pandemic and taking into account personalised medicine (ie, phenotypes of the patients in intensive care units).¹⁰

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