Pharmacological therapy for the prevention and treatment of weakness after critical illness: a systematic review

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Abstract

Objective: Intensive care unit acquired weakness (ICUAW) is a common complication of critical illness and can have significant effects upon functional status and quality of life. As part of preliminary work to inform the design of an randomized trial of a complex intervention to improve recovery from critical illness, we sought to identify pharmacological interventions which may play a role in this area.

Data Sources: We systematically reviewed the published literature relating to pharmacological intervention for the treatment and prevention of ICUAW.

Study Selection: We searched Medline, Embase, CINAHL+, Web of Science and both US and European trial registries up to July 2014 alongside reviews and reference lists from populations with no age or language restrictions. We included studies that reported a measure of muscle structure or physical function as an outcome measure. We estimated pooled odds ratios (OR) and 95% confidence intervals (CI) using data extracted from published papers or where available, original data provided by the authors. Assessment of bias was performed using the Cochrane Collaboration's risk of bias tool.

Data Synthesis: Ten studies met the inclusion criteria. The current body of evidence does not support the use of any pharmacological agent in this setting although maintaining euglycemia may reduce the incidence of critical illness polyneuropathy.

Conclusions: At present no pharmacological intervention can be recommended to prevent or treat ICUAW. Further research is required into this field including into more novel agents such as myostatin inhibitors. Challenges in the conduct of research in this area are highlighted.

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Introduction

Patients who survive significant periods of critical illness may suffer long lasting reductions in their quality of life, much of which can be attributed to muscle weakness (1). Weakness caused by critical illness is termed 'intensive care unit acquired weakness' (ICUAW) and has been defined by consensus as 'clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness' (2). It is a common complication which prolongs both hospital and intensive care unit (ICU) stay and the duration of mechanical ventilation (3).

At present, there is an imprecise understanding of the mechanisms of ICUAW. It appears weakness may result from abnormalities of the peripheral nervous system, peripheral musculature or a combination of the two (4). Critical illness polyneuropathy (CIP) is a symmetrical condition affecting the limbs, particularly the lower extremities (4). Weakness is most pronounced in proximal muscles but can involve the respiratory musculature and impede weaning from mechanical ventilation (5). Proposed mechanisms of CIP include injury and subsequent degeneration due to microcirculatory dysfunction that may be aggravated by hyperglycemia, sodium channel inactivation or mitochondrial dysfunction. Mitochondrial dysfunction is also implicated in critical illness polymyopthy (CIM), a primary disease of muscle which may be clinically indistinguishable from CIP. Histopathology reveals selective loss of thick filaments in muscle, reflecting a combination of myosin loss and muscle necrosis (6). There is evidence to suggest overlap between CIP and CIM with CIM carrying a better prognosis (7).

Risk factors for ICUAW were recently reviewed (3). Sepsis, inflammation and multiple organ failure all appear particularly relevant to development of this syndrome, with hyperglycemia likely to be a significant risk factor for CIP (8). Studies exploring the role of glucocorticoids and neuromuscular blockers in ICUAW have reported inconsistent results. Inactivity is a possible risk factor but the case for

an independent causative effect has not yet been made (7). Despite mechanistic advances, effective pharmacological treatments are lacking, and treatment is supportive.

The primary research question of this study was to ask 'is there any evidence from randomized controlled trials (RCT) to support the use of any particular pharmacological intervention in the prevention or treatment of ICUAW?'

Materials and Methods

Protocol and registration

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (9).

Eligibility criteria and data sources

Sources included a range of biomedical databases including grey literature sources. We searched MEDLINE and EMBASE (via OVID), Cochrane, Web of Science, CINAHL+, the European (EUDRACT) and American (www.clinicaltrials.gov) trial registries in July 2014. The search strategies were designed to identify randomized trials of pharmacological interventions used in critically ill patients (or survivors) that employed physical function, muscle function, muscle strength, or muscle mass (or equivalent) as outcome measures. An example of the search strategy used for Medline is included in *the Supplemental Digital Content - Appendix 1*. We screened the reference lists of the included articles for relevant publications not retrieved in the initial search. All citing articles and related references were also screened using the Web of Science tool. No language or age restrictions were imposed. Studies considered were published between 1946 and July Week 4 2014 were included.

Study selection and inclusion criteria

Two reviewers (SJS and RN) screened articles at both the title/abstract and full text stages. Disagreements were resolved by discussion with a third reviewer (DMG) (see *Figure 1*). Randomized and

quasi-randomized, comparative interventional studies of intensive care patients or intensive care survivors were considered. We included studies that reported on a measure of physical function, muscle strength, muscle bulk or physical mobility. We included both direct (e.g. grip strength) and indirect (e.g. lean body mass) measures. We also retrieved systematic reviews of such studies. Studies remained in the review at the title and abstract screening stage if there was not enough information in the title and abstract on which to exclude them.

Data collection process

A dedicated extraction tool was adapted from the Cochrane Collaboration and was used to extract relevant data; this is included in *Supplementary Digital Content - Appendix 2*. Data extraction was carried out by a single reviewer (SJS). Only published data were extracted; however, authors were contacted by e-mail if verification of data was necessary. Where numerical values of mean and standard deviation results were not supplied within published papers, the author, where available, was contacted by email. Where the information was still not obtained, enlarged-scale visual estimation was undertaken using the figures in the published studies (10).

Data items

We recorded the study location and the recruitment dates to detect duplicate publications. We recorded the nature of the intervention including timing, the study setting (e.g. intensive care unit, hospital ward, or rehabilitation unit), age and outcome measure. Performance of formal meta-analysis was not carried out due to the heterogeneity of outcome measures and study populations.

Risk of bias assessment

Two reviewers (SJS and RN) independently assessed risk of bias in individual studies using the Cochrane Collaboration Risk of Bias tool (11). Using the tool, risk of bias in key domains was assessed in each study and given an “low”, “unclear” or “high” risk of bias for each. Disagreements were resolved by discussion

with a third reviewer (DMG). Studies were graded as a "low" overall risk of bias where the individual risk in each domain (sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting) was deemed to be low, as "high" where the risk of bias was deemed to be high in one or more of these domains and similarly "unclear" where the risk was deemed unclear in one or more of these domains. (11)

Secondary Analysis

Due to the low number of papers identified by the primary question of the review, and the lack of any definitive treatment of any of the therapies tested in these trials, we performed a secondary analysis of the articles identified in the initial search. During this analysis, all other study designs were included with the inclusion and exclusion criteria otherwise remaining the same. These additional studies were analysed using GRADE methodology (12). The purpose of this secondary review was to identify other treatments that might be considered in the formulation of a trial intervention, even if the level of evidence was lower than that of the primary review question.

Results

Study selection

Full details of the study selection process are shown in *Figure 1*. After de-duplication, 13,057 references were retrieved. An additional 9 articles were identified from the reference lists of included studies. Full text articles were retrieved for 51 studies. Thirty-seven were excluded at the full text stage (see *Figure 1* for reasons). A further 5 trials were excluded as they involved duplicate study populations of other retrieved publications and one further publication discarded as it was an interval analysis of subsequently reported trial which had also been retrieved and excluded. Another publication was a systematic review from which relevant publications were extracted from the reference list (8). The remaining 10 studies that were eligible were published between 1996 and 2012. Full details including

sample size, duration of follow-up, outcome measure(s) and a synopsis of relevant results are shown in *Supplementary Digital Content - Table 1*. Interventions were broadly divided into the categories below. Results are reported as mean (95% confidence intervals) unless otherwise stated.

Oxandrolone

Oxandrolone, an anabolic steroid which promotes growth of muscle mass, has been used in a single trial including 45 patients who had suffered severe thermal injury (13). Participants received nutritional supplementation with or without the addition of oxandrolone 20 mg per day upon admission to a burn rehabilitation unit (13). Oxandrolone was discontinued when at least 80% of the involuntary weight loss that had occurred during the acute burn period had been restored. The primary outcome measure was the rate at which body mass was regained with the percentage of lean body mass a secondary outcome. Patients receiving oxandrolone regained weight faster than those who received nutrition alone with a mean increase of 1.5 (1.38,1.62) vs. 0.7 kg (0.62,0.78) at four weeks, $p < 0.05$. Lean body mass at discharge was greater in those who received oxandrolone when measured at discharge from the rehabilitation unit [76 (74.37,77.63) vs. 71% (69.75,72.25) , $p < 0.05$]. This difference was maintained at six months after discontinuation of oxandrolone. Lost lean mass was not restored in the nutrition alone group by six months; at this time point, the control group had gained on average 4.1 kg (3.57,4.63) from their discharge weight whereas the oxandrolone group had gained an additional 2.8 kg (2.37,3.23). No data was provided on exercise or other rehabilitation undertaken. The overall risk of bias in this study was deemed to be unclear; although a significant clinical effect was reported, missing detail pertaining to most of the important sources of bias make the internal validity of this trial impossible to assess and we were unable to successfully contact the authors concerned.

Euglycemia

As hyperglycemia is thought to be a significant risk factor for CIP, the effect of insulin to maintain euglycemia has been investigated (14). Furthermore, insulin itself has anabolic effects (15). Two trials

examining the use of supplemental insulin were included in this review (16, 17). In the first, Mikaeili and colleagues randomized 40 medical ICU patients to insulin therapy to maintain euglycemia of 80-140 mg/dL vs. a less restrictive regimen to maintain 180-200 mg/dL (17). Their primary outcome measure was the incidence of CIP as detected by electrophysiological study with the duration of mechanical ventilation a secondary outcome. Rates of CIP were significantly lower in the euglycemic group [10 (-3.15,23.15) vs. 45% (23.2,66.8), $p = 0.01$]. The duration of mechanical ventilation was also reduced with tighter glycemic control [9.72 (8.04-11.4) vs. 14.05 days (10.48,17.62), $p = 0.04$). The lack of blinding may have introduced performance bias although investigators blinded to treatment allocation carried out the outcome assessment.

The second study of insulin therapy was performed in 8 patients following major abdominal resection for cancer (16). Patients received conventional (to maintain levels of 149-200 mg/dL) versus intensive insulin therapy (to maintain 79-124 mg/dL) on ICU for 24 hours on the first and second days after elective surgery using a cross over design. All patients received total parenteral nutrition (TPN) from the first day post-operatively. Their primary outcome measures were the rates of skeletal muscle protein synthesis and degradation, leucine oxidation, glutamine *de novo* synthesis and dimethylarginine production. Rates of skeletal muscle protein synthesis were considered relevant to our review. Tighter glycemic control was associated with greater muscle protein synthesis (as determined by radio-isotope assay of glutamine uptake and leucine loss) and a less negative nitrogen balance [inferred from phenylalanine balance -3 (-5.08,-0.92) vs. -11 nmol/100mL/min (-13.08,-8.92), $p < 0.05$]. The clinical sequelae of these results were not explored and minimal detail was provided regarding the degree of post-operative organ dysfunction or clinical course, hence the generalizability and utility of this data is questionable. Rates of hypoglycemia were not reported. As with the previous study, blinding of the clinical team to the treatment allocation was not possible introducing an unavoidable source of

performance bias. Furthermore, the outcome assessors were also un-blinded, introducing a risk of detection bias. Therefore, whilst interesting, these findings were considered to be at high risk of bias.

Growth Hormone

Anabolic hormone therapy has been utilized in 3 trials comparing treatment with recombinant human growth hormone (rhGH) versus placebo on the intensive care unit including a total of 552 patients (10, 18). One publication included data from two parallel trials (10). In the first trial, a Swedish study, a mean dose of 0.43 IU/kg was given for a period of 12 days to 20 patients who had failed to wean from mechanical ventilation after at least 7 days (18). The primary outcome measure was actually mortality but lean body mass and muscle strength were secondary outcomes considered relevant to our review. Lean body mass increased in the rhGH group [0.8 (-0.38,1.98) vs. -1.1 kg (-2.08,-0.12), $p < 0.03$] but no significant effects were seen on peripheral muscle function assessed by sequential electrical stimulation of adductor pollicis, the cumulative time spent on a mechanical ventilator during the 12 day study period or the rate of weaning (see *Supplementary Digital Content* - *Table 1* for the relevant summary outcome measures). The article did not include sufficient detail to adequately assess risk of bias.

A subsequent publication described two parallel Finnish and European multi-national trials in which a mean dose of 0.3 IU/kg of rhGH was administered for up to 21 days to patients on ICU after cardiac surgery, abdominal resection, major trauma or in whom there was a diagnosis of Acute Respiratory Distress Syndrome (ARDS) (10). Relevant secondary outcome measures were grip strength, exercise tolerance and self-reported fatigue. Both trials reported a significant excess of in-hospital mortality with the use of rhGH [Finnish trial: 39% versus 20%, relative risk of death 1.9 (1.3,2.9}, $p < 0.001$; multi-national trial: 44% versus 18%, relative risk of death 2.4 (1.6,3.5) $p < 0.001$). Given this strong signal of harm, further analysis of functional improvement was deemed inappropriate.

Gamrin and colleagues randomized 20 critically ill patients on a surgical ICU to treatment with rhGH at 0.3 IU/kg/day or placebo for 5 days after which they measured the fractional synthesis rate of muscle

and performed biopsies of the quadriceps muscle (19). All patients received parenteral nutrition; supplementary enteral nutrition was given in small amounts to 4 patients in the rhGH group and 8 controls. The primary effect variables were the protein content of skeletal muscle (measured as alkali-soluble protein) and the rate of muscle protein synthesis. rhGH was associated with an increased protein content [+207% (-26.92,+440.92), $p < 0.05$] and increased muscle protein synthesis but the variability of response was high. The clinical utility of these observations was also not explored. Overall, the risk of bias was felt to be high in this study; treating clinicians were not blinded although during preparation and analysis, investigators were. Protocol violations also occurred in 3 participants.

Propranolol

Propanolol may attenuate the hypermetabolic state seen in ICU and thus reduce the catabolic response (20). Herndon and colleagues randomized 25 pediatric burn patients to propranolol at a mean dose of 1.05 ± S.D. 0.15 mg/kg every 4 hours targeting a 20% reduction in heart rate from the average of the preceding day (21). Treatment was initiated 5 days after initial burn excision and continued for a 2 week period. Patients received conventional enteral feeding via naso-duodenal tube. Primary and secondary outcome measures were not specifically stated as thus; however, relevant outcome measures included fat-free (i.e. lean) body mass and fractional synthesis rates of skeletal muscle inferred by phenylalanine uptake. Those receiving propranolol demonstrated less reduction in their lean body mass [-1 (-7.60,+5.60) vs. -9% (-16.43,-1.57), $p = 0.003$], results which were maintained until full healing and discharge from hospital. Propranolol was strongly anabolic and increased the fractional synthetic rate of muscle [0.337 (0.20,0.47) vs. 0.142 µmol/100 mL/min (0.07,0.22), $p = 0.07$). No patient required a prolonged period of mechanical ventilation in this study and the degree of organ dysfunction was not reported. The risk of bias was judged to be high: only 22/25 patients underwent evaluation of body composition due to technical issues with the scanning equipment over a 3 month period and the radioisotope study of a single patient was excluded from the analysis due to a failed study.

Immunoglobulin

Weak evidence has previously suggested that early use of IgM-enriched Immunoglobulin (IVIG) may prevent CIP and CIM (22). This is based on a possible association of CIPNM with the pro-inflammatory cytokines released during critical illness, the effect of which may be attenuated by the immunomodulating properties of IVIG. A single trial examined the use of IVIG on the incidence of both CIP and CIM (23). Thirty-eight critically ill patients with multiple organ failure (MOF) secondary to presumed sepsis with early clinical signs of CIP or CIM were included. Patients were randomly assigned to either IVIG at 0.25g/kg/day or 1% human albumin solution over a period of 3 days. CIP was diagnosed based upon electrophysiological criteria and CIM histological evaluation. Results were quantified over a 2 week period using a novel summative score that combined data from both of these assessments. No treatment effect was reported upon any of pre-specified endpoint relevant and the study was terminated at its first interim analysis due to futility (see *Supplementary Digital Content - Table 1* for relevant summary measures).

Glutamine

Glutamine is the most abundant free amino acid in the body and is normally synthesized and stored in skeletal muscle, with smaller amounts made by the lungs, liver and brain (24). During sepsis and catabolic states, increased glutamine demands may be met in part by increasing breakdown of protein in skeletal muscle but glutamine deficiency can occur (25). Tjader and colleagues randomized 40 critically ill patients with a variety of presentations to glutamine enhanced parenteral nutrition at doses of 0.00, 0.28, 0.57 or 0.86 g/k/day, corresponding to 0, 20, 40 or 60 g of glutamine per day for a 70 kg man (26). The primary outcome measures were wet muscle glutamine concentration, protein synthesis and protein content as alkali-free protein. Protein synthesis rates were determined by phenylalanine uptake radioisotope study and muscle amino acid content analysed by muscle biopsy after five days. The treatment successfully normalised plasma glutamine concentration in a dose-dependent way but no

significant difference was seen between the muscle glutamine concentrations before and after treatment for any subgroup (see *Supplementary Digital Content - Table 1*). Protein fractional synthesis rate did also not differ significantly between any dose-group of glutamine [2.08 (0.81,3.34) vs. 1.95 (1.50,2.40) vs. 1.85 (1.29,2.41) vs. 1.58% (0.69,2.47), $p > 0.05$ for all]. The risk of bias was deemed to be high due to incomplete datasets; 37/40 of those randomized completed the full protocol due to clinical and organisational reasons. Blood and tissue samples were blinded throughout the procedure for sample analysis, but treatment was not blinded for attending physicians.

Risk of bias across studies

Overall, the risk of bias was judged to be high for eight out of the ten included studies (10, 16, 17, 19, 21, 23, 26). For the remaining two trials the risk of bias assessment was unclear (13, 18). A full description of the the risk of bias assessment is shown in *Table 1*.

Secondary analysis of studies not meeting eligibility for primary review

From our secondary analysis, another 18 articles were identified (27-44). One article was excluded as it described an interim analysis of another included paper (44). Interventions were broadly divided into exogenous insulin with or without metformin, maintenance of euglycemia, exogenous growth hormone, insulin-like growth factor and oxandrolone. A summary of the included articles is given in *Supplementary Digital Content - Table 2*. The GRADE of evidence in the majority of studies was deemed low (27). Only maintenance of euglycemia demonstrated any significant effects (37, 39, 42). The GRADE of evidence for these trials was deemed to be moderate.

Discussion

Summary of evidence

Our review identified a number of promising treatments but given the current evidence base we are unable to recommend routine adoption of any particular strategy at this time. The overall risk of bias within the published evidence and lack of clinical correlates for studies which target surrogate measures such as lean body mass and protein synthesis are of particular concern. Therefore, at this time, the evidence does not support the utility of any pharmacological intervention in the treatment or prevention of ICUAW.

Within the setting of general intensive care, only insulin therapy appears to offer any significant preventative effects upon CIP/CIM although the included trial was small (17). Evidence from sub-analyses of two larger trials of intensive insulin therapy showed similar benefits but these were not included in our review as they were not felt to represent randomized controlled trials as only those who survived to seven days were screened for CIP/CIM by weekly electrophysiological examination (37, 45). Concerns regarding tight glycemic control have been raised in the past decade since publication of the Van den Berghe studies; in these original trials, rates of hypoglycemia were not insignificant, although morbidity associated with these events low (46, 47). In the Mikaeli study 25% of patients suffered an episode of hypoglycemia below 45 mg/dL requiring intervention although serious adverse events did not occur (17). A subsequent multi-centre randomized trial of 6,104 mixed medical and surgical patients demonstrated increased mortality with this approach, mainly from cardiovascular causes (48). Rates of hypoglycemia were significantly higher than in either of the Van den Berghe single-centre trials and a subsequent post-hoc analysis showed that these patients, i.e. those in whom blood sugar was less than 2.2 mmol/L were twice as likely to die (49). Therefore, intensive insulin therapy cannot be routinely recommended as a strategy to combat weakness amongst critically ill patients. However, more modest glycemic targets may be appropriate such as those adopted by Mikaeili and colleagues if adequate protection against hypoglycemia can be achieved (17). Improvements in technology, in particular

continuous glucose monitoring and computer controlled administration of insulin may in the future allow this to be achieved (50).

For patients who have suffered severe thermal injury, oxandrolone appears to offer benefits in recovery and maintenance of lean body mass (13). Outside of this setting, the benefits are less clear: although not reporting on our primary outcome measures, a study of trauma patient of oxandrolone 10 mg versus placebo in combination with enteral nutrition failed to show any improvement in mortality, length of hospital or ICU stay or duration of mechanical ventilation (51). A similar prospective, double-blind trial in 41 ventilator-dependent surgical patients found that those who received oxandrolone spent longer on a ventilation (21.7 vs. 16.4 days, $p = 0.03$), had higher rates of re-intubation (44% vs. 13%, $p = 0.02$) and showed a non-significant trend towards more days in ICU (52). Both trials were small and single centre, hence further studies would be required to assess effects upon muscle function.

Our review suggests that agents such as immunoglobulin and glutamine do not appear to offer benefit in this setting. It had been postulated that immunoglobulin could have a role in the prevention of CIP/CIM as this condition has been associated with pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1, and IL-12 (53). It is believed that IVIG exerts its anti-inflammatory and immunomodulating properties through regulating such cytokines (23). Glutamine supplementation has been suggested to have a role in preventing undesired muscle wasting as skeletal muscle is the main producer and exporter or this amino acid which may be required for proper immune system functioning and subsequent deficiency during times of physiological stress.

Limitations and challenges

A major obstacle to our review was the heterogenous definition of ICUAW. Whilst entities such as CIP may be defined upon seemingly strict electrophysiological criteria, namely a reduction in the amplitude of compound muscle action (CMAP) and sensory nerve action potentials (SNAP) with normal or mildly reduced nerve conduction velocity, a consensus definition is lacking by how much these potentials must

be reduced (4). Varying degrees of fibrillation potentials and positive sharp waves can be recorded in both CIP and CIM and motor unit potentials may be unrecordable if consciousness is depressed; however, if present, they can be normal or myopathic, therefore the distinction between CIM and CIP is not absolute (54). Mikaeili and colleagues used a 10% reduction in CMAP/SNAP amplitude but more precise definitions are lacking (17).

Our search strategy deliberately used broadly defined outcome measures so as to offer a more comprehensive review of current evidence. A significant limitation concerns the use of surrogate outcome measures, such as lean body mass or muscle bulk to infer functional improvement. This is clearly a large assumption. Nevertheless, trials targeting 'harder' functional outcomes are lacking outside of insulin therapy, the caveats to which have been discussed above.

A further challenge comes from competing risk; these are events which prevent or significantly alter the probability a subject will experience a particular outcome (55). Mortality in ICU studies is high, hence death from other causes may preclude the observation of outcomes such as muscle weakness, leading to inaccurate estimations of effect. This is particularly problematic where interventions affect both competing risk and the measured outcome, such hyperglycemia as seen in the large glycemic control trials (46-48). Composite outcome measures can been used to account for competing risks but the relative contributions of each component cannot be determined (56). A more satisfactory approach which is infrequently employed in ICU studies is to use statistical adjustment, such as multi-state modelling (57). In our review, the most promising therapy is euglycemia; however, in a large studies (albeit one which did not not meeting the inclusion criteria for our primary analysis), ICU mortality rates of 21% and 12% in the intervention and control groups respectively represent competing risks not taken into account in the analysis (37). The effects on this therapy upon the incidence of CIP/CIN may therefore be overestimated.

Avenues for Future Research

Whilst experimental work is ongoing into strategies to cope with ICUAW, functional decline and loss of strength are not unique to critical illness and may be an inevitable consequence of growing old. Pharmacological treatments which have been trialed in the setting of age-related sarcopenia are similar to those trialed in critical illness and include the administration of testosterone, growth hormone and supplementation of vitamin D (58-61). Results to date have been disappointing and largely reflect the evidence we have discussed in this review, in that whilst improvements in markers such as lean body mass may be seen, these do not translate into improvements in function and any benefit may be severely limited by serious side effects, particularly for rhGH.

A number of more novel approaches may be of interest. Myostatin is an endogenous, TGF-β family member which functions as an endogenous inhibitor of muscle growth in diverse species including humans (62). The myostatin gene is expressed almost exclusively in skeletal muscle cells of skeletal muscle embryonic development as well as in adult animals (63). In adult animals, myostatin appears to inhibit the activation and differentiation of satellite cells, resident stem cells in skeletal muscle that are critical to muscle regeneration (63). Targeted disruption of the myostatin gene in mice leads to muscle hypertrophy and hyperplasia, approximately doubling of muscle mass (64). The function of myostatin as a negative regulator of muscle growth was recently shown to be conserved in humans (65). Selective inhibition of this moeity may have broad clinical utility for a variety of muscle disorders including weakness associated with critical illness. The role of myostatin in the development of critical illness weakness is currently being investigated (clinicaltrials.gov reference NCT01321320). Other approaches including IL-6 antagonism and administration of synthetic ghrelin have also been promising in animal models of cachexia (66). A definitive answer on these molecules may well be with us in the next decade.

As well as focusing upon which pharmacological agent to test, careful consideration must be given to study design. We urgently require consensus as to which physical outcome variables are best utilised in assessing weakness in ICU survivors as these vary enormously. Competing risks should also be identified

and planned for. Qualifying which interventions were delivered at each stage of the ICU survivor's journey (i.e. during ICU, between ICU and hospital discharge and after hospital discharge) and agreeing on taxonomy will allow us to assess optimal timing in addition to optimal agent. Finally, consideration needs be given how best to account for pre-existing physical decline. It is plausible those with considerable neuromuscular dysfunction (whether pathological or 'functional') prior to the development of critical illness will have poorer outcomes than those without; future studies should identify and account for this in their design.

Conclusions

To date, only intensive insulin therapy has been shown to positively affect the incidence of critical illness acquired weakness; however, this cannot be routinely recommended due to the significant risk of adverse effects, particularly hypoglycemia. Clinicians should be aware that the current body of evidence points to a detrimental impact of uncontrolled hyperglycemia in critically ill adults and that avoidance of hyperglycemia may have an important impact on reducing the incidence of ICUAW but with the risk of hypoglycemia remains high. Further large-scale investigation into the safe provision of more moderate glycemic targets is warranted. Whilst novel agents show promise in small observational studies, it is important that key methodological challenges are addressed. Similarly, clinicians interpreting new studies in this area must remain mindful of these key challenges in mind when appraising new research.

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Declaration of interests

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the paper.

Legends - Main Manuscript

Table 1: Assessment of bias risk

Figure 1: Flow chart of study assessment process

Legends - Supplementary Digital Content

Table 1: PICOS table of studies included in primary analysis

Table 2: PICOS summary table of potentially interesting studies not included in the systematic review

Appendix 1: Search strategy employed for Medline

Appendix 2: Data extraction form

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Figure 1 flowchart

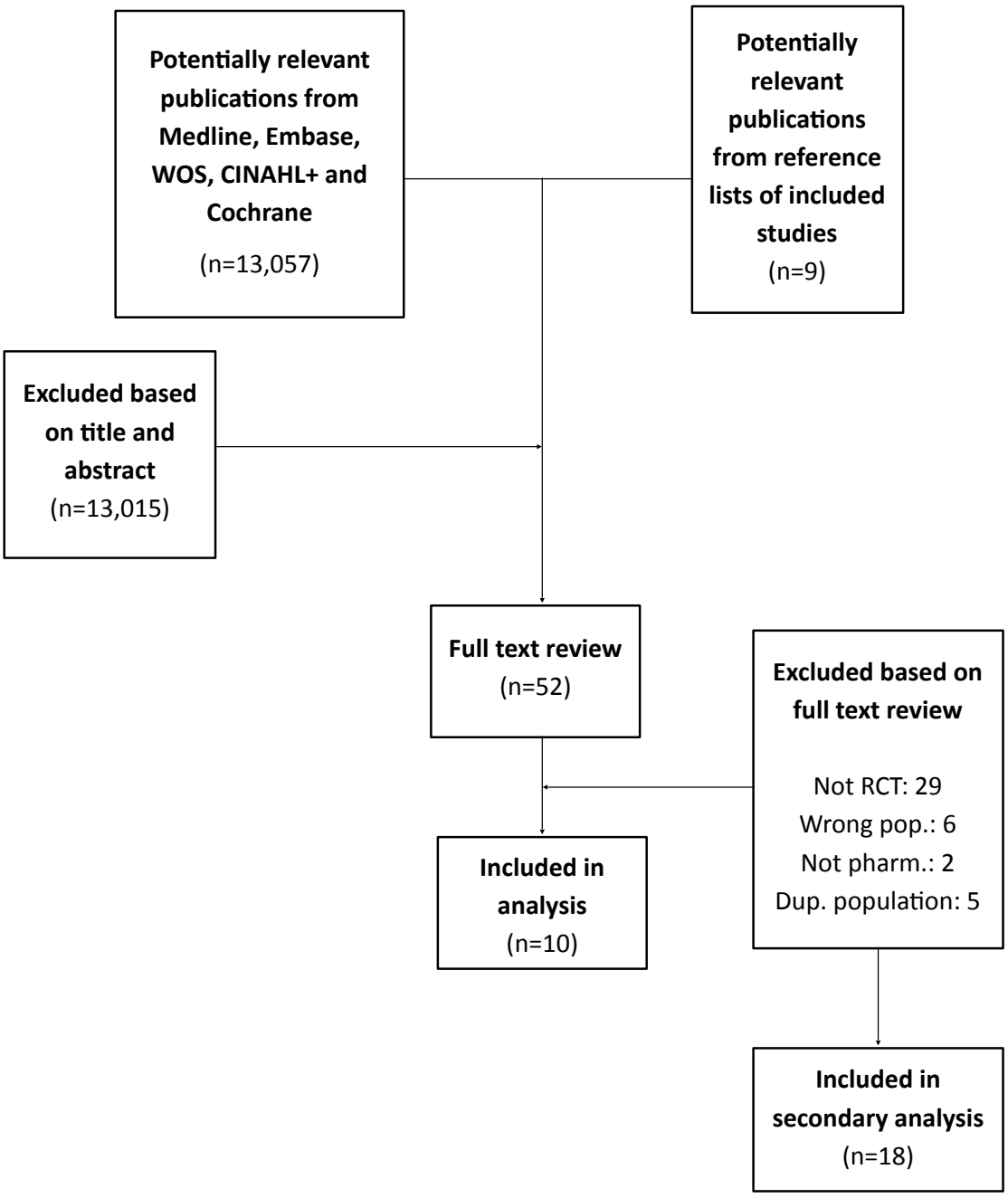

Table 1

Table 2: Assessment of bias risk

Reference	Year	No.	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk of bias
			Selection		Performance	Detection	Attrition	Reporting	
Biolo	2008	16	Unclear	Unclear	High	High	Low	Low	High
Brunner	2012	23	Low	Low	Low	Low	High	Low	High
Demling	2003	13	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Gamrin	2000	19	Unclear	Low	High	Low	High	Low	High
Herndon	2001	21	Low	Unclear	Low	Unclear	High	Low	High
Mikaeili	2012	17	Unclear	Unclear	High	Low	Low	Low	High
Pichard	1996	18	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Takala - 1	1999	10	Unclear	Unclear	Unclear	Unclear	High	Low	High
Takala - 2	1999	10	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High
Tjader	2004	26	Unclear	Low	High	Low	High	Low	High

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