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REVIEW

Neuromuscular Blocking Agents and Reversal Agents Usage, and Neuromuscular Blockade Monitoring in the Intensive Care Unit – Review Article

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Abstract: Neuromuscular blocking agents (NMBAs) are widely used in anesthesiology. However, their use in Intensive Care Units (ICUs) has yet to be fully standardized. Due to numerous conflicting reports or insufficient scientific evidence, there are significant controversies surrounding the use of these drugs, particularly in patients requiring ventilatory support for ARDS, those with increased intracranial pressure, or patients undergoing therapeutic hypothermia (especially after cardiac arrest resuscitation). ICU patients are typically critically ill, often in sepsis, with multiple comorbidities, multi-organ failure, homeostasis disturbances, and requiring multiple medications. These conditions can significantly affect the potency and action of skeletal muscle relaxants. In recent years, the importance of monitoring neuromuscular blockade has been emphasized. Clinical examination, although widely used, has limited applicability in ICU settings. Peripheral nerve stimulation (PNS) and train-of-four (TOF) monitoring are qualitative methods, whereas quantitative techniques, which provide objective measurements, are increasingly recommended for managing neuromuscular blockade. Most guidelines currently focus on perioperative monitoring, and there is a lack of detailed recommendations for using these methods in the ICU. This article discusses existing research on the use of skeletal muscle relaxants, neuromuscular blockade reversal agents, and monitoring methods for neuromuscular blockade in intensive care units.

Keywords: intensive care units, neuromuscular blocking agents, neuromuscular monitoring, investigative techniques, peripheral nervous system agents

Introduction

Neuromuscular blocking agents (NMBAs), also known as skeletal muscle relaxants, have found widespread use in daily anesthesiology practice. They are commonly used to prepare patients for surgical procedures, facilitate and reduce tissue trauma during intubation, and support mechanical ventilation. Depending on the mechanism by which this occurs, they are categorized as non-depolarizing agents which are divided on chemical structure into: steroidal, benzylisoquinoline compounds, asymmetrical mixed-onium chlorofumarate, and depolarizing muscle relaxants.[1–5]

NMBAs relaxants differ not only in their structure, metabolism, and mechanism of action but also in their duration of effect, which influences their clinical applications. The onset time and duration of action of these drugs may be influenced by various factors.[1,6–8]

Despite their usefulness, use of NMBAs may be connected with risk of adverse effects and complications. Therefore, it is crucial to monitor neuromuscular block, which is commonly done using the Train-Of-Four (TOF) technique. In clinical practice, it is important to understand the potential effects of these drugs and to know how to counteract them. To gain better control over neuromuscular block, reversal agents are used, with sugammadex being the primary representative.[1,2,5,9]

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While working in the Intensive Care Unit (ICU), patients may require intubation, mechanical ventilation, or management of increased intra-abdominal pressure. The ICU may also house patients with multiple organ injuries or recurrent hypoxemia, particularly in cases of Acute Respiratory Distress Syndrome (ARDS), where NMBAs are sometimes used as part of the treatment.[10] Patients with obesity, neuromuscular diseases, or inflammatory myopathies may also be encountered, which will have significant implications for the use of this group of drugs.[11–13]

Research on the use and benefits of muscle relaxants in patients in the intensive care unit is still ongoing. In most cases, the decision regarding the use of this group of drugs must be made based on an individual risk-benefit assessment for the patient.[10]

This paper will discuss the different classes of NMBAs, reversal agents, techniques for monitoring neuromuscular blockade, as well as the impact of various organ dysfunctions and acid-base imbalances on the effects of the aforementioned drugs. It will also discuss the use of NMBAs in specific clinical situations, such as in elderly patients, obese patients, pregnant and postpartum women, oncology patients, patients with increased intracranial pressure, increased intra-abdominal pressure/abdominal compartment syndrome, and other cases, with particular emphasis on the use of these drugs and techniques in the intensive care unit.

Materials and Methods

This work is based on the available literature and the authors' experience. The purpose of this article is to present the use of NMBAs, reversal agents and monitoring of neuromuscular blockade in ICU. We have thoroughly searched electronic databases such as Google Scholar, PubMed, Cochrane Library, University of Warmia and Mazury A knowledge and research potential platform, and other databases for relevant articles using chosen keywords. We also checked the drugs' monographs and medically checked pages with revised drug monographs. The search terms included among others "muscle relaxants", "neuromuscular blocking agents", "neuromuscular blockade", "depolarizing neuromuscular blocking blocking agents", "non-depolarizing neuromuscular blocking agents", "reversal agents", "succinylcholine", "train of four", "TOF", "qualitative monitoring methods", "quantitative monitoring methods", "pancuronium", "vecuronium", "rocuronium", "atracurium", "cisatracurium", "mivacurium", "neostigmine", "glycopyrrolate", "atropine", "sugammadex", "intensive care unit", alone or combined. We searched for articles written fully in English or with abstracts written in English. We thoroughly examined both recent publications and fundamental principles of anesthesiology.

Depolarizing Neuromuscular Blocking Agents – Characteristic and Usage

Currently, the only widely used drug in clinical practice from this group is succinylcholine. It is a short-acting (5–10 minutes) and fast-acting (onset within 30 seconds) neuromuscular blocking agent (NMBA). Due to its mechanism of action, it's administered as a single dose without the possibility of repeated dosing. However, in some cases, such as short surgical procedures requiring deep neuromuscular block, succinylcholine can be used as an infusion.[3,14]

This drug undergoes hydrolysis by various plasma cholinesterases, including butyrylcholinesterase.[3] Due to its properties, it has found use in the Rapid Sequence Intubation (RSI) procedure, which will be described in further part of the article.[15] The dosage of succinylcholine is 0.3–1 mg/kg intravenously.[3]

One of the primary adverse effects of succinylcholine is the release of potassium ions, leading to hyperkalemia. Potassium levels can typically increase by up to approximately 1 mEq/L. This requires particular attention, as hyperkalemia can cause arrhythmias and pose a life-threatening risk. It is especially important to monitor critically ill patients, as they may have an elevated risk of hyperkalemia due to various etiological factors that can cause upregulation of nicotinic receptors.[3,16]

In a study conducted by Blanié in 2012, 131 critically ill patients were evaluated who received succinylcholine as a NMBA prior to intubation in the ICU—a total of 153 intubations were performed using succinylcholine. Potassium ion levels were measured before and after intubation. Multivariate analysis revealed that factors influencing the occurrence of hyperkalemia (≥6.5 mmol/L) included the length of ICU stay and acute cerebral pathology. Thus, a significant risk factor for an increase in ΔK and the development of hyperkalemia was an ICU stay exceeding 16 days before intubation with succinylcholine.[16]

Other complications after usage of succinylcholine include malignant hyperthermia, bronchospasm, anaphylactic reactions. After administration of the drug, there is also a risk of rhabdomyolysis and myoglobinuria. Prolonged effects can occur in cases of pseudocholinesterase deficiency. Succinylcholine can also cause masseter muscle contraction, although this should not affect intubation.[3] In patients with inflammation of the oral and esophageal mucosa, administration of succinylcholine may induce hyperkalemia through a mechanism similar to that of a burn.[16]

It should be noted that the use of succinylcholine can cause an increase in intraocular, intracranial, and intra-abdominal pressure.[14]

Non-Depolarizing Skeletal Muscle Relaxants – Characteristics and Usage

Non-depolarizing skeletal muscle relaxants are classified based on their structure into aminosteroidal (pancuronium, vecuronium, rocuronium), benzyl (atracurium and cisatracurium), and the recently developed asymmetrical mixed-onium chlorofumarate (gantacurium), which is still under investigation.[1,2,4,5,17]

Steroidal Non-Depolarizing Muscle Agents

Aminosteroidal non-depolarizing NMBAs include pancuronium, vecuronium, and rocuronium. This group of drugs has potential vagolytic effects, particularly pancuronium, which can lead to tachycardia and increased blood pressure, a consideration that should be kept in mind during their use.[1,2,5]

Rocuronium binds to plasma proteins by about 30%.[18] It is a drug used alternatively to succinylcholine in Rapid Sequence Intubation (RSI).[15] During the pandemic, rocuronium was sometimes used in the ICU due to a shortage of other muscle relaxants. In a retrospective study conducted by Aldhaeefi et al in 2023, the dosing of continuous rocuronium infusion and the monitoring of neuromuscular blockade were assessed in ICU patients with hypoxemic respiratory failure during the COVID-19 pandemy (excluding those for whom the infusion was administered for less than 6 hours). The study included 71 patients (59 of whom were COVID-19 positive) and 97 rocuronium infusions. The doses used in the study were compared to those recommended by the SCCM 2002 guideliness and drug's package insert – they were significantly lower than those. Despite the lower doses used, nearly half of the Train-of-Four (TOF) assessments indicated that patients were over-paralyzed. The results of this study suggest that the initial and maintenance doses of rocuronium may be smaller in ICU patients.[19]

Benzylisoquinolinium Non-Depolarizing Neuromuscular Blocking Agents

The benzyllisoquinolinium group consists of atracurium, cisatracurium, and mivacurium. A notable action of this group is the dose-dependent, non-immunologic release of histamine.[1,2,17]

It is currently suggested that some non-depolarizing NMBAs may have anti-inflammatory effects. In a randomized study by Iavarone et all on patients with ARDS, it was found that cisatracurium reduced interleukins and tumor necrosis factor-alpha in plasma and bronchoalveolar lavage fluid.[10,20]

In a study provided by Dieye in 2014 on the pharmacodynamic changes of cisatracurium in ICU patients, it was found that the doses of cisatracurium required to achieve neuromuscular blockade in ICU patients may be higher than those used in standard anesthesia. Alternatively, when similar doses are used, additional boluses of the drug may be necessary. The authors pointed to potential causes for this, such as receptor deregulation and an increase in the volume of distribution.[21]

Table 1 summarizes the currently used skeletal muscle relaxants along with their clinically significant characteristics.[1,2,5,10,12,13,17,19,22–31]

Monitoring of Neuromuscular Blockade

In clinical practice, it is very important to control the neuromuscular blockade being performed. Various methods are used to assess its degree and to evaluate the potential for residual blockade, which can be divided into subjective (qualitative) and objective (quantitative) methods. To avoid complications from the blockade and to ensure proper drug dosing, in addition to physical examination, other methods, preferably quantitative, should always be used.[1,2,32–35]

Table 1 Summarize of Clinical Characteristics of the Currently Used Skeletal Muscle Relaxants

Group	Drug	Time of Acting	Onset of Action [min]	Time of Action [min]	ED95 mg/kg	Intubation Dose, mg/kg	Infusion Dose, µg/kg/ minute	Reversal Agent	Adverse Effects	Additional Properties
Depolarizing										
	Succinylcholine	Short-acting	0.5	5–10	0.5–0.6	1–1.2	Not recommended in the critically ill			Utilized in RSI
Non-depolarizing										
Steroidal	Rocuronium	Intermediate-acting	1–3	20–70	0.3	0.6 (1.2 for RSI)	5–12	Sugammadex, Anticholinesterases (neostigmine, edrophonium, pyridostigmine)	Vagolytic activity (especially pancuronium)	Utilized in RSI
	Vecuronium	Intermediate-acting	1.5	20–60	0.05	0.08–0.1	0.8–1.7			
	Pancuronium	Long-acting	3–5	90	0.07	0.1	0.8–1.7			
Benzylisoquinolines	Atracurium	Intermediate-acting	1–1.5	45–60	0.23	0.4–0.5	5–20	Anticholinesterases (neostigmine, edrophonium	Release histamine	
	Cisatracurium	Intermediate-acting	2	60–90	0.05	0.15	1–3			Potential antiinflammatory properties
	Mivacurium	Short-acting	1–1.5	15–20	0.06–0.08	0.16*-0.24	8 to 10 (0.5 to 0.6 mg/kg/hr)			Metabolized by butyrylcholinesterase enzyme (BChE)

Notes: Mivacurium 2xED95 dose may be insufficient – metabolism begins before full blockade is developed; however 2–3xED95 dosage should enable to proceed tracheal intubation within approximately 2.5 minutes.

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Clinical Evaluation

The simplest way to assess recovery is through the clinical evaluation of the patient.

Despite lack of sufficient sensitivity and specificity in detecting residual blockade, these tests (Box 1)[36,37] are still commonly used. Particularly in ICU settings, performing these tests can present numerous challenges. It is essential to understand that these signs do not definitively indicate the patency of the upper airway or complete recovery of the accessory muscles used for breathing. As a result, they serve as unreliable indicators of residual neuromuscular blockade. For this reason, neuromuscular blockade should also be monitored using other methods.[36,37]

Train-of-Four, Train-of-Four Count, Train-of-Four Ratio

Qualitative methods include the use of peripheral nerve stimulation and monitoring using the Train-of-Four (TOF) method (including derivatives such as the Train-of-Four ratio (TOFR) and Train-of-Four Count (TOFC)).[9]

In TOF test, two electrodes are positioned about 2 cm apart and the peripheral stimulator delivers 4 identical supramaximal impulses at a frequency of 2 hz through the electrodes on the skin, each of which causes a muscle contraction.[5,38–40] TOFC is the number of detected muscle responses, ranging from 0 to 4.[39] TOFR measures the level of blockade by calculating the ratio between the amplitude of the fourth twitch and that of the first twitch. The ratio of these amplitudes indicates the level of blockade achieved/maintained.[5,38,39]

In TOF, the twitch that causes muscle contraction, which is innervated by the nerve being stimulated, is assessed. The usual site of assessment is the ulnar nerve, however, in case of difficulties with assessment at this site or if it is not possible to perform the test on the upper limb, monitoring using TOF can also be applied in other areas – the facial nerve or posterior tibial nerve can be used for assessment.[1,5,10,17,39] There are many devices used for performing the TOF test, allowing measurements at different parts of the body. Recent studies confirms that neuromuscular blockade assessment can be performed on the brachialis muscle, lower limb muscles, or even the corrugator supercilii muscle, especially when the standard site (adductor pollicis muscle) is not accessible (using devices such as TOF-Cuff or TOF-Scan). However, factors such as the variability of muscle responses in a given location must be taken into account.[41–43]

A disadvantage of TOF is the subjective component of the assessment – even an experienced anesthesiologist may encounter difficulties in evaluating the fading of the twitch response, which corresponds to the strength of the fourth twitch, a sign of deep neuromuscular blockade. Factors that may affect the assessment using a peripheral nerve stimulator include electrode loss or improper attachment to the skin, incorrect electrode placement, and hypothermia. Furthermore, different muscle groups will exhibit varying sensitivity. Facial muscles are more resistant to the effects of NMBAs, which should be kept in mind when stimulating the facial nerve to avoid overdosing.[44,45]

In the 2023 ASA recommendations, it was mentioned that if the hand is not accessible, the orbicularis oculi (facial) or posterior tibial (ankle) nerve can be used (with strong evidence against using the posterior tibial nerve in patients with peripheral neuropathy).[35]

Box 1 Physical Examinations Tests for Assessment of Residual Neuromuscular Blockade

Sustained hand grip
Ability to lift head for five seconds
Eye-opening
Tongue protrusion test
Presence of spontaneous respiration
Ability to hold up the arm or the leg for 5 seconds
Adequate swallowing and coughing

Post Tetanic Count

Post-tetanic count (PTC) is a test used to assess neuromuscular blockade when it is no longer possible to detect twitches in TOF stimulation (TOFC = 0). In this test, a 5-second impulse, called tetanic stimulation, is generated at a frequency of 50Hz, followed by single stimulations at a frequency of 1Hz. The number of twitches observed after tetanic stimulation inversely correlates with the level of neuromuscular blockade— the more twitches present, the weaker the blockade, and the quicker twitches will be detectable in TOFC. However, post-tetanic count is rarely used in clinical practice.[45,46]

TOF Usage in ICU SCCM Recommendations

In the 2016 recommendations from the Society for Critical Care Medicine, weak guidelines were issued suggesting that peripheral nerve stimulation with TOF may be useful for assessing the depth of neuromuscular blockade when using a continuous infusion of muscle relaxants. However, it was emphasized that this should be part of a comprehensive assessment of blockade depth, which also includes clinical evaluation, and that PNS and TOF should not be used alone in such cases.[47]

Quantitative Methods of Monitoring

Despite the frequent use of NMBAs in intensive care units, TOF or PTC are not routinely used, increasing the risk of residual neuromuscular blockade going unnoticed. Due to the significant influence of the examiner's subjective assessment, the only methods capable of providing an objective evaluation are quantitative methods, including acceleromyography (AMG), kinemyography (KMG), and electromyography (EMG).[48]

Using quantitative measurement, the dosing of NMBAs can be individualized, ensuring each patient receives the appropriate degree of neuromuscular blockade, including when reversing the blockade with reversal agents. This helps avoid premature intubation, residual blockade, and the complications associated with them.[49]

Mechanomyography

Mechanomyography is a method in which muscle contraction is measured after electrical stimulation, and it is considered the "gold standard" for directly measuring the force of contraction post-stimulation. Importantly, this test can only be performed to assess a few muscles, primarily the adductor pollicis muscle and the flexor digitorum brevis muscle. This test is time-consuming and therefore not recommended for routine clinical practice (although it is considered the gold standard in clinical trials of NMBAs).[9]

Acceleromyography

AMG is probably the most widely used of the quantitative methods. It assesses the acceleration of a group of muscles between the thumb and index finger. Due to the measurement of muscle acceleration, this test is sensitive to movement. To perform it correctly, it is necessary to ensure that muscles other than those being assessed are immobilized—eg, by immobilizing the arm and the fingers between the second and fifth fingers during the evaluation of the adductor pollicis, while allowing free movement during ulnar nerve stimulation. The equipment used for AMG tends to overestimate TOFR—the measurement is typically 10–20% higher than with other methods. Therefore, it is recommended to refer to the baseline.[9,50,51]

Kinemyography

KMG is a technique used to monitor neuromuscular function by measuring muscle movement in response to nerve stimulation. During the response assessment using a KMG device, free movement of the thumb and index finger is essential. The mechanical sensor is placed between the thumb and index finger. Stimulation of the ulnar nerve causes contraction of the adductor pollicis muscle, and the device measures the electrical current. A limitation of this method is capturing the movement of the thumb toward the index finger, and it can only be performed on the adductor pollicis muscle.[9,32,52]

Electromyography

EMG is a test based on measuring the peak-to-peak amplitude or the area under the waveform curve induced by the muscle action potential and measuring the intensity of the response. EMG and mechanomyography are related, with the assessment of electrical signals being a significant advantage of EMG, as it more accurately measures the response where muscle relaxants act—at the neuromuscular junction. Another advantage is that the measurement is not affected by thumb movement, hand position, or changes in muscle contractility.

EMG offers a lower risk of error related to movement compared to AMG. However, it is important to note that the assessment with properly used AMG equipment is of comparable quality.

Modern electromyography equipment, however, allows for reliable TOF assessment. The test can be performed by evaluating muscles on the upper limb, lower limb, or face. However, the most frequently used muscle is the adductor pollicis muscle.[9,50,53] It has been shown that the placement of equipment – electrodes and tools for measuring transmission – can be easily positioned at the site for measuring the posterior tibial nerve, compared to testing on the upper limb. There is also a study indicating that there is no statistically significant difference between the measurement of onset and recovery of neuromuscular block when testing the ulnar and posterior tibial nerves.[9,54]

For the measurement to be conducted, the limb where the measurement takes place should be warm, as cooling of the limb can affect the readings. In ICU conditions, to minimize the risk of interference from other devices, a notch filter should be used and, if possible, all unnecessary devices should be disconnected, even the bed from the power source.[55]

In 2019, Elanagan Nagarajan provided a retrospective study in which he assessed the use of needle EMG for superficial and deep muscles in critically ill patients in the ICU, burdened with multimorbidity. The study evaluated 30 patients, who were observed for two weeks after the procedure. No complications were found in the patients, and it was concluded that the procedure can be safely performed, even in patients with two or more comorbidities that increase the risk of bleeding or infection.[56]

In a study conducted in 2014 by Stewart, EMG and KMG techniques were compared in terms of reproducibility and assessment of late recovery from neuromuscular blockade. TOFR was evaluated in 30 patients using KMG and EMG on the adductor pollicis muscle. The results indicated that KMG and EMG are comparable in terms of precision and quantitative assessment of TOFR using the adductor pollicis muscle.[52]

Reversal Agents

Due to the need to control neuromuscular blockade and the possibility of its reversal at an appropriate time, drugs that reverse the effects of skeletal muscle relaxants are used. For this purpose, acetylcholinesterase inhibitors (neostigmine, pyridostigmine, edrophonium) and sugammadex, which is used to reverse blockade caused by steroidal non-depolarizing muscle relaxants, are applied. Research is ongoing to find drugs that could serve as reversal agents. Recently, reports have emerged about Calabadion 1 and Calabadion 2, but these drugs require further investigation.[1,4,57,58]

Acetylcholinesterase Inhibitors – Neostigmine, Pyridostigmine, Edrophonium

Neostigmine, pyridostigmine, and edrophonium cause the enzymatic breakdown of acetylcholine at the neuromuscular junction, increasing its concentration in the synaptic cleft. This enhances the competitiveness of acetylcholine relative to muscle relaxants at the receptor. However, the effect of these drugs is limited, so in the case of deep neuromuscular blockade, further increasing the dose may be insufficient to achieve adequate competition and reverse the effects of NMBAs.[53,58–61]

When using neostigmine, an anticholinergic drug (atropine or glycopyrrolate) should be administered simultaneously. Their use reverses/prevents the vagal reflex and bradycardia, as well as the muscarinic effect.[59]

In cases of attempting to reverse blockade using neostigmine in patients paralyzed with pancuronium or vecuronium, and who have renal failure, the return of conduction may occur with signs of recurarization.[61]

Absolute contraindications for the use of neostigmine include peritonitis, mechanical bowel obstruction, urinary tract obstruction/urinary retention, and hypersensitivity to the drug. Neostigmine should not be used when TOF is 1 or TOF is 0. It should also be avoided when TOF > 0.7 due to the increased risk of paradoxical anticholinesterase-induced muscle weakness, which is another complication of using neostigmine (and other acetylcholinesterase inhibitors). This manifests as a decrease in the tone of upper airway dilator muscles, immobilization of respiratory muscles, and a reduction in minute ventilation.[53,59] Neostigmine overdose can lead to a cholinergic crisis, presenting as increased muscle weakness, including respiratory muscles, which may result in respiratory arrest and death. In this case, atropine should be administered to the patient without delay.[59]

Edrophonium, despite its faster onset in reversing neuromuscular blockade compared to neostigmine or pyridostigmine, is characterized by greater variability when used to reverse blockade induced by vecuronium. Due to its unpredictability, it is now rarely used.[61]

The most commonly used doses for reversing neuromuscular blockade are: neostigmine at 0.04 mg/kg, pyridostigmine at 0.2 mg/kg.[61] Anticholinergic drugs should be administered early (ie, 15–20 minutes before extubation) and in shallower depths of blockade (TOFC = 4) to increase the chances of complete recovery.[37,61] Neostigmine is an acceptable alternative for reversing a blockade when TOFC = 4/4 with TOFR between 0.4–0.9. The drug dose should not exceed 40 µg/kg (due to the likelihood of a paradoxical effect occurring). If the maximum effect of neostigmine has already been achieved, with TOFC at 4/4 but TOFR < 0.9, spontaneous recovery from the blockade should be allowed (if the situation permits). If not, and the maximum dose of neostigmine has not been used, an additional dose can be given (the total dose cannot be greater than 50 µg/kg). If rocuronium or vecuronium was used for the blockade, sugammadex should be administered.[37]

Sugammadex Characteristics

Sugammadex is a drug that is a modified gamma-cyclodextrin, which binds to aminosteroid muscle relaxants, forming easily water-soluble inclusion complexes.[57,62] Using sugammadex before a blockade with succinylcholine can delay the onset of the blockade. On the other hand, when sugammadex is used before a blockade with cisatracurium, the onset occurs more quickly and the level of blockade is deeper.[58] When administering sugammadex, a linear dose-dependent pharmacokinetic relationship exists within the dose range of 2–16 mg/kg.[58]

In a study provided by Mesa in 2015, it was evaluated that even doses of 2 mg/kg of sugammadex may be sufficient for reversing blockade in patients where the blockade was induced by a continuous infusion of rocuronium while under anesthesia with sevoflurane. The lower dose did not significantly affect the recovery time or increase the risk of residual re-curarization.[63]

In the case of using rocuronium and vecuronium to induce a blockade, when TOFC <4/4, sugammadex is recommended to reverse deep and moderately deep neuromuscular blockade. For TOF ≥2/4 (moderate neuromuscular blockade), the dose of sugammadex should be 2 mg/kg, while for TOF <2/4 or one to two post-tetanic counts, the dose should be 4 mg/kg. In situations where emergency reversal is required or when a standard intubating dose of rocuronium (ie, 1.2 mg/kg) has been used, the drug should be administered in a maximum single dose of 16 mg/kg.[37]

The contraindications for using sugammadex are subjective (eg patients with impaired kidney function). However, if the decision to use the drug is made for patients with renal insufficiency, they should be closely monitored. It is important to note that in the case of using rocuronium for neuromuscular blockade, the sugammadex-rocuronium complexes can be removed by hemodialysis.[58]

It has been shown that reversal of blockade with sugammadex during the use of rocuronium or vecuronium had the lowest frequency of residual blockade in moderate and deep block cases and also is faster and and more effective compared to reversal using neostigmine.[64]

According to MPOG reversal with sugammadex is recommended for deep and moderate levels of neuromuscular blockade from rocuronium or vecuronium.[37]

Comparison of Reversal Agents

The preferred drug for reversing blockade caused by aminosteroid NMBAs is sugammadex. Its effect is more predictable compared to pyridostigmine, but it does not guarantee a return without quantitative monitoring.[53]

Available literature shows that sugammadex, regardless of the depth of the blockade, reverses neuromuscular blockade more quickly and effectively compared to neostigmine. This has been detailed in previous systematic reviews and meta-analyses, including studies by Hristovska et al in 2017 and Amit D. Raval et al in 2020.[64,65] The effect of sugammadex can be seen within 1–2 minutes, compared to 9–10 minutes with neostigmine. When used in a high dose of 16 mg/kg, sugammadex will also quickly antagonize deep neuromuscular blockades.[49] At the same time, sugammadex seems to have a better safety profile—patients who received sugammadex experienced 40% fewer adverse effects compared to those who received neostigmine.[49,64,65]

In a study provided by An et al in 2019, It has been shown that in patients after laparoscopic cholecystectomy, the use of sugammadex compared to a mixture of pyridostigmine and glycopyrrolate was associated with a faster return of peristalsis (assessed by the first postoperative passage of flatus).[66]

A systematic review by Abad-Gurumeta et al of sugammadex versus neostigmine for reversing neuromuscular blockade demonstrated superiority of sugammadex in reducing the number of patients with postoperative residual paralysis.[37,67]

Table 2 Summarize of Reversal Agents with Clinical Characteristics

Reversal Agent	Dosage	Onset of Action/Time to Peak/Duration of Action	Drugs Whose Action is Reversed	Additional Information
Sugammadex	2–16mg/kg IV	Reversal (to TOFR 0.9) in 1,5–3 minutes	Rocuronium, Pancuronium, vecuronium	• excreted by kidneys
Neostigmine	Initial dose: 0.03 to 0.07 mg/kg IV Maximum dose: 0.07 mg/kg IV or up to a total of 5 mg IV, whichever is less (accompanied by glycopyrrolate 0.006 mg/kg) intravenously; 0.014 mg/kg intravenously	The peak effect (antagonism) occurs at approximately 7 to 10 minutes, and the duration of action is approximately 55 to 75 minutes	Cisatracurium, Atracurium, Rocuronium (0.03 mg/kg dose is recommended), Pancuronium (0.07 mg/kg dose is recommended), Vecuronium (0.07 mg/kg dose is recommended)	• Administer over a period of at least 1 minute. • Smaller dose is recommended for NMBAs with short half-lives, bigger dose for NMBAs with longer half-lifes, or first twitch response is relatively weak or there is a need of faster recovery • must be accompanied by an anticholinergic drug • excreted by the kidneys • duration of action of neostigmine is increased in patients with renal failure
Edrophonium	0.5 to 1 mg/kg	- Onset of Action – 3 min	Cisatracurium, Atracurium, Rocuronium, Pancuronium, Vecuronium	• Administer IV slowly over 45 seconds to 1 minute • must be accompanied by an anticholinergic drug
Pyridostigmine	0.1 to 0.25 mg/kg.	Effect is dose-dependent	Rocuronium, Pancuronium, vecuronium	• Must be accompanied by an anticholinergic drug • return of twitch height to 90% of control occurs within approximately 6 minutes following administration of a - 0.25 mg/kg dose; at lower doses, full recovery usually occurs within 15 minutes in most patients, although others may require a half-hour or more. • Additional doses of pyridostigmine not recommended if reversal is inadequate; instead, manage with manual or mechanical ventilation until adequate recovery occurs.

Abbreviations: NMBAs, neuromuscular blocking agents; ACH, acetylcholine; TOFR, train-of-four ratio; IV, intravenously.

According to MPOG Reversal with neostigmine is acceptable for patients with minimal blockade from vecuronium or rocuronium or for patients receiving cisatracurium[37] (Table 2).[58–61,68–73]

Usage of Muscle Relaxants in Patients with Kidney and/or Liver Insufficiency

Patients in the ICU are often those with multiple comorbidities and organ dysfunctions. Both liver and kidney dysfunctions will affect the metabolism and excretion of skeletal muscle relaxants and their metabolites. Through the accumulation of drugs and their metabolites, there may be an intensification of the blockade, the onset or worsening of adverse effects, or difficulties with weaning from mechanical ventilation, or even venous thrombosis.[6–8,10]

In a study by Circeo et al, a significant prolongation of rocuronium action was observed during continuous infusion in critically ill patients with multi-organ failure (MOF) compared to single organ failure.[74] In another study assessing continuous rocuronium infusion to maintain neuromuscular blockade in the ICU, rocuronium infusions were performed in patients with MOF and those with at least one organ failure. In patients with MOF, a continuous infusion of rocuronium resulted in profound blockade levels and an extended recovery period.[75]

In the previously mentioned retrospective study by Mohammed Aldhaeefi, patients with organ dysfunction, despite receiving significantly lower doses of rocuronium in infusion, likely due to drug accumulation, had a longer time to reversal of the blockade, although this difference was not statistically significant.[19]

In a study by Rodríguez-Blanco et al on the use of muscle relaxants in the ICU, it was concluded that when considering continuous infusion of a muscle relaxant, the preferred drugs might be atracurium and cisatracurium, as their metabolism is independent of liver or kidney function.[12]

In another randomized study conducted by Nazemroaya, researchers evaluated the impact of atracurium and cisatracurium on the neutrophil-to-lymphocyte ratio (NLR) as well as hemodynamic changes during anesthesia induction. The study involved 80 patients, with 40 receiving atracurium and 40 receiving cisatracurium. In the cisatracurium group, mean arterial pressure (MAP) significantly dropped after intubation. In the atracurium group, MAP significantly increased post-intubation. The NLR was notably higher in the cisatracurium group after intubation. Based on the study, it was concluded that while atracurium is considered safe for use, it is more strongly associated with hemodynamic instability compared to cisatracurium.[76]

A summary of the relationship between muscle relaxants and liver and kidney function can be found in a table further in the article (Table 3).

Usage of Muscle Relaxants in Acid-Base Balance Disorders and Electrolyte Abnormalities

Acid-base disturbances are another factor influencing the effects of skeletal muscle relaxants. Respiratory and metabolic acidosis enhance the effects of non-depolarizing NMBAs, while alkalosis weakens. The opposite is true for succinylcholine. The only exception is cisatracurium, whose action in the context of acid-base disturbances is not fully understood.[8] The only study on the impact of acid-base imbalances on the action of cisatracurium was conducted in cats, and it concluded that such disturbances significantly affected the potency of cisatracurium, although the change in recovery index could have resulted from hemodynamic instability caused by the prolonged experiment.[77] The product monograph states that acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents.[78,79] However, the impact of these disturbances should be the subject of further research, including during ICU use.

It is believed that other disturbances, such as electrolyte imbalances, may also affect the duration of action of these drugs (hypocalcemia, hypokalemia, hypermagnesemia, hypophosphatemia are thought to enhance neuromuscular blockade, while hypercalcemia and hyperkalemia are believed to diminish neuromuscular blockade).[8]

For cisatracurium, electrolyte disturbances such as hypocalcemia, hypokalemia, and hypermagnesemia remain unclear, which is explained by its metabolism dependent on ester hydrolysis and Hoffmann degradation[8] (Table 3). [6–8]

Muscle Relaxants in Sepsis

In the case of sepsis, there can be disturbances in both hemodynamics and acid-base balance, as well as in acetylcholinesterase activity in the synaptic cleft of the neuromuscular junction, which can affect NMBAs action.[8,79]

Table 3 The Impact of Organ Dysfunction and Electrolyte Imbalances on Drug Action

Group	Drug	Metabolism/Excretion	Liver Insufficiency	Kidney Insufficiency	Acidosis	Alkalosis
Depolarizing NMBAs	Succinylcholine	Plasma cholinesterases	Extended the activity time; Prolonged blockade in cirrhotic patients	If no neuropathy/ hyperkalemia seems to be safe; Repeated doses in kidney failure should be avoided	Diminish	Enhance
Non-depolarizing NMBAs	Rocuronium	Excreted unchanged in bile and in around 30% by kidneys	High variability response in those patients; extended activity time, especially in cirrhotic patients	Prolonged time of action	Enhance	Diminish
	Vecuronium	40% is cleared through the bile and 20% to 30% is eliminated by kidneys	Prolonged time of elimination and duration of blockade	Prolonged neuromuscular blockade; Not favorable NMBAs in those patients	Enhance	Diminish
	Pancuronium	Excreted mainly by kidneys (80%); hepatic degradation in 10%; biliary excretion in 10%	Limited usage in those patients due to prolonged half-time and activity	Prolonged blockade	Enhance	Diminish
	Atracurium	Hofmann elimination and ester hydrolysis; less than 5% of atracurium is excreted by kidneys	No impact of hepatic insufficiency	Action not prolonged	Enhance	Diminish
	Cisatracurium	Hofmann elimination and ester hydrolysis; partially excreted by organ-dependent manner – mostly by kidneys	No impact; safe and favorable muscle relaxant in hepatic disorders	In patients with renal impairment clearance can be reduced and lead to prolonged effects of drug	Not clear	

Abbreviation: NMBAs, neuromuscular blocking agents.

Usage of Neuromuscular Blocking Agents in Obese Patients at ICU

Obesity is associated with numerous challenges in patient care in the ICU. Obesity is linked to an increased fat tissue content and a decrease in the free water compartment. Obese patients have higher morbidity and may also experience multi-organ dysfunction. This affects the distribution volumes and metabolism of many drugs.[11,80]

There is ongoing discussion about how neuromuscular blocking drugs should be used in obese patients. Currently, it is considered that the dosing of rocuronium, vecuronium, atracurium, and cisatracurium should be adjusted based on ideal body weight (IBW), while for mivacurium and succinylcholine (its dosage should not exceed 200 mg), the dose should be calculated based on total body weight (TBW). Pancuronium should not be used in morbidly obese patients.[81]

There are no established clear guidelines for the use of reversal drugs either. Some authors suggest that the dosing of sugammadex should be based on IBW or calculated as 40% of corrected body weight (CBW).[11,81] It should be kept in mind that dosage calculated on IBW may be insufficient to achieve full recovery from neuromuscular blockade.[58] In the case of neostigmine, it is suggested that the dose for such patients should be calculated on TBW.[81]

In the 2016 recommendations from the Society for Critical Care Medicine, a weak recommendation was issued suggesting that for obese patients, the dose of muscle relaxants should be adjusted to IBW or adjusted body weight.[47]

Tracheal Intubation and Rapid Sequence Intubation

Patients in the ICU are at high risk of having an anatomically and/or physiologically difficult airway (up to 30% of tracheal intubations fail on the first attempt in critically ill patients). The use of NMBAs, by relaxing the respiratory muscles, facilitates both ventilation via a facemask and the placement of a supraglottic airway device, as well as improves visibility during laryngoscopy.[13]

Rapid Sequence Intubation (also known as Crush Intubation/Crush Induction) is a procedure performed when rapid intubation is necessary—such as in cases of significant ventilation disturbances, unconscious patients who are unable to maintain their own airway, or to prevent aspiration, eg, in cases of upper airway bleeding. Currently, muscle relaxants used include succinylcholine or rocuronium, with no specific advantage of one over the other. The choice should depend on availability, clinical experience, or the clinical scenario. The use of muscle relaxants significantly facilitates intubation. It also allows for a reduction in the amount of intravenous anesthetic agents required (which has a beneficial effect to prevent increased intracranial pressure). However, their use carries the risk of "can't ventilate, can't intubate" situations, where, due to various difficulties, the patient cannot be intubated and there is a prolonged period without spontaneous breathing, directly threatening the patient's life.[15]

Succinylcholine is used for this procedure at a dose of 1.0 mg/kg. It is currently believed that succinylcholine can cause an increase in intraocular pressure. As long-lasting (1–2 min) contraction of the extraocular muscles pulls the eye against the orbit, succinylcholine should be avoided in patients with eye injuries.[15,58] As mentioned earlier, an alternative to succinylcholine is rocuronium. Its use carries no risk of hyperkalemia or malignant hyperthermia, unlike succinylcholine.[12] In the case of rocuronium, the dose should be at least 1.0–1.2 mg/kg rocuronium (dosage according to IBW).

If the attempt at intubation fails, 16 mg/kg body weight of sugammadex is recommended for the immediate reversal of the neuromuscular block produced by rocuronium, but not for other muscle relaxants.

To perform RSI correctly, one must be well-versed in its process and able to implement it in practice. This will reduce the risk of confusion and potential errors and complications[15] (Figure 1).

In a 2015 study by Johnson et al, comparing the use of succinylcholine and rocuronium in RSI in the Emergency Department, it was shown that patients who received rocuronium had a significantly longer time to sedation or analgesia compared to those who received succinylcholine. This puts the group that received rocuronium at an increased risk of remaining paralyzed without sedation or analgesia. Proper attention to post-intubation sedation and analgesia is the responsibility of all healthcare professionals involved but can be better assisted with the presence of an emergency medicine pharmacist.[82]

In a 2011 prospective randomized controlled single-blind trial by Marsch et al, involving 401 patients who required emergent RSI, the use of succinylcholine (1mg/kg) vs rocuronium (0,6mg/kg) was compared. No differences were found in the incidence and severity of oxygen desaturations, the quality of intubation conditions, or number of failed intubation attempts.[83]

In a retrospective single-center analysis provided by Dukes et al, the number of patients who received additional sedation within 15 minutes of intubation in the ICU using rocuronium was examined. It was shown that a total of 192 intubations using rocuronium were included, and 77 (40.1%) received sedation within 15 minutes of the induction agent administration. This study indicated that a significant number of intubated patients did not receive additional sedation within 15 minutes of induction, exposing them to the risk of awareness while paralyzed. This is extremely important and suggests that more attention should be paid to appropriate sedation when using muscle relaxants.[84]

In 2023, the Society of Critical Care Medicine Clinical Practice issued the Guidelines for Rapid Sequence Intubation in the Critically Ill Adult Patient. A strong recommendation (with low-quality evidence) was made to administer a neuromuscular blocking agent (NMBA) when a sedative-hypnotic induction agent is used for intubation. Additionally, a conditional recommendation (with low-quality evidence) was issued, suggesting the administration of either rocuronium or succinylcholine for RSI, provided there are no known contraindications to succinylcholine.[85]

Muscle Relaxants Usage in Patients with Increased Intracranial Pressure

The results of previous studies regarding the use of NMBAs in patients with increased intracranial pressure (ICP) or those undergoing neurosurgical procedures vary in terms of the potential effects of these drugs. However, these studies differed significantly from one another, and the number of patients studied was small, making it impossible to specify a particular muscle relaxant that could be universally used in these patients.[86]

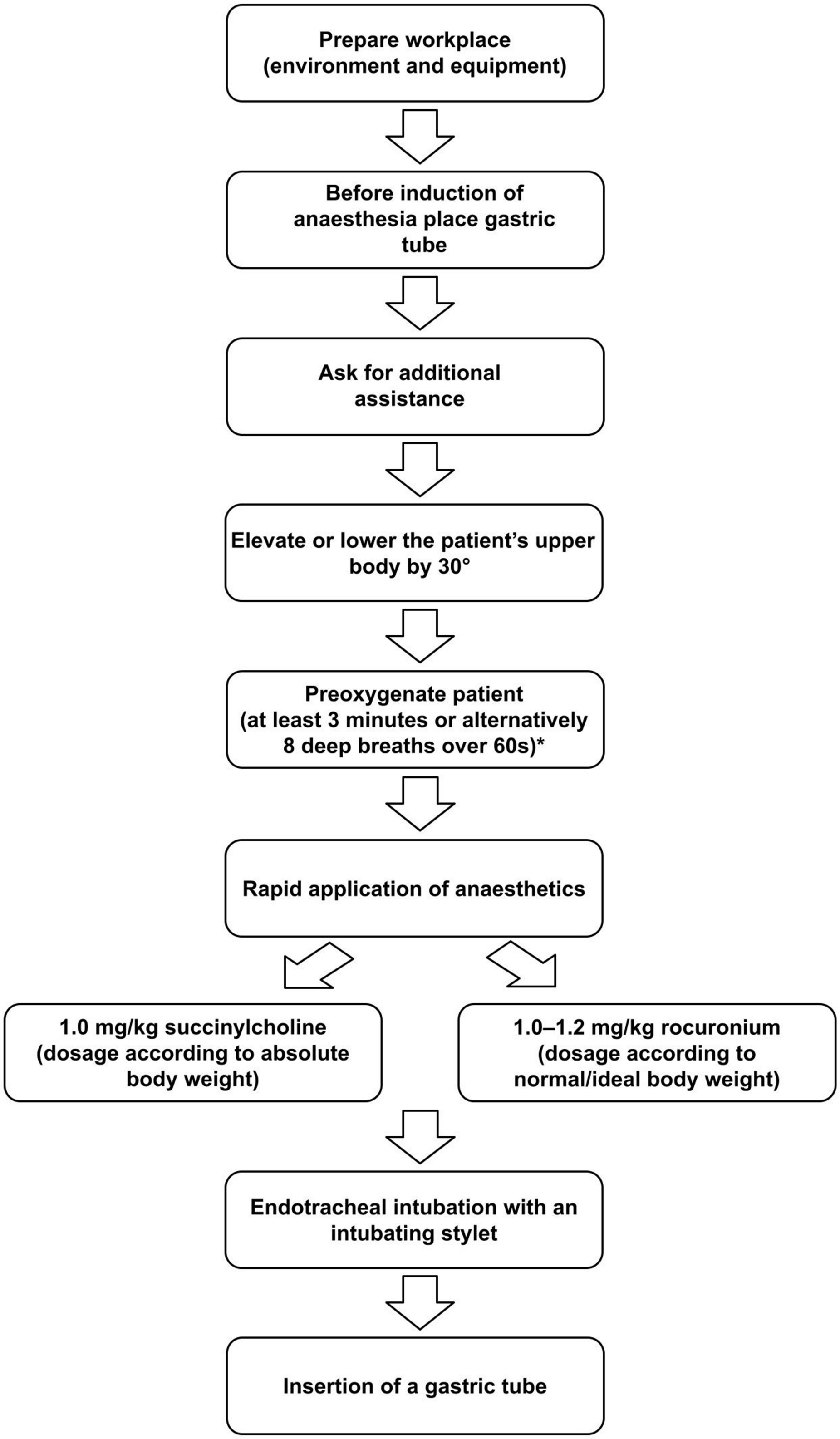

Figure 1 Rapid Sequence Intubation scheme.

Notes: Data from Radkowski et al[15] * - Effectiveness of denitrogenation can be monitored by end-expiratory oxygen concentration; ** Alternatively, at the anesthesiologist's discretion, in the absence of contraindications, succinylcholine may be used. If contraindications to succinylcholine are present, rocuronium should be used.

A 2024 study indicated that existing research suggests that drugs such as mivacurium, pipercuronium, vecuronium, or rocuronium are unlikely to affect intracranial pressure. However, available studies suggest that atracurium and cisatracurium may lower intracranial pressure and cerebral perfusion pressure, although some studies suggest no effect on these aspects. It is also important to remember that the metabolite of these two drugs, laudanosine, may cause seizures. It appears that pancuronium may insignificantly decrease ICP.[86]

The effect of succinylcholine on ICP is different. Many authors suggest that ICP may increase after administration of succinylcholine. However, there are also studies in which it seems that the drug does not affect ICP.[86]

In another review article published in 2024 on the use of NMBAs in patients with traumatic brain injury (TBI), it was emphasized that the use of non-depolarizing NMBAs could be safer than succinylcholine concerning their short-term effects on intracranial pressure (ICP). However, it was highlighted that there is a lack of studies, particularly regarding their impact on the long-term outcomes of TBI patients.[87]

In summary, there is currently insufficient evidence to choose a specific drug when there is an increase in ICP. It seems that promising drugs may be atracurium and cisatracurium, while potential increases in ICP with succinylcholine should be considered in advance.[86]

Increased Intraabdominal Pressure

In the ICU, patients may be encountered with intra-abdominal hypertension (IAH), which is defined as an increase in intra-abdominal pressure above 12 mmHg. This condition negatively affects lung function. In such cases, the use of muscle relaxants can influence and improve the condition.[10]

The literature mentions that succinylcholine may increase intragastric pressure from 0 to 85 cmH2O, depending on the source. This is attributed to the occurrence of muscle fasciculations or a vagal reflex. This can lead to the risk of opening the lower esophageal sphincter (usually at 28 cm H2O, although this also depends on the position of the esophagus relative to the cardia of the stomach; the risk is higher in individuals with a hiatal hernia, gastric and intestinal dilatation, ascites, and intra-abdominal tumors) and regurgitation. Pregnant patients are especially susceptible, as the tone of the lower esophageal sphincter can also be reduced during pregnancy. However, it has been suggested that succinylcholine causes, either by direct action on the lower esophageal sphincter or indirectly through diaphragm contraction, increased resistance to opening of the lower esophagus, which counteracts the increased intragastric pressure. Attenuating fasciculation by giving small doses of non-depolarizing blockers can reduce the rise in gastric pressure.[88]

In 2012, the World Society of the Abdominal Compartment Syndrome (WSACS), in its updated recommendations, listed several methods for treatment, including NMBAs, which are the focus of our study. In recommendations it was noted that a reduction in intra-abdominal pressure with the use of muscle relaxants occurs through decreased abdominal muscle tone and increased abdominal compliance. The recommendations suggested that in the treatment of IAH, short-term neuromuscular blockade may be used as a temporary measure.[89]

A 2020 guideline for managing IAH and abdominal compartment syndrome in critically ill patients emphasized the potential benefit of using NMBAs in cases of persistent IAH. It noted that deepening sedation or using NMBAs may help in reducing intra-abdominal pressure (IAP) and management of IAH for a limited period of time.[90]

Muscle Relaxants in ARDS and Ventilation Asynchrony

In intensive care units, acute respiratory distress syndrome (ARDS) is often responsible for respiratory failure. ARDS is a severe inflammatory condition of the lungs characterized by hypoxemic respiratory failure. It can result from lung damage caused by pneumonia or conditions such as sepsis. This condition is associated with increased mortality. The severity of ARDS is assessed using the inspired oxygen ratio (PF ratio).[57]

In 2012, the previous update to the definition and classification of ARDS—Acute Respiratory Distress Syndrome: The Berlin Definition—was published, initiated by the European Society of Intensive Care Medicine and endorsed by the American Thoracic Society and the Society of Critical Care Medicine- a panel of experts was convened.[91] The newest definition of ARDS comes from 2023, conducted by 32 critical care ARDS experts (from several critical care societies).[92]

For many years, studies have focused on the use of neuromuscular blocking agents (NMBAs) to evaluate their efficacy and potential for improving outcomes. However, the results of these studies are often conflicting.

In a study by Bellani et al, ARDS was diagnosed in approximately 10% of all ICU admissions and in nearly one-fourth of patients who required mechanical ventilation. The study highlighted that ARDS was underdiagnosed, with only 60.2% of all ARDS patients being recognized by clinicians.[93]

The potential mechanisms by which NMBAs may positively influence treatment outcomes include reducing oxygen consumption, decreasing cardiac output and pulmonary blood flow, their anti-inflammatory properties, and minimizing respiratory effort, which in turn reduces alveolar collapse and overdistention. Additional mechanisms thought to reduce ICU mortality include decreasing ventilator asynchrony, the need for mechanical ventilation, and preventing atelectrauma.[94]

In a study by Fanelli in 2016, conducted on an animal model of lung injury using rats, it was demonstrated that cisatracurium and pancuronium exhibit protective effects against ventilator-induced lung injury (VILI) through a dose-dependent anti-inflammatory effect.[95]

The anti-inflammatory properties of NMBAs were further supported by a study conducted by Sottile et al in 2018. It showed that in patients with an initial PF ratio ≤120 and receiving low tidal volume ventilation (LTVV), the administration of NMBAs was associated with decreasing concentrations of serum surfactant protein-D, von Willebrand factor, and IL-8 over time. Based on the results, it was suggested that adding NMBAs to LTVV may reduce lung injury in patients with moderate to severe ARDS.[94]

The frequently referenced ACURASYS study from 2010 demonstrated that early administration of cisatracurium for 48 hours in patients with severe ARDS improved 90-day survival and increased the number of ventilator-free days.[96]

However, another randomized trial, PETAL, published in 2019, evaluated 1,006 patients divided into two groups: one receiving cisatracurium with general anesthesia and the other receiving only anesthesia, assessing the impact of muscle relaxants on outcomes. This study challenged the ACURASYS findings. The population in the PETAL study was similar to that of ACURASYS, including patients with moderate-to-severe ARDS (PF ratio ≤150 mmHg on a PEEP of 8 cmH_2O or higher). In the intervention group, cisatracurium was administered as a 15 mg bolus followed by a 37.5 mg/hour infusion for 48 hours. Patients were mechanically ventilated using low tidal volume, high PEEP, and a conservative fluid management strategy. The study found no significant difference in 90-day mortality compared to the control group. Additionally, 28-day hospital mortality, ventilator-free days, hospital-free days, and ICU-free days were also not significantly different.[97]

In a 2018 review by Torbic et al, summarizing earlier prospective, multicenter, randomized studies (Gainnier et al, 2004; Forel et al, 2006; Papazian et al, 2010, Huang et al, 2017), it was concluded that the use of cisatracurium as a bolus followed by continuous infusion for 48 hours, alongside deep sedation, was associated with positive outcomes (reduced 28-day and 90-day mortality, increased ventilator-free days, increased organ failure-free days, and reduced levels of IL-6 and IL-8 in bronchoalveolar lavage fluid).[98–101]

A meta-analysis provided by Tarazan et al in 2020 highlighted significant methodological differences in studies examining the use of NMBAs in ICU ARDS patients resulting in different outcomes in mortality based on the level of sedation. However, regardless of the differences, it was noted that the use of NMBAs was associated with a reduced risk of barotrauma.[102]

In a 2020 review by Mefford et al, it was concluded that data on mortality in the NMBA group for ARDS are conflicting, with attention drawn to potentially severe side effects and significant controversies surrounding their use.[103]

In a study by Iavarone et al in 2024, it was described that the use of NMBAs may help minimize the risk of ventilator-induced lung injury (VILI) in cases of increased respiratory drive and ventilatory asynchrony. On the other hand, their use may be associated with prolonged mechanical ventilation, extended ICU stays, and an increased risk of ventilator-associated pneumonia (VAP).[10,104–107]

Minimizing the risk of VILI may result from the reduced required PEEP when using NMBAs. NMBAs lower the respiratory rate, which decreases the energy delivered to the patient per minute — a crucial consideration, as increased mechanical power has been associated with reduced survival. However, it remains under investigation whether modifications in mechanical power lead to improved outcomes. NMBAs also reduce dyssynchrony and reverse triggering, which are associated with decreased survival.[108] It has been demonstrated that the presence of asynchrony is linked to the depth of sedation — deeper sedation correlates with a higher incidence of asynchrony.[105–107]

In this study, Iavarone et al also discussed discussed the use of TOF monitoring as a method for guiding neuromuscular blockade.[10] However, a 2021 study reported no significant differences in mortality or ventilator-free days when comparing TOF monitoring with clinical assessment alone.[109] It did note increased atracurium consumption with TOF monitoring compared to clinical assessment. The authors suggested that TOF monitoring may not be necessary for all patients receiving neuromuscular blockade for ARDS, though further research on TOF and other monitoring methods is needed. Current recommendations advocate for the use of TOF whenever possible and for employing objective monitoring methods.[108]

On one hand, a study by Goligher et al described that reduced diaphragmatic muscle activity in ventilated ICU patients is associated with decreased diaphragm thickness, which may be linked to delayed ventilator weaning. On the other hand, proof-of-concept studies have demonstrated that partial neuromuscular blockade using low doses of rocuronium was sufficient to achieve pressures consistent with both lung-protective and diaphragm-protective ventilation.[109,110]

In 2021, Torbic et al presented a meta-analysis evaluating six studies (Gainnier et al, Forel et al, Papazian et al, Lyu et al, Guervilly et al, and PETAL). Based on this analysis, it was concluded that early use of NMBAs improves oxygenation, reduces the incidence of VILI, and decreases 21–28-day mortality, though it does not improve 90-day mortality in patients with moderate-to-severe ARDS.[20]

In the 2020 meta-analysis by Ho et al (which included five studies: Gainnier et al, Forel et al, the ACURASYS trial, Guervilly et al, and the ROSE trial), it was found that the use of NMBAs did not reduce the 28-day or 90-day mortality risk, ventilator-free days, or the duration of mechanical ventilation moderate to severe ARDS patients. While NMBAs improved oxygenation, the effect was only observed until 48 hours. NMBAs were associated with reduced barotrauma but did not impact ICU-acquired weakness. The 28-day mortality risk with NMBAs was not influenced by the baseline severity of ARDS.[111]

In the article provided by Radkowski et al in 2021, it was noted that the usefulness of NMBAs in ICU patients with ARDS is limited to specific clinical situations, such as difficulties in achieving proper patient–ventilator synchronization despite sedation, challenges in attaining target tidal volumes, or the presence of hypoxemia or hypercapnia. The study emphasized the importance of objective monitoring methods for neuromuscular blockade as a way to minimize drug usage without compromising the quality of the blockade. If muscle relaxation is necessary, it is recommended to use a non-depolarizing neuromuscular blocking agent within the first 48 hours of mechanical ventilation in patients with ARDS and a PF ratio <150 mmHg, as this approach has been shown to reduce mortality and the incidence of pressure-related lung injury in patients with moderate to severe ARDS.[57]

In 2019, The Faculty of Intensive Care Medicine and Intensive Care Society Guideline Development Group published guidelines for the management of ARDS in adult patients. These were supported by The British Thoracic Society. The guidelines stated that NMBAs should not be used for all ARDS patients. It was proposed to use cisatracurium through continuous infusion for 48 hours in patients with early moderate-severe ARDS.[112]

In article by Rathi et al in 2024 it was recommended avoiding the routine use of NMBAs and deep sedation in mechanically ventilated patients with ARDS. Before implementing such treatment, it was advised to first optimize the ventilation method and achieve light sedation, followed by prone positioning in cases of early ARDS (within 48 hours). It was mentioned that NMBAs should be used in patients with patient–ventilator dyssynchrony. It was suggested that cisatracurium might be the preferred drug, administered as a bolus dose of 15 mg followed by an infusion at a rate of 37.5 mg/h. However, it was emphasized that there is currently no scientific evidence to establish the best dosing method or to determine the optimal NMBA. In cases of improved PaO2, treatment for less than 48 hours was preferred. Conversely, in the event of failure, an assessment and preparation for VV-ECMO or transfer to an ECMO center should be undertaken without delay.[113]

In 2016, the Society for Critical Care Medicine issued a weak recommendation suggesting the use of a NMBAs in continuous intravenous infusion for early ARDS in patients with a PF ratio less than 150.[47]

In summary, the ESICM guidelines on ARDS, published in 2023, strongly recommended against the routine use of continuous infusions of NMBAs to reduce mortality in patients with moderate-severe ARDS.[114]

The latest recommendations regarding usage NMBAs in patients with ARDS, which emerged after the publication of the new ARDS definition, come from 2024 and were developed by the American Thoracic Society. It was suggested (conditional recommendation with low certainty of evidence) to use neuromuscular blockers in patients with early severe ARDS (≤48 hours from MV therapy and PF ratio ≤ 100).[115]

In summary, based on all the above reports, the use of NMBAs in patients with ARDS should be approached with caution and tailored to each individual patient. It appears that the use of these drugs can be considered in a group of patients who might benefit from them—specifically, patients with early ARDS who are mechanically ventilated with a PF ratio <150, particularly if they experience patient–ventilator desynchrony. The optimal use of these drugs should ideally be limited to less than 48 hours if improvement is observed. In the absence of improvement, consideration and potential qualification of the patient for ECMO treatment should be undertaken.

It should be emphasized that further high-quality studies are needed (Figure 2).

Comparison of Safety and Outcomes of NMBAs in ARDS Patients

Albert et al presented a retrospective, single-center cohort study in 2022 comparing the use of cisatracurium and rocuronium in ARDS patients. The study revealed no significant differences in clinical or safety outcomes, including 28-day ventilator-free days, the highest PF ratio (except at 24 hours, which was higher for cisatracurium), the duration of mechanical ventilation, or the length of ICU stay.[116]

In 2023, Li et al conducted a study with 94 ARDS patients, randomly assigning them to either a study group or a control group (47 patients in each). Both groups received mechanical ventilation, but the study group also received continuous intravenous cisatracurium for 48 hours. The study group showed a reduction in the duration of mechanical ventilation, ICU stay, ICU mortality, and the occurrence of complications. The use of cisatracurium helped reduce the length of mechanical ventilation and ICU stay, lowered mortality rates, and improved lung function in ARDS patients.[117]

In 2023, Carabetta et al conducted a multicenter, retrospective, observational noninferiority cohort study involving ARDS patients who were treated with either atracurium or cisatracurium for a minimum of 12 hours.[118] The results showed no significant differences in the PF ratio and a significant reduction in costs in favor of atracurium.[119]

Vallabh et al conducted a single-center, retrospective, propensity-matched review in which continuous infusions of cisatracurium or vecuronium were used in ARDS patients and compared. Based on results it was concluded that vecuronium may be an alternative option neuromuscular blockade in ARDS patients requiring administration of NMBAs.[120]

Usage of Muscle Relaxants in Patients with Neurosmuscular Diseases and Myopathies

In neuromuscular disorders (NMDs), NMBAs should be used with caution. In all patients with neuromuscular diseases, the use of succinylcholine should be avoided. In 2007, the American College of Chest Physicians published the consensus statement, in which it was said that the use of depolarizing NMBAs is absolutely contraindicated in patients with Duchenne muscular dystrophy.[121] The choice of muscle relaxant should therefore be limited to one of the non-depolarizing NMBAs.

In the case of myasthenia gravis, studies have shown that patients with this disease exhibit significant resistance to succinylcholine. It seems that the best options for them are mivacurium and atracurium, although their duration of action may be prolonged. Therefore, the dosage should be reduced by 10–20% of the recommended dose. In these patients, the progression of the blockade should be carefully monitored using TOF. In cases of myasthenia gravis, NMBAs should be administered only when absolutely essential, as hypersensitivity and unexpected resistance to neuromuscular blockers may occur.[122,123]

Uncertainty often arises regarding whether patients with neuromuscular diseases should be monitored postoperatively in the ICU. Intensive monitoring should be applied to adolescent patients with neuromuscular diseases.[122,123]

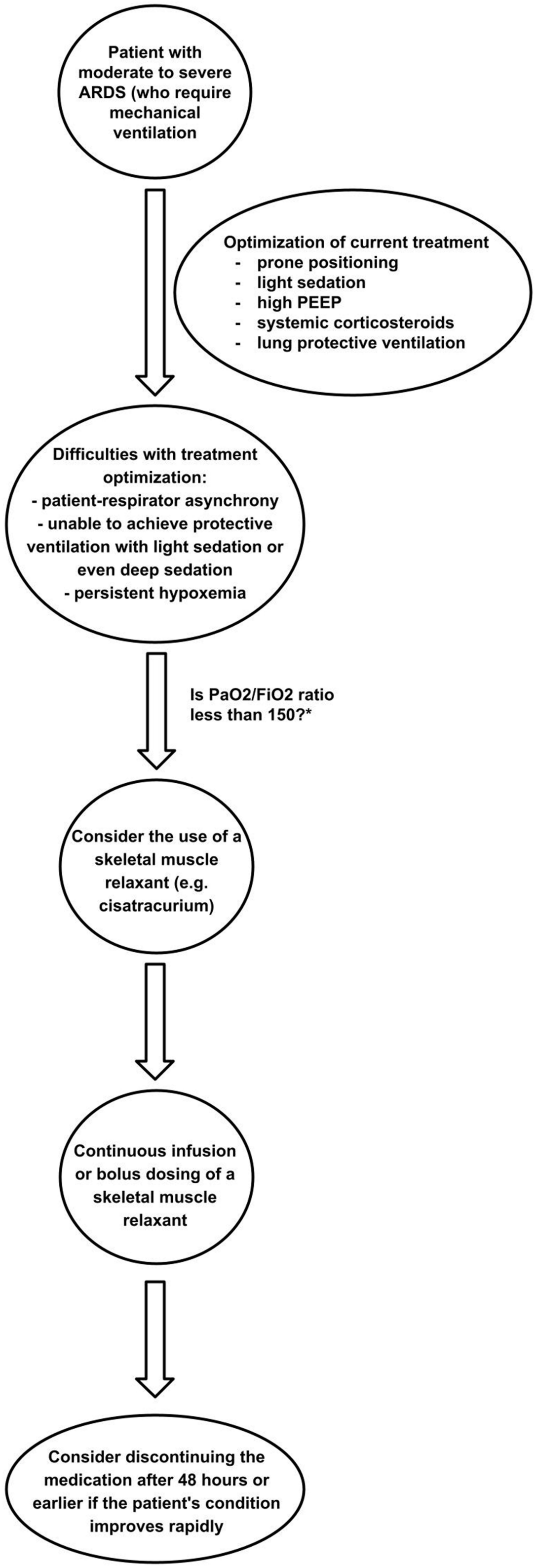

Figure 2 Example algorithm for the use of skeletal muscle relaxants in patients with moderate/severe ARDS.

Notes: *In American Thoracic Society Clinical Practice Guideline PaO2/FiO2 ratio mentioned in considerations of using muscle relaxants is $\leqslant$100 mmHg.

Abbreviations: ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; PaO2/FiO2, the ratio of partial pressure of oxygen in arterial blood (PaO2) to the fraction of inspiratory oxygen concentration (FiO2).

Daum et al, in a review on perioperative care, recommended the use of rocuronium in patients with myasthenia gravis, as the blockade can be reversed with sugammadex.[123]

In 2016, the recommendations issued by the Society of Critical Care Medicine stated that good clinical practice suggests using reduced doses of skeletal muscle relaxants in patients with myasthenia gravis, guided by peripheral nerve stimulation with TOF.[47]

Neostigmine should be avoided for reversal of neuromuscular blockade, due to its mechanism of action, it can expose patients with myasthenias to a cholinergic crisis. In such patients, when using steroidal skeletal muscle relaxants, sugammadex should be selected.

In patients with Guillain-Barré syndrome, the dosage of muscle relaxants should be carefully tailored to the patient, and the blockade should be monitored using TOF.

The action of NMBAs in patients with Charcot-Marie-Tooth disease may have a prolonged onset time and could lead to an extended duration of blockade.[122,123]

In patients with inflammatory myopathies, such as polymyositis and dermatomyositis, attention should be given to the potential aggravated or delayed reactions to NMBAs. These patients, due to pituitary-adrenal axis suppression from prior steroid therapy, may be more sensitive to the effects of NMBAs. Attention should also be paid to interactions between NMBAs and immunosuppressive drugs, which can lead to disturbances in temperature regulation and hyperkalemia, potentially decreasing the effectiveness of NMBAs. Due to the adverse effects of succinylcholine, such as hyperkalemia and malignant hyperthermia, it is recommended not to use this drug. It seems that atracurium is a safer choice.[123,124]

The Use of NMBAs in Therapeutic Hypothermia

It is believed that hypothermia may prolong the duration of the neuromuscular blockade.[8] One should expect changes in muscle strength when the temperature drops below 36°C. Lowering body temperature by 2°C can double the length of neuromuscular blockade. Core body and muscle temperatures decrease at the same rate, as long as peripheral vasoconstriction is absent.[125]

It is also important to monitor the blockade. Central temperature plays a key role in assessing TOF at the adductor pollicis muscle, but local cooling of the hand may impair the accuracy of monitoring twitch tension at the adductor pollicis during clinical anesthesia. Both the duration of action and recovery time are significantly prolonged by hypothermia during anesthesia, mainly due to a reduced elimination rate. To avoid overdosing with NMBAs, methods such as peripheral nerve stimulation should be used, and dosing should be adjusted based on the results.[125]

One of the FDA-approved uses of NMBAs is their use in therapeutic hypothermia after cardiac arrest.[125]

In a 2014 study by Lascarrou et al, 311 cardiac arrest survivors were retrospectively assessed, with 144 receiving therapeutic hypothermia (TH) (divided into neuromuscular group and group without NMBAs). The ICU mortality rate was lower in the neuromuscular blockade group. Although early-onset pneumonia was more common in the neuromuscular blockade group, the difference was not significant after adjusting for the propensity score. The study concluded that continuous intravenous infusion of NMBAs during TH after cardiac arrest may positively impact ICU survival, with a tendency for an increased incidence of early-onset pneumonia. However, further studies on the use of muscle relaxants in this context are required.[126]

In a 2014 study by Ciuraszkiewicz et al, the effects of mild therapeutic hypothermia after cardiac arrest due to acute coronary syndrome were evaluated. The study group consisted of five women and eight men (mean age 59 years). The medications used at admission included 2 antiplatelet agents (300 mg of acetylsalicylic acid and 600 mg of clopidogrel), 5000 IU of unfractionated heparin, proton pump inhibitors, antibiotics (cefuroxime 1.5 g IV every 8 hours), sedatives (midazolam or propofol), and muscle relaxants (atracurium or pipecuronium). Muscle relaxants were administered via continuous intravenous infusion. After reaching a body temperature of 36.0°C, the muscle relaxants and then sedatives were discontinued. In the analysis of the study results, it was found that 8 patients were eligible for mild therapeutic hypothermia, but were not selected for it. These patients required the administration of sedatives and muscle relaxants to optimize ventilation or undergo other procedures. The authors concluded that the use of mild therapeutic hypothermia could have improved their prognosis.[127]

In a 2015 study by Lee et al, 60 patients were analyzed. The impact of mild hypothermia on the reversal of neuromuscular blockade in patients who underwent induced blockade with rocuronium and blockade reversal with sugammadex was assessed. Patients with hypothermia were compared with those with normothermia, in a 1:1 ratio. Patients were administered 0.6 mg/kg of rocuronium, followed by a continuous infusion of 7–10 µg/kg/min to sustain a deep neuromuscular blockade. Post-surgery, the deep blockade was reversed with 4.0 mg/kg of sugammadex. The study found that sugammadex can completely restore neuromuscular blockade from deep rocuronium-induced neuromuscular blockade in hypothermic conditions. An additional 46 seconds was required for the time to TOFR of 0.9 from deep neuromuscular blockade in hypothermic patients.[128]

The 2016 guidelines from the Society of Critical Care Medicine should be noted, as they included a weak recommendation for the use of NMBAs to control severe shivering during therapeutic hypothermia. These recommendations, grounded in good clinical practice, also advised that in patients undergoing therapeutic hypothermia, peripheral nerve stimulation should be used to evaluate the depth of neuromuscular blockade, alongside the consideration of other clinical observations. Additionally, it was recommended that patients undergoing therapeutic hypothermia should receive a NMBAs.[47]

Management of Muscle Spasm

One of the uses of muscle relaxants may be in the treatment of tetanus and the need for better control of muscle spasms, especially when they are difficult to manage and interfere with proper ventilation. Due to anti-vaccination movements, the lack of booster vaccinations, and the low awareness in society, particularly among those over 60, we should be aware of the risks posed by this disease. Tetanus treatment should take place in the ICU.[129]

In cases of ineffective treatment, such as with baclofen or benzodiazepines, the use of neuromuscular blockade may be considered, for example, with pancuronium or vecuronium (which has been found to be effective in treating severe tetanus). When neuromuscular blockade is used, it is important to maintain intravenous benzodiazepine treatment at the same doses to prevent autonomic nervous system hyperreactivity. The duration of neuromuscular blockade should be kept as short as possible. Currently, there is little scientific evidence supporting the use of NMBAs in this context. Existing reports are mainly case reports or case report series.[129]

Another situation where muscle relaxants may be potentially used is in status epilepticus.[130]

In 2006, the Italian League Against Epilepsy published the guideline *Treatment of Status Epilepticus in Adults: Guidelines*, recommending the use of NMBAs in the treatment of convulsive status epilepticus (SE) in the ICU. They should only be used in association with EEG monitoring to assess cerebral seizure activity. These recommendations were based on reports indicating that continuous muscular activity during generalized convulsive status epilepticus may cause systemic complications that worsen the patient's condition and prognosis. Neuromuscular blocking agents have been used to prevent these complications.[130,131]

In a 2017 study by Newey et al, a retrospective analysis was conducted on the change in the quality of continuous electroencephalography (EEG) recordings following neuromuscular blockade in patients admitted with cardiac arrest and post-anoxic myoclonus. Cisatracurium was used to reduce artifacts. A total of 12 patients were evaluated. It was concluded that the use of NMBAs in those patients may be useful in identifying background cortical activity.[132]

In the 2020 status epilepticus guideline, it was noted that when using ketamine (an N-methyl-D-aspartate (NMDA) receptor antagonist), potentiation of atracurium's effect and prolonged neuromuscular blockade may occur.[133]

NMBAs may also be effective in managing trismus occurring postoperatively. A case report described trismus as a complication of general anesthesia, which emerged after the patient's extubation, preventing proper ventilation and subsequently causing oxygen desaturation and bradycardia. The spasm resolved only after the administration of a maximum dose of succinylcholine, which allowed for the placement of a laryngeal mask.[134]

Usage of Muscle Relaxants in Patients After Oncological Treatment in ICU

Cancer patients admitted to the ICU are most often in the postoperative period. However, in cases of unplanned ICU admissions for these patients, the most common cause is acute respiratory failure. For such patients, it is important to consider the possibility of paraneoplastic syndromes such as Eaton-Lambert syndrome or myasthenia gravis.[134]

Due to the aging population and increasingly accessible cancer treatments, anesthesiologists are more frequently encountering patients who are undergoing or have undergone oncological treatment. There are few reports regarding the use of NMBAs in such patients. It has been observed that in patients after treatment (chemo- or radiotherapy), pseudocholinesterase activity may decrease, while in patients with an active cancer process, it may increase, affecting the action of drugs metabolized by it (succinylcholine, mivacurium).[135]

Meanwhile, the action of cisatracurium in patients undergoing chemotherapy has been reported to have a prolonged onset and a significantly shortened, faster recovery time.[135]

Reports regarding rocuronium are varied, therefore, increased caution should be maintained when using this drug in these patients.[135]

In the case of atracurium and cisatracurium, there are reports of a potentially beneficial impact in patients with certain types of cancers. Thus, the use of atracurium as a muscle relaxant can be considered in patients with glioblastoma, hepatocellular carcinoma, or astrocytoma. Cisatracurium appears to have a potential application in patients with stomach cancer, breast cancer, or colorectal cancer.[135]

Usage of Muscle Relaxants in Pregnant Women or During Perpedue

Pregnancy is a special period when, in addition to the patient, we must also consider the fetus. This is important when selecting a muscle relaxant and a neuromuscular blockade reversal agent. Fewer than 2% of pregnant or peripartum patients require admission to an intensive care unit (ICU). The primary reasons for ICU admission in this population are postpartum hemorrhage and hypertensive disorders, such as severe preeclampsia or eclampsia. Critical illness in pregnant women can result from both obstetric and non-obstetric causes.[136]

Pregnant patients have a reduced tolerance for hypoventilation and apnea compared to non-pregnant individuals. As a result, special attention is needed when managing pregnant patients admitted to the ICU with COVID-19 pneumonia and ARDS. In a 2022 article by Griffin et al, the authors emphasized that treatment should always follow the most up-to-date clinical guidelines. In cases of persistent hypoxemia, they recommended considering skeletal muscle relaxants, prone positioning, and nitric oxide therapy for all pregnant patients.[137]

Currently, the most commonly used muscle relaxant during pregnancy and the puerperium period is rocuronium. The onset of action is approximately 25% shorter in pregnant women, while the duration of action is prolonged.[138] Vecuronium in pregnant and postpartum women has prolonged duration of action. It passes through the placenta to a small extent, making it worth considering for women undergoing cesarean section. In the case of choosing cisatracurium, a shorter duration of blockade can be expected in pregnant women.[138]

For succinylcholine, the effect depends on the activity of pseudocholinesterase, the concentration of which changes during pregnancy. During pregnancy, the enzyme concentration may decrease by up to 30%. In the first trimester, there is a significant drop in pseudocholinesterase levels. In the second trimester, there is a further, though slight, decrease in enzyme levels, which lasts until the beginning of the third trimester. After delivery, there is a gradual increase in enzyme levels to normal values, usually around six weeks post-labor. Therefore, using standard doses of succinylcholine in patients with a physiological pregnancy should not result in prolonged apnea.[139]

In the case of magnesium sulfate administration to pregnant women with eclampsia or preeclampsia, the effect of muscle relaxants may be enhanced.[78]

It is important to remember that neostigmine passes through the placenta, so its administration to a pregnant woman to reverse neuromuscular blockade may cause bradycardia in the fetus. In this case, atropine administration (which also passes through the placenta) should be considered.[59]

Studies on sugammadex indicate that it passes through the placenta to a minimal extent. It binds to progesterone, which may decrease its concentration and pose a risk to maintaining the pregnancy, particularly in the early stages.[139]

Drugs Interactions

Given the wide range of situations encountered in ICU work and the multimorbidity of ICU patients, it is crucial to consider potential drug interactions—specifically how the medications patients are taking might affect the action of NMBAs.

Succinylcholine may interact with some of chemotherapeutic agents leading to a prolonged duration of the neuromuscular block.[140]

A commonly used clinical practice is the administration of a small dose of a non-depolarizing muscle relaxant before succinylcholine—known as *precurarization*—to reduce muscle fasciculations. However, this approach is unwarranted and should be avoided, as the prior administration of a non-depolarizing agent weakens the effect of succinylcholine. Conversely, administering succinylcholine enhances the onset and prolongs the duration of the subsequent dose of a non-depolarizing agent, with just 1/3 of the standard intubation dose being sufficient in such cases. Succinylcholine, despite its different mechanism of action, sensitizes acetylcholine receptors, and the degree of muscle relaxation depends on the tissue saturation with inhaled anesthetics. When anesthesia is maintained with an inhaled agent, the dose of muscle relaxants required for maintenance is 20–50% less than with intravenous agents.[49,141]

Lithium can enhance and prolong the effects of both depolarizing and non-depolarizing muscle relaxants. Antibiotics such as penicillin G, clindamycin, and lincomycin intensify the block, while aminoglycosides can reduce the efficacy of neostigmine in reversing the neuromuscular block.[141]

Steroid use is another factor to consider. Corticosteroids antagonize the effects of non-depolarizing muscle relaxants. Chronic prednisone use (for at least four weeks) or even a single dose of methylprednisolone—whether administered 30 minutes before induction or immediately after intubation—shortens the duration of the neuromuscular block.[141]

Anticonvulsants have varied effects depending on their use. Acute administration of anticonvulsants typically increases sensitivity to muscle relaxants, whereas patients on chronic antiepileptic therapy exhibit resistance to non-depolarizing muscle relaxants. Studies have shown that individuals taking phenytoin or carbamazepine experience faster recovery from neuromuscular relaxation induced by rocuronium or cisatracurium.[141]

Adverse Effects of Muscle Relaxants

An extremely important adverse effect that can occur during neuromuscular blockade with insufficient sedation is the patient remaining conscious in a situation where they cannot breathe. To avoid this situation, which can negatively impact the patient's mental health, it is crucial to always ensure proper sedation. Adverse effects of muscle relaxants also include situations such as residual blockade, difficulties, and prolonged time in disconnecting the patient from the ventilator. Patients may also experience visual disturbances (such as diplopia), general weakness, and delayed extubation. The use of NMBAs can also be associated with delayed discharge from the ICU, increased risk of critical respiratory events, hypercapnia, impaired respiratory response to hypoxia (the hypoxic respiratory drive remains attenuated even with recovery to a TOFR $\geq$0.9), and upper airway obstruction. There may also be reduced motility of the upper esophagus. In some cases, reintubation may be required.[48,142]

In cases of blood-brain barrier damage (eg, in the course of a COVID-19 infection), consideration should be given to the potential passage of rocuronium into the brain, which could lead to pupillary dilation.[143]

In cases where the patient remains paralyzed, complications associated with NMBAs, such as corneal abrasions, venous thrombosis, and complications related to prolonged immobilization, such as ICU-acquired weakness (ICUAW) and myopathy, should be considered.

ICU-Acquired Weakness

ICU stays, as well as the use of skeletal muscle relaxants, are associated with conditions such as critical illness polyneuropathy (CIP), critical illness myopathy (CIM), and intensive care acquired weakness (ICUAW). These conditions worsen patient prognosis—both in the short and long term—increase mortality, and are linked to difficulties in transitioning the patient from mechanical ventilation to independent breathing. It is estimated that the occurrence of ICUAW in patients undergoing mechanical ventilation for more than 7 days may be as high as 25–100%.[144–146]

The impact of muscle relaxants on ICUAW remains uncertain. Recent SCCM guidelines did not associate the use of NMBAs with the risk of ICUAW, instead linking it to prolonged immobility and muscle disuse. It seems that steroidal compounds (vecuronium, pancuronium, and rocuronium) may carry the highest risk of myopathy, although myopathy has also been reported with benzylisoquinolines, including cisatracurium besylate. Studies have found that multi-organ dysfunction, severe sepsis, and hyperglycemia are associated with the development of CIP/CIM.[10,96]

Another meta-analysis found that the use of NMBAs was not linked to a higher risk of ICU-acquired weakness.[147]

To assess the presence of the aforementioned conditions, physical examination (which may be difficult in ICU patients—manual testing of muscle strength requires an awake and cooperative patient, which is challenging in sedated patients or those with delirium or other disturbances of consciousness), laboratory tests, and electromyography can be used. Conditions such as sepsis, multi-organ failure, and hyperglycemia are associated with the development of CIP and/or CIM. The best and most reliable method for diagnosing and distinguishing between CIPNM/CIM/CIP is skin and muscle biopsy. However, patients are usually not subjected to biopsies if the clinical and EMG/NCS findings are diagnostic of one of these subtypes. EMG is the optimal way to diagnose CIP.[148–153]

Performing EMG in the ICU presents many challenges. To accurately diagnose CIP, at least 3 extremities should ideally be examined, performing sensory and motor nerve conduction studies and needle EMG testing in both proximal and distal muscles. EMG/NCS are primarily used in the ICU for diagnosis and prognosis in patients with neuromuscular disorders, including CIP/CIM and ICUAW. Nevertheless, electrodiagnostic testing is an essential tool in evaluating profound weakness in the ICU setting, which can guide the clinical team in determining further management.[149]

ICUAW is clinically defined using the Medical Research Council (MRC) scale to assess strength in functional limb muscle groups when weakness cannot be explained by an alternative diagnosis.

There is no clear evidence whether ICUAW can be adequately measured using PNS. Evaluation of these measurements should be approached with caution[153] (Table 4).

Table 4 Funding Situation, Potential Conflicts of Interest in Cited Articles

Cited Article	Financial Support/Funding/Conflict of Interest
Neuromuscular Blockade.	No relevant financial relationships with ineligible companies
Depolarizing Neuromuscular Blocking Drugs.	No relevant financial relationships with ineligible companies
Succinylcholine Chloride.	No relevant financial relationships with ineligible companies
New Drug Developments for Neuromuscular Blockade and Reversal: Gantacurium, CW002, CW011, and Calabadion.	No conflict of interest
Peripheral Nerve Stimulation/Train of Four (TOF) Monitoring	Financial support not mentioned
Navigating Anesthesia: Muscle Relaxants and Reversal Agents in Patients with Renal Impairment.	None declared
Impact of Liver Disease on Use of Muscle Relaxants in Anesthesia: A Comprehensive Review.	None declared
The Influence of Acid-Base Balance on Anesthetic Muscle Relaxants: A Comprehensive Review on Clinical Applications and Mechanisms.	None declared
Methods for Clinical Monitoring of Neuromuscular Transmission in Anesthesiology - A Review	None declared
Management of Neuromuscular Blocking Agents in Critically Ill Patients with Lung Diseases	No external funding. P.R.M.R. was supported by the Brazilian Council for Scientific and Technological Development (408124/2021-0) and the Rio de Janeiro State Research Foundation (E-26/010.001488/2019).
Problems during hospitalisation of morbidly obese patients in intensive care units: a narrative review.	Research was funded by the authors.
Neuromuscular blocking agents in the intensive care unit.	Research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.
Neuromuscular blocking drugs in the critically ill.	No interests to declare

(*Continued*)

Table 4 (Continued).

Cited Article	Financial Support/Funding/Conflict of Interest
Does succinylcholine have a future in anaesthesiology?	No conflict of interest
RAPID SEQUENCE INTUBATION. THE CURRENT STATE OF KNOWLEDGE.	Not mentioned
The limits of succinylcholine for critically ill patients.	No conflicts of interest
Atracurium.	No relevant financial relationships with ineligible companies.
Evaluation of Rocuronium Continuous Infusion in Critically Ill Patients During the COVID-19 Pandemic and Drug Shortages.	No financial support for the research, authorship, and/or publication of this article
Neuromuscular Blocking Agents for ARDS: A Systematic Review and Meta-Analysis	Authors have disclosed no conflicts of interest.
Pharmacodynamics of cisatracurium in the intensive care unit: an observational study	Authors declare that they have no competing interests
THE ROLE OF MIVACURIUM IN CONTEMPORARY ANESTHESIOLOGY: A NARRATIVE REVIEW.	Research was funded by the authors.
Neuromuscular blockade management in the critically Ill patient.	None funding. The authors have disclosed potential conflicts of interest.
Guidelines on muscle relaxants and reversal in anaesthesia.	The entire guidelines process was conducted independently of any industrial funding (ie pharmaceutical, medical devices).
Peri-operative management of neuromuscular blockade: A guideline from the European Society of Anaesthesiology and Intensive Care.	The work was funded exclusively by ESAIC. The authors have disclosed potential conflicts of interest.
2023 American Society of Anesthesiologists Practice Guidelines for Monitoring and Antagonism of Neuromuscular Blockade: A Report by the American Society of Anesthesiologists Task Force on Neuromuscular Blockade.	Members disclosed all relationships (industry and other entities) that might pose a conflict of interest. Members with conflicts of interest related to particular recommendations did not participate in the formulation, discussion, or approval of the relevant recommendations.
Residual Neuromuscular Block Remains a Safety Concern for Perioperative Healthcare Professionals: A Comprehensive Review.	Research received no external funding. Conflict of interest: Potential conflicts of interest has been disclosed by authors.
Neuromuscular Blockade: Summary of Recommendations. Multicenter Perioperative Outcomes Group (MPOG).	Not mentioned
GUIDELINES FOR USE OF THE PERIPHERAL NERVE STIMULATOR AND TRAIN-OF-FOUR MONITORING INTENSIVE CARE UNIT RAIGMORE HOSPITAL.	Not mentioned
Neuromuscular Transmission. GE Healthcare Quick Guide.	GE Healthcare
Postoperative residual curarization as a complication after general anesthesia.	None declared.
Comparison of measurements obtained with TOF-Cuff placed on the arm and the TOF-Scan on the adductor pollicis muscle during general anaesthesia using mivacurium: a prospective observational clinical trial.	None declared.
Comparing Neuromuscular Blockade Measurement Between Upper Arm (TOF Cuff®) and Eyelid (TOF Scan®) Using Mivacurium during General Anesthesia.	None declared.

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Table 4 (Continued).

Cited Article	Financial Support/Funding/Conflict of Interest
Evaluation of Neuromuscular Blockade: A Comparative Study of TOF-Cuff® on the Lower Leg and TOF-Scan® on the Ulnar Nerve During Mivacurium Anesthesia.	Funded by the Minister of Science under the Regional Initiative of Excellence Program. No conflict of interest.
Monitoring Depth of Neuromuscular Blockade	Not mentioned.
Conceptual and technical insights into the basis of neuromuscular monitoring.	Potential conflicts of interests has been disclosed by authors.
Use of the post-tetanic count to monitor recovery from intense neuromuscular blockade in children.	Not mentioned.
Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient.	Funded by the Society for Critical Care Medicine. No industry support was provided.
Considerations in Neuromuscular Blockade in the ICU: A Case Report and Review of the Literature.	No conflicts of interest.
Eliminating residual neuromuscular blockade: a literature review.	No funding. Both authors have completed the ICMJE uniform disclosure.
The latest trend in neuromuscular monitoring: return of the electromyography.	No potential conflict of interest relevant to the article.
Acceleromyography for use in scientific and clinical practice: a systematic review of the evidence.	Not mentioned
Comparison of electromyography and kinemyography during recovery from non-depolarizing neuromuscular blockade.	Study was supported by research grants from the Australasian Research Institute and the Jackson Rees Research Grant of the Australian Society of Anaesthetists. The NMT EMG and KMG monitors were loaned for the duration of the study by DatexOhmeda, GE Healthcare. Authors have disclosed potential conflicts of interest.
The latest trend in neuromuscular monitoring: return of the electromyography.	No potential conflict of interest relevant to the article was reported.
Neuromuscular block management: evidence-based principles and practice.	Potential conflicts of interest has been disclosed.
Comparison of relaxometry between ulnar nerve and posterior tibial nerve after cisatracurium administration using electromyography.	None declared
Electrodiagnostic Evaluation of Critical Illness Myopathy.	No relevant financial relationships with ineligible companies.
Safety of Needle Electromyography in Critically Ill Intensive Care Unit (ICU) Patients	Not mentioned.
Muscle relaxants in anaesthesiology, intensive care and emergency medicine, including recent reports about patients with COVID-19 infection.	No conflicts of interests.
Sugammadex.	No relevant financial relationships with ineligible companies.
Neostigmine.	No relevant financial relationships with ineligible companies
Cholinergic Medications.	No relevant financial relationships with ineligible companies
Variability in the effect of muscle relaxants. Factors involved in the pharmacodynamic profile of neuromuscular blocking agents. Part II.	Not mentioned

(*Continued*)

Table 4 (Continued).

Cited Article	Financial Support/Funding/Conflict of Interest
Residual neuromuscular block: lessons unlearned. Part II: methods to reduce the risk of residual weakness	Not mentioned
Efficacy of different doses of sugammadex after continuous infusion of rocuronium.	Authors declared no personal conflict of interest
Incidence of residual neuromuscular blockade and use of neuromuscular blocking agents with or without antagonists: A systematic review and meta-analysis of randomized controlled trials.	Funding for the work was provided by Merck & Co., Inc. Funding from Merck & Co. Inc. to conduct this study and prepare the manuscript. The sponsor collaborated on the study design, analysis, interpretation of results, and writing of the manuscript. Authors have disclosed potential conflicts of interests.
Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults.	No conflict of interest. This review was not funded.
Neuromuscular blockade reversal with sugammadex versus pyridostigmine/glycopyrrolate in laparoscopic cholecystectomy: a randomized trial of effects on postoperative gastrointestinal motility.	No potential conflict of interest relevant to this article was reported.
A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade.	Authors have disclosed potential conflicts of interests.
Comparison of sugammadex and pyridostigmine bromide for reversal of rocuronium-induced neuromuscular blockade in short-term pediatric surgery: a prospective randomized study	No potential conflict of interest relevant to this article was reported.
Multicenter trial of prolonged infusions of rocuronium bromide in critically ill patients: effects of multiple organ failure.	Not mentioned
An Evaluation of Continuous Infusion Rocuronium for Sustained Neuromuscular Blockade in Critically Ill Adults.	The authors received no financial support for the research, authorship, and/or publication of this article. No potential conflicts of interest
Comparison of the Impact of Atracurium and Cisatracurium on the Neutrophil-To-Lymphocyte Ratio in Addition to Hemodynamic Changes during Anesthesia Induction.	No conflicts of interest
Lee JH, Choi MY, Shim YH et al. The Effects of Acid-Base Imbalance on the Cisatracurium-Induced Neuromuscular Blockade in the Cat.	Not mentioned
Kim YB, Sung TY, Yang HS. Factors that affect the onset of action of non-depolarizing neuromuscular blocking agents	Not mentioned
Emergencies in obese patients: a narrative review.	No funding or sponsor of article. Authors have disclosed potential conflicts of interests.
Problems during hospitalisation of morbidly obese patients in intensive care units: a narrative review.	Research was funded by the authors. Authors report that there were no conflicts of interest.
The Dosage of Muscle Relaxants in Morbidly Obese Patients in Daily Practice - A Narrative Review.	This research received no external funding. The authors report no conflicts of interest in this work.
Impact of Rocuronium and Succinylcholine on Sedation Initiation After Rapid Sequence Intubation.	Not mentioned.
Succinylcholine versus rocuronium for rapid sequence intubation in intensive care: a prospective, randomized controlled trial.	Trial was investigator-driven and was performed without external funding. Authors declared no competing interests.

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Table 4 (Continued).

Cited Article	Financial Support/Funding/Conflict of Interest
Proportion of intensive care unit patients receiving sedation after rapid sequence intubation with rocuronium	No relevant conflicts of interest or financial relationships
Society of Critical Care Medicine Clinical Practice Guidelines for Rapid Sequence Intubation in the Critically Ill Adult Patient.	Authors have disclosed potential conflicts of interests. A formal conflict of interest policy was followed and enforced throughout the guidelines-development process.
Skeletal Muscle Relaxants and Their Impact on Intracranial Pressure in Neurosurgery.	None declared.
The role of neuromuscular blockade in patients with traumatic brain injury: a systematic review.	The authors declared that they have no conflicts of interest.
Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome.	Authors have disclosed potential conflicts of interests.
A Clinician's Guide to Management of Intra-abdominal Hypertension and Abdominal Compartment Syndrome in Critically Ill Patients	Publication costs were funded by the authors. Authors have disclosed potential conflicts of interests.
Acute respiratory distress syndrome: the Berlin Definition.	This work was supported by the European Society of Intensive Care Medicine and grant. R01HL067939 from the National Institutes of Health (Dr Rubenfeld). Dr Ferguson was supported by a Canadian Institutes of Health Research New Investigator Award (Ottawa, Canada). All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.
A New Global Definition of Acute Respiratory Distress Syndrome.	This workshop was not an Official American Thoracic Society Workshop. Therefore, it was not initiated, funded, reviewed, or approved by the leadership of the ATS.
Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries	This work was funded and supported by the European Society of Intensive Care Medicine (ESICM), Brussels, Belgium, by St Michael's Hospital, Toronto, Canada, and by the University of Milan-Bicocca, Monza, Italy. No conflicts of interest were reported.
Neuromuscular blockade is associated with the attenuation of biomarkers of epithelial and endothelial injury in patients with moderate-to-severe acute respiratory distress syndrome.	PDS and MMM were funded by the National Institute of Health (K24 hL069223) and NIH/NCATS Colorado CTSA (UL1 TR001082). DA was supported by NLM RO1 LM06910. The authors declared no competing interests.
Neuromuscular Blocking Agent Cisatracurium Attenuates Lung Injury by Inhibition of Nicotinic Acetylcholine Receptor-α1.	Not mentioned
Neuromuscular blockers in early acute respiratory distress syndrome.	Supported by the Assistance Publique–Hôpitaux de Marseille and a grant from the Ministère de la Santé (Programme Hospitalier de Recherche Clinique Régional 2004–26). GlaxoSmithKline France provided the study drugs.

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Table 4 (Continued).

Cited Article	Financial Support/Funding/Conflict of Interest
Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome.	Supported by grants (U01HL123009, U01HL122998, U01HL123018, U01HL123023, U01HL123008, U01HL123031, U01HL123004, U01HL123027, U01HL123010, U01HL123033, U01HL122989, U01HL123022, and U01HL123020) from the National Heart, Lung, and Blood Institute. Authors have disclosed potential conflicts of interests.
Neuromuscular blocking agents for acute respiratory distress syndrome.	No funding was received for this manuscript. The authors of this manuscript have no conflicts of interest or financial interests to disclose.
Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome;	Not mentioned
Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome	Not mentioned
Design and rationale of the reevaluation of systemic early neuromuscular blockade trial for acute respiratory distress syndrome	Supported by National Institute of Health, National Heart, Lung, and Blood Division U01 grants HL123009-01, HL123010-01, HL123004-01, HL123022-01, HL122989-01, HL123008-01, HL123027-01, HL123020-01, HL123018-01, HL123031-01, HL123033-01, HL122998-01, and HL123023-01.
Neuromuscular blocking agents in acute respiratory distress syndrome: updated systematic review and meta-analysis of randomized trials.	No conflict of interest.
To Block or Not: Updates in Neuromuscular Blockade in Acute Respiratory Distress Syndrome.	The authors received no financial support for the research and/or. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Role of Neuromuscular Blocking Agents in Acute Respiratory Distress Syndrome: An Updated Meta-Analysis of Randomized Controlled Trials.	This study was supported by grants from Medical Science and Technology Research Funding of Guangdong (grant no. A2019409), the Fundamental Research Funds for the Central Universities (grant no. 2019MS136), Science and Technology Projects of Guangzhou (grant no. 201903010097) and National Clinical Key Specialty Construction Project of China (grant nos. 2012–649 and 2013–544). The funders had no role in the study design, data collection and analysis, decision to publish, nor preparation of the manuscript. The work was not funded by any industry sponsors. Authors declared no conflict of interest
Early deep sedation is associated with decreased in-hospital and two-year follow-up survival.	Authors declared no conflict of interest
Patient Ventilator Asynchrony in Critically Ill Adults: Frequency and Types.	The contribution of Karen G. Mellott to this work was supported in part by a National Research Service Award (F31: NR009623-02) at the Virginia Commonwealth University from the National Institutes of Health, National Institute of Nursing Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Nursing Research or the National Institutes of Health.
Early neuromuscular blockade in acute respiratory distress syndrome: to personalize or paralyze?	Authors declared no conflict of interest

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Table 4 (Continued).

Cited Article	Financial Support/Funding/Conflict of Interest
Neuromuscular Blockade Monitoring in Acute Respiratory Distress Syndrome: Randomized Controlled Trial of Clinical Assessment Alone or With Peripheral Nerve Stimulation.	Authors have written conflict of interest disclosure attached to the article.
Mechanical Ventilation-induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes.	Supported by Canadian public funding agencies, including the Canadian Institutes of Health Research, the Physician Services Incorporated Foundation, and the Ontario Thoracic Society.
Lung- and Diaphragm-Protective Ventilation.	Supported by the Smart Meeting Anesthesia Resuscitation Intensive Care (SMART) Congress (Pleural Pressure Working Group Meeting, Milan, Italy) and by Early Career Investigator Award AR7-162822 from the Canadian Institutes of Health Research (E.C.G).
Neuromuscular blockade in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials.	There has been no financial support for this work that could have influenced its outcome. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that they have no competing interests.
Guidelines on the management of acute respiratory distress syndrome.	None declared.
Muscle relaxants in ARDS - The final verdict with the updated evidence.	Not mentioned
ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies.	Funding - this work was supported by the European Society of Intensive Care Medicine. Authors declared potential conflicts of interest.
An Update on Management of Adult Patients with Acute Respiratory Distress Syndrome: An Official American Thoracic Society Clinical Practice Guideline.	All committee members disclosed potential conflicts of interest and financial relationships in accordance with ATS policy.
1095: CISATRACURIUM VERSUS ROCURONIUM IN ACUTE RESPIRATORY DISTRESS SYNDROME	Not mentioned
Therapeutic effect of cisatracurium in patients with acute respiratory distress syndrome; Yanping Li	No funding provided. Authors declared no conflict of interest associated with this work.
Atracurium Versus Cisatracurium in the Treatment of Acute Respiratory Distress Syndrome. J Pharm Technol. 2023;39(5):212–217. doi:10.1177/87551225231194031	The authors received no financial support for the research, authorship, and/or publication of this article. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Efficacy and Safety of Cisatracurium Compared to Vecuronium for Neuromuscular Blockade in Acute Respiratory Distress Syndrome.	Not mentioned
American College of Chest Physicians consensus statement on the respiratory and related management of patients with Duchenne muscular dystrophy undergoing anesthesia or sedation.	Authors have disclosed potential conflicts of interests.
A Review on the Anesthetic Management of Patients with Neuromuscular Diseases.	None of the authors received any funding or support related to this work.
A Review of Muscle Relaxants in Anesthesia in Patients with Neuromuscular Disorders Including Guillain-Barré Syndrome, Myasthenia Gravis, Duchenne Muscular Dystrophy, Charcot-Marie-Tooth Disease, and Inflammatory Myopathies. 5	Funded by the Minister of Science under the Regional Initiative of Excellence Program. The authors declare that they have no conflict of interest.

(*Continued*)

Table 4 (Continued).

Cited Article	Financial Support/Funding/Conflict of Interest
Perioperative management of myasthenia gravis.	The authors declare that they have no conflict of interest.
Impact of hypothermia on the response to neuromuscular blocking drugs. Anesthesiology.	Not mentioned
Neuromuscular Blocking Agents. oks/NBK537168/	No relevant financial relationships with ineligible companies.
Neuromuscular blockade during therapeutic hypothermia after cardiac arrest: observational study of neurological and infectious outcomes.	The authors declare that they have no competing interests.
Mild therapeutic hypothermia after cardiac arrest due to acute coronary syndrome experience from the implementation of the method.	The authors declared no conflicts of interest.
The influence of mild hypothermia on reversal of rocuronium-induced deep neuromuscular block with sugammadex.	The authors declared potential conflicts of interest.
Tetanus.	No relevant financial relationships with ineligible companies.
Treatment of status epilepticus in adults: guidelines of the Italian League against Epilepsy.	Not mentioned
The Benefit of Neuromuscular Blockade in Patients with Postanoxic Myoclonus Otherwise Obscuring Continuous Electroencephalography (CEEG).	The authors declared no competing interests.
STATUS EPILEPTICUS GUIDELINE. The Walton Centre NHS Fundation Trust.	Not mentioned
Trismus during tracheal extubation as a complication of general anaesthesia - A case report.	None declared.
Critically ill patients with cancer: A clinical perspective.	The authors declared no potential conflict of interest.
The Use of Muscle Relaxants After Chemotherapy and Radiotherapy.	The authors report no conflicts of interest in this work.
Critical illness during pregnancy and the peripartum period.	Not mentioned
Obstetric Disorders and Critical Illness.	Dr. Ghada Bourjeily had grant funding number: NHLBI R01-HL130702Dr.
The Use of Muscle Relaxants in Pregnancy and Puerperium Period.	The authors report no conflicts of interest in this work.
T. Sugammadex administration in pregnant patients undergoing non-obstetric surgery: a case series. Braz J Anesthesiol. 2022;72(4):525–528. doi:10.1016/j.bjane.2021.07.034	The authors declared no conflicts of interest.
Pharmacodynamic interactions between muscle relaxants and other medications in practice of anesthesia.	None declared.
Delayed return of neuromuscular conduction as an adverse effect of myorelaxants combination – a case report.	The authors declared no conflicts of interest.
Eliminating residual neuromuscular blockade: a literature review.	None funding
Fixed dilated pupils in Covid-19 ARDS patients under rocuronium, reversed after discontinuation.	None declared

(*Continued*)

Table 4 (Continued).

Cited Article	Financial Support/Funding/Conflict of Interest
ICU-Acquired Weakness.	S. E. J. was supported in part by the National Institute of General Medical Sciences of the National Institutes of Health [Grant 1 U54 GM104940], which funds the Louisiana Clinical and Translational Science Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
Molecular mechanisms of intensive care unit-acquired weakness.	S. Bloch was funded by the UK Medical Research Council. The project was supported by the National Institute for Health Research Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College (London, UK).
Intensive care unit-acquired weakness.	Authors declared no conflicts of interest.
The effect of neuromuscular blocking agents uses in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials.	The authors certified that there was no conflict of interest with any financial organization regarding the material discussed in the manuscript.
A framework for diagnosing and classifying intensive care unit-acquired weakness.	Not mentioned
Electromyography and nerve conduction studies in critical care: step by step in the right direction.	Authors declared no conflicts of interest.
Electrophysiology of neuromuscular disorders in critical illness.	Not mentioned
A guided approach to diagnose severe muscle weakness in the intensive care unit.	Authors declared no conflicts of interest.
ICU-Acquired Weakness: A Rehabilitation Perspective of Diagnosis, Treatment, and Functional Management.	Not mentioned
Editorial: Intensive care unit acquired weakness: potential role of medical nutrition treatment quantity, timing, and composition.	The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Critical illness polyneuropathy and myopathy: a systematic review.	None declared.

Notes: How factors such as comorbidities, age, and homeostasis disturbances influence the efficacy and potency of these drugs.
Abbreviations: ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

Conclusions

The use of NMBAs undoubtedly has its application in patients in the ICU. However, there are still no clear guidelines and algorithms indicating when and which drug is best to use in a given situation. Often, the choice of appropriate treatment remains individualized based on the clinical situation and need. There are still debates regarding the use of muscle relaxants in the course of ARDS. It seems that in the case of ARDS, respiratory asynchrony, and the "patient-ventilator conflict", particularly in the presence of recurrent hypoxemia or hypercapnia, performing a short-term neuromuscular blockade (preferably using cisatracurium) may be a potential course of action.

Also in other situations, such as abdominal compartment syndrome, post-traumatic brain injury/increased intracranial pressure, severe muscle spasms in the course of tetanus, or therapeutic hypothermia, there is no clear consensus regarding the optimal choice of muscle relaxant. Further research is needed to better tailor drug selection to specific clinical scenarios. In cases of increased intracranial pressure, atracurium and cisatracurium appear to be potentially good choices. In patients with neuromuscular disorders and myopathies, succinylcholine should not be used; if muscle relaxation is

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necessary, a non-depolarizing skeletal muscle relaxant should be chosen, and neuromuscular blockade should be monitored using TOF.

In cases where RSI is required, the drugs currently used are succinylcholine and rocuronium. In pregnant women undergoing RSI, both of these agents can be used to perform the procedure. However, when using succinylcholine or mivacurium in pregnant women, it is important to consider possible changes in the duration of action due to altered plasma cholinesterase activity, depending on the stage of pregnancy.

In obese patients, the dose of muscle relaxants should be adjusted to ideal body weight or adjusted body weight (Box 2).

It is important to remember that conditions such as impaired liver or kidney function, as well as acid-base imbalances, will affect the duration of action of NMBAs.

When using neuromuscular blockade, its depth should always be monitored using TOF (Train-of-Four). Current guidelines emphasize the need for monitoring with quantitative methods. These methods are still not widely adopted in ICU settings. The introduction of peripheral nerve stimulators (PNS) for clinical assessment of blockade has led to a decrease in the incidence of prolonged muscle recovery.

We would like to emphasize that when using NMBAs in the ICU, it is important to ensure adequate sedation levels and proper patient care, including appropriate eye lubrication to prevent ulcers, pressure ulcer prevention, thromboprophylaxis, and physiotherapy with passive exercises to limit muscle atrophy.

Future Directions

Further high-quality studies, particularly those involving large patient populations, are needed to evaluate the use of muscle relaxants in the context of Intensive Care Units. Questions remain regarding the long-term impact of these drugs on health, as well as their effects on kidney and liver function. Clear, evidence-based guidelines on when to use muscle relaxants in the ICU are currently lacking (Box 3).

The use of quantitative methods for monitoring neuromuscular blockade remains uncommon in ICU settings. Research into determining the best monitoring methods and their optimal timing for ICU patients is crucial.

With the advent of new devices and technologies, these methods should become increasingly accessible in ICU environments. Utilizing quantitative monitoring in ICUs is essential, as it can help reduce complications, minimize drug dosages, and lower costs associated with excessive drug use.

Box 2 Clinical Situations in Which the Potential Usage of Muscle Relaxants in the ICU Is Actually Considered

The need for intubation, particularly in the Rapid Sequence Intubation protocol
Facilitating procedures or transfers/transport of the patient
In mechanically ventilated patients with early ARDS and patient-ventilator asynchrony, hypoxemia/hypercapnia, who experience significant difficulties in setting ventilation parameters
In cases of tetanus, where better control of muscle contractions is required to improve patient ventilation
Status epilepticus
Therapeutic hypothermia
Increased intracompartmental pressure/abdominal compartment syndrome

Box 3 Key Areas That Require Further Exploration

The effects of specific muscle relaxants on intracranial pressure (including in ICU patients).
The use of muscle relaxants in therapeutic hypothermia, especially following cardiac arrest resuscitation.
The role of muscle relaxants in ARDS treatment.

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