Review article

Recurrence of neuromuscular blockade after sugammadex reversal of rocuronium: mechanism, stoichiometry, high-risk populations, and dosing evidence

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Sugammadex is increasingly used as the primary antagonist for rocuronium-induced neuromuscular blockade and has reduced, but not eliminated, residual paralysis. A small but continuing series of reports describes a different failure: adequate recovery of the train-of-four ratio followed by a secondary decline in neuromuscular function, sometimes more than an hour later and occasionally after a recommended dose. Sugammadex encapsulates rocuronium in a 1-to-1 ratio, and binding occurs only in plasma. Sustained reversal therefore depends on the molar relationship between the administered dose and the rocuronium remaining in the body, rather than on the milligram-per-kilogram dose. At or above molar equivalence, no uncaptured rocuronium remains, and recurrence is mechanistically excluded while free sugammadex remains in excess; below equivalence, a free fraction persists whose effect is the product of that fraction and the residual burden. A weight-based dose is fixed, whereas the burden varies, concentrating risk where the burden is large or the dosing weight is small: prolonged infusions and repeated boluses, deep block, advanced age, renal impairment, and ideal-body-weight dosing in obesity. Randomized dose-finding trials reported recurrent block almost exclusively in the lowest-dose groups, and a dosing-weight trial reproduced it by reducing the dose alone. Neither 2023 guideline addresses dosing after prolonged infusion or the duration of subsequent observation. Reported events have occurred up to about 100 minutes after reversal, usually without quantitative monitoring. We propose estimating the burden, dosing above equivalence with a margin for uncertainty, and continuing measurements beyond the first confirmed recovery.

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Keywords: Neuromuscular blockade; Neuromuscular monitoring; Renal insufficiency; Rocuronium; Sugammadex

Introduction

Reversal practice aims to prevent residual neuromuscular blockade, which remains common when recovery is assessed using clinical signs alone and is associated with hypoxemia, upper airway obstruction, reintubation, and postoperative pulmonary complications [1,2]. Sugammadex was introduced to address this problem. This modified gamma-cyclodextrin antagonizes rocuronium by encapsulating the free drug in plasma [3]. It reverses even profound block within minutes without requiring spontaneous recovery [4]. The 2023 guidelines from both the American Society of Anesthesiologists and the European Society of Anaesthesiology and Intensive Care favor sugammadex over neostigmine for deep and moderate block, together with quantitative monitoring [5,6]. Where available, it is increasingly used as the primary antagonist. However, its adoption has extended beyond the licensing evidence. In a multicenter analysis of 243,944 anesthetics, use of rocuronium with sugammadex increased from 4.4% to 95.2% of cases and remained the primary strategy in patients with moderate-to-severe renal impairment, outside the labeled indication [7].

A small but continuing series of reports describes a different failure: neuromuscular function recovers, the patient is extubated, and the block subsequently returns. Events have occurred after prolonged infusions in patients with low body weight despite a documented train-of-four (TOF) ratio of 1.0 [8], after low-dose reversal in patients with obesity [9], and after unmonitored reversal in older patients with renal impairment [10]. They have also occurred in children within an hour of dosing [11]. Recent reports describe respiratory arrest both on the ward and in the recovery room [12,13]. This phenomenon, usually termed recurarization, is rare; one estimate places its incidence after standard dosing at about 0.02% [8]. However, the denominator is poorly established because quantitative monitoring rarely continues beyond extubation.

This review argues that recurarization is predictable when a stoichiometric reaction is dosed against an unmeasured quantity. Because sugammadex binds rocuronium in a 1-to-1 ratio, sustained reversal depends on the molar relationship between the administered dose and the rocuronium remaining in the body. The milligram-per-kilogram dose is only a proxy for that relationship, a useful one after a single intubating bolus but a poor one after prolonged infusion. We review encapsulation pharmacology, the pharmacokinetics of the residual burden, populations in which this proxy fails, dosing trials, and the monitoring needed to detect failure. We conclude by outlining the research priorities.

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PubMed and Embase were searched from inception through August 2026 using the terms sugammadex, rocuronium, recurarization, recurrence of neuromuscular blockade, residual neuromuscular blockade, molar ratio, renal impairment, obesity, and elderly. Eligible English-language publications included randomized trials, pharmacokinetic and pharmacodynamic studies, observational cohorts, guidelines, and case reports. The reference lists of retrieved articles were also searched manually. This was a narrative rather than a systematic review: studies were selected for their contribution to the mechanistic argument, without predefined quality criteria, risk-of-bias assessment, or quantitative synthesis. Institutional review board approval and informed consent were not required because the review involved no patients and used only published data.

Definitions and what has actually been reported

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Terminological distinctions are essential because the literature groups together events with different mechanisms and remedies. Here, recurarization denotes recovery to an adequate level, conventionally a TOF ratio of 0.9, followed by a secondary decline. Three other phenomena are often given the same name. In incomplete reversal, the TOF ratio never reaches 0.9, and extubation is based on clinical signs. In reparalysis, rocuronium is administered again while sugammadex or the complex remains present [14,15]. In prolonged block, a volatile anesthetic deepens the residual block, delaying recovery rather than allowing recovery followed by its loss. Reports also use different criteria to detect recurrence. Some studies counted an event only when the TOF ratio reached 0.9 and then fell below it again; in the cardiac surgical titration study, 2 patients' ratios declined to 0.87 and 0.81 [16]. Others counted any sustained negative slope of the TOF ratio during a defined late interval, regardless of its magnitude [17]. This latter criterion detects smaller and earlier changes. Estimates based on the 2 definitions cannot be pooled, contributing to the orders-of-magnitude variation in published incidence [18]. Some case reports document recurrence quantitatively, whereas others base the diagnosis on clinical findings supported mainly by the response to additional sugammadex (Table 1).

Three circumstances recur in published events. First, the sugammadex dose is low relative to the rocuronium burden, whether because a low milligram-per-kilogram dose or a fixed vial dose is selected, or

because sugammadex is dosed using ideal body weight after rocuronium was dosed using actual body weight [9,19,20]. Second, quantitative monitoring is absent during or after reversal; a single unconfirmed reading from an uncalibrated device is considered equivalent to absent monitoring [10,21]. Third, rocuronium exposure is prolonged or repeated, through infusion or intermittent boluses, with a short interval between the final dose and reversal [8,10].

The most informative reports combine these features, each illustrating how a dose that appeared adequate in milligrams was inadequate in molar terms. In the first case, the total infused rocuronium dose exceeded the sugammadex dose on a molar basis. A 41-year-old woman with a body mass index of 17.9 received 320 mg of rocuronium by infusion over nearly 6 hours. Reversal at a TOF count of 4 used a single 200 mg vial, equivalent to 4.25 mg/kg at her weight of 47 kg and more than twice the 2 mg/kg labeled dose for that depth of block. A TOF ratio of 1.0 was confirmed before extubation, but weakness recurred about 105 minutes later and required a further 400 mg [8]. In the second case, a fixed vial dose provided a patient with obesity less than the recommended dose per kilogram of actual body weight. A woman with morbid obesity received a single 200 mg vial, equivalent to 1.74 mg/kg of actual body weight and just below the recommended 2 mg/kg. She was extubated after 1 kinemyographic reading, and the block recurred [9]. In the third case, a fixed vial dose was administered without neuromuscular monitoring. A non-peer-reviewed newsletter described 2 older Japanese patients who received repeated rocuronium boluses followed by a fixed 200 mg dose of sugammadex, without any neuromuscular monitoring. One had chronic renal insufficiency. Both experienced arrest after extubation and responded to a second dose [10]. Other reports show that recurrence can occur an hour or more after reversal, usually after monitoring has stopped. An octogenarian experienced arrest 35 minutes after ward arrival [12]. Another patient deteriorated about an hour after sugammadex, 50 minutes into recovery-room care, despite documented recovery [13]. A pediatric series reported events up to 52 minutes after dosing, prompting its authors to recommend at least an hour of observation [11].

Prospective data are limited but show a similar pattern. In a cardiac surgical titration study that continued monitoring into intensive care, 2 of 97 patients developed recurrent paralysis [16]. In another study, a low-rate sugammadex infusion was started during deep block and stopped when the TOF count reached 3. During the following 30 minutes, the TOF ratio declined again in 35% of older patients and 5% of younger

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patients, with 20 patients in each group. Renal function and the speed of spontaneous recovery, rather than age itself, contributed to these declines [17]. A trial comparing 4 with 6 mg/kg in older patients with deep block recorded 1 recurrence requiring rescue (Table 2) [22]. Table 1 summarizes the reported events.

Why the milligram dose is the wrong unit

Each sugammadex molecule encapsulates 1 rocuronium molecule. The association constant is on the order of 10^7/mol [3]. The resulting dose relationship follows from stoichiometry rather than empirical observation. Based on molecular weights of 2,178 and approximately 610, equimolarity corresponds to about 3.57 mg of sugammadex per mg of rocuronium bromide [8,23]. The relevant comparison is therefore between the moles of sugammadex administered and the moles of rocuronium present at reversal, rather than between the dose and the patient's weight.

This relationship defines a boundary rather than a graded risk. At or above molar equivalence, no uncaptured rocuronium remains available for redistribution, so recurrence is mechanistically excluded while free sugammadex remains in excess. Below equivalence, a free fraction persists. The concentration reaching the neuromuscular junction is the product of that fraction and the absolute residual burden, and the fraction itself depends steeply on the molar relationship. Thus, 2 patients receiving the same fraction of the equimolar dose have different risks if their residual burdens differ. This explains why a single milligram-per-kilogram rule cannot ensure safety on its own and why recurrence has both an upper and a lower bound. When the uncaptured amount is very large, the block never resolves, producing incomplete reversal rather than recurrence.

Two additional structural features are relevant. First, binding is confined to plasma because sugammadex neither enters cells nor reaches the neuromuscular junction. Reversal creates a gradient that draws rocuronium from the effect site and peripheral tissues into plasma, where it is captured [3,24]. The peripheral depot is therefore reversed indirectly over time, and returning drug must encounter sugammadex that remains available. Second, although highly stable, the complex is governed by a dynamic rather than instantaneous equilibrium, as population modeling has shown [25]. Dissociation has no effect while free

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sugammadex remains available to recapture released rocuronium; it matters only below equivalence, under the same condition described above.

The underlying process is universal rather than exceptional. Among 74 patients reversed with a titrated dose averaging 2.2 mg/kg, modeled effect-site rocuronium increased again after reaching its nadir in 72, but remained below the threshold for clinical weakness [26]. Recurarization represents the clinically apparent extreme of a rebound that occurs in nearly everyone and is ordinarily contained by an adequate molar margin. Fig. 1 illustrates this mechanism.

The residual burden: what a bolus hides and an infusion reveals

Rocuronium distributes into at least 2 peripheral compartments. Its burden at reversal depends much more on the administration pattern than on the total dose. Although population models differ in their parameters, they agree on this behavior [24,25,27]. After a single intubating bolus, most of the dose has undergone distribution and clearance by the time of reversal. The residual burden is therefore small, and a weight-based dose of 2 mg/kg is comfortably above molar equivalence. This safety margin reflects pharmacokinetic timing rather than a molecular excess at the time of injection.

A maintenance infusion removes this protection. Typical deep-block infusion rates are around 7 μg/kg/min, or roughly 0.4 to 0.45 mg/kg/hr. Immediately before reversal after such infusions, measured plasma rocuronium concentrations are on the order of 1 to 1.7 μg/mL and vary widely among patients [28]. Infusion loads the peripheral compartments, so the burden at reversal includes both plasma drug and the depot that will return to plasma over the following hours. Consequently, the same 2 or 4 mg/kg dose provides a lower molar ratio than it would after a bolus of the same nominal size.

Immediate reversal illustrates this principle most clearly. Antagonizing a 1.2 mg/kg bolus 3 to 5 minutes after administration requires 16 mg/kg [29,30]. In the same patient, the licensed dose is 2 mg/kg once spontaneous recovery reaches a TOF count of 2 [5]. This eightfold difference reflects the amount of drug remaining in the body, not only the depth of block. These findings do not imply that standard dosing is inadequate after infusion: after a 2-hour infusion, 4 mg/kg produced rapid recovery without recurrence in 51 patients monitored until the end of anesthesia [28]. Rather, the margin above equivalence is narrower

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and less predictable than the milligram-per-kilogram dose suggests. The same reasoning applies to repeated boluses, for which a short interval between the last dose and reversal increases concern rather than providing protection.

The residual burden can be estimated at the bedside. In 1 trial, sugammadex was dosed as a multiple of the simulated residual rocuronium amount. Reversal was reliable, with no recurrence in any molar-ratio group among patients with normal organ function [23]. Closed-loop data support this approach: simulated and measured rocuronium concentrations agreed before reversal, whereas measured concentrations were higher afterward, as expected with tissue redistribution [31]. These studies establish the principle but not its applicability to higher-risk populations, because they excluded the patients for whom it matters most.

Sugammadex is excreted almost entirely unchanged by the kidneys, with 90% to 93% of the dose recovered in urine. Its pharmacokinetics are dose-proportional across 32 to 96 mg/kg, without evidence of saturation [32]. The complex follows the same renal elimination route [33]. In severe renal failure, sugammadex clearance decreases approximately 17-fold, from 95.2 to 5.5 mL/min, and its terminal half-life increases from about 2 to 36 hours [33]. Exposure increases 2- to 5-fold across moderate and severe impairment [34], allowing the complex to persist for days. In the same patients, rocuronium clearance decreases much less, approximately 4-fold, from 167 to 41.8 mL/min [33]. This challenges the assumption that renal failure necessarily increases recurrence risk, as discussed below. Because the assay could not distinguish free from encapsulated drug, these clearance values describe total rocuronium. An additional caution applies throughout: published rocuronium models predict TOF ratio recovery earlier than is observed with electromyography [35]. Reassurance based on such models should therefore be interpreted as optimistic. Table 3 summarizes these determinants.

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High-risk populations

The populations in which recurrence has been reported are characterized by alterations of the same underlying relationships: specifically, each of the relevant mechanisms increases the residual burden, reduces the dose, or prolongs the period over which drug returns from the depot.

Advanced age

Rocuronium clearance decreases by about a quarter in patients over 70, whereas sensitivity at the neuromuscular junction remains unchanged [36]. An independent population analysis identified only one significant age covariate: transfer of drug into tissue, which increases steeply with age [27]. In the older study, the volume of distribution was smaller, rather than larger, in older patients. Thus, both datasets indicate slower disposition rather than a larger depot, and neither indicates greater junctional sensitivity. Clinically, recovery after reversal is slower, with 2.9 minutes versus 2.3 minutes required to reach a TOF ratio of 0.9 [37]. Titrating sugammadex to partial recovery requires more drug and is more often followed by a late decline, mediated by renal function rather than chronological age [17]. Increasing a fixed dose from 4 to 6 mg/kg in older patients with deep block neither accelerated recovery nor prevented recurrence [21,22].

Renal impairment

Sugammadex use is near-universal despite product-label advice against use at a creatinine clearance below 30 mL/min. Neither 2023 guideline discusses renal impairment [5-7]. Evidence on initial reversal is reassuring. In patients with a creatinine clearance below 30 mL/min, 2 mg/kg reversed moderate block faster than a cisatracurium–neostigmine strategy [38], and a meta-analysis in end-stage renal disease found no excess recurrence with standard dosing [39]. The concern is the late period rather than initial capture, but these studies could not assess it because observation ended when the TOF ratio first reached 0.9 [38,40]. Renal failure reduces sugammadex clearance proportionally more than rocuronium clearance, which alone would protect against recurrence. The reported renal cases involved low or fixed doses and absent monitoring, rather than renal failure alone [10].

Obesity and the dosing weight

Body mass index does not meaningfully affect sugammadex pharmacokinetics; exposure reflects the dose administered [41]. In a randomized trial involving patients with morbid obesity, 2 mg/kg calculated using ideal body weight resulted in slower recovery and 1 recurrence, whereas dosing using actual body weight produced no recurrence [20]. Earlier randomized comparisons expressed the same principle as dose adjustments: an ideal-body-weight calculation works only when increased to ideal body weight plus 40%

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for moderate block or to 4 mg/kg of ideal body weight for deep block [42,43]. The association with obesity therefore reflects stoichiometry, because a mismatch between dosing-weight scalars directly lowers the molar ratio.

Deep block, infusions, and repeated dosing

These exposures produce the largest and least apparent residual burdens. The dose tiers reflect this relationship: 2 mg/kg from a TOF count of 2, 4 mg/kg from a post-tetanic count of 1, and 16 mg/kg for immediate reversal after 1.2 mg/kg [5]. After a 2-hour infusion, 4 mg/kg reversed neuromuscular blockade without recurrence in all 51 monitored patients [28], indicating an adequate safety margin under those conditions. Reported failures involved longer exposures, lower doses, or both.

Low body weight and female sex

Low body weight and female sex recur in case reports, most clearly in the index infusion case [8]. Both are mechanistically plausible factors through lower absolute clearance and lower estimated creatinine clearance. However, neither has been tested as an independent covariate in a study designed for that purpose, so both remain hypotheses.

Children

Recurrence has been reported in infants and young children up to 52 minutes after dosing [11]. A separate analysis of children under 2 years identified contributing factors similar to those observed in adults [44].

Potentiating comedication

Magnesium sulfate administered after reversal reestablished measurable block in 64% of patients reversed from deep block and 73% of those reversed from moderate block [45]. Although this is not recurarization in the stoichiometric sense, it produces the same clinical presentation. Table 4 summarizes the populations, mechanisms, and practical implications.

What the dosing trials show

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Dose-finding trials identify a threshold rather than a gradient, at the point predicted by the stoichiometric argument. During deep block under sevoflurane, recurrent blockade occurred in 5 patients, all in the 0.5 and 1.0 mg/kg groups, and in none receiving 2 mg/kg or more [19]. For profound block, 1 mg/kg was inadequate, whereas 4 to 8 mg/kg produced rapid, sustained recovery supported by measured plasma concentrations [4]. The dose-response relationship under sevoflurane resembled that under propofol, although that trial also recorded recurrent block in 7 patients, including 1 after 2.0 mg/kg [46]. These low-dose groups provide the closest human analogue of deliberate substoichiometric reversal and are unlikely to be studied again.

A dosing-weight trial supports the same principle by a different approach. With the patient and block held constant, only the dose was reduced by calculating it from ideal rather than actual body weight. Recovery was slower, and 1 patient developed recurrence [20].

Titration studies demonstrate substantial variation in individual dose requirements. In cardiac surgery, 87% of patients required less than the labeled dose and 13% required more; 2 of 97 developed recurrent paralysis during prolonged monitoring [16]. Titration of a sugammadex infusion to a TOF count of 3 required more drug in older patients, 0.76 mg/kg versus 0.59 mg/kg, and one-third subsequently had a late decline in the TOF ratio [17]. Dosing as a multiple of the residual rocuronium amount reversed block without recurrence in patients with normal organ function [23]. A recent randomized trial comparing titration with labeled dosing used quantitative monitoring throughout and reduced the administered dose without increasing residual paralysis [47]. These trial conditions support the use of titration: the measurement confirming recovery, rather than titration itself, makes a smaller dose safe. Titrating to the smallest dose that produces a single recovery reading, without monitoring or a defined observation period, is indistinguishable from underdosing.

Two further observations inform the practical choice. First, pharmacokinetics provide no argument against a larger dose: exposure increases proportionally up to 96 mg/kg, elimination does not saturate, and single doses of that magnitude were tolerated by healthy volunteers [32]. This finding concerns disposition in young, healthy participants and does not justify dose escalation. It means only that objections to a larger dose require other grounds, such as cost, hypersensitivity reactions, or false reassurance from the larger

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dose. Second, a larger fixed dose cannot replace monitoring. In an underpowered trial of 33 older patients with deep block, 6 mg/kg did not shorten recovery compared with 4 mg/kg, and recurrence still occurred [21,22]. Table 2 presents the dose–recurrence evidence.

The two 2023 guidelines strongly emphasize monitoring while leaving important dosing questions unaddressed. Both recommend quantitative monitoring at the adductor pollicis and confirmation of a TOF ratio of at least 0.9 before extubation. The European guideline makes this a strong recommendation based on moderate-quality evidence and sets a threshold of 1.0 when raw, uncalibrated acceleromyography is used. Both favor sugammadex over neostigmine for deep, moderate, and shallow aminosteroid block [5,6]. The European guideline specifies the block depths at which sugammadex should be used but provides no milligram-per-kilogram recommendation [6]. The American guideline reproduces the licensed tiers: 2 mg/kg from a TOF count of 2, 4 mg/kg from a post-tetanic count of 1 to a TOF count of 1, and 16 mg/kg for immediate antagonism after rocuronium 1.2 mg/kg. It explicitly states that its evidence synthesis did not address antagonist dosing and that lower-than-recommended doses are potentially associated with reparalysis [5]. Neither document addresses the weight scalar in obesity, which the American task force identifies as a research gap; renal impairment; dosing after prolonged infusion or large cumulative exposure; or the duration of observation after reversal. The only observation interval specified is 10 minutes after neostigmine antagonism when quantitative monitoring is unavailable [5,6]. These omissions define the clinical circumstances in which reported events occur.

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Translating stoichiometry to the bedside

Quantitative monitoring is the most effective safeguard, and its deficiencies are common to reported failures. Every adequately documented event involved absent quantitative monitoring, a single unconfirmed reading, or an unreliable device at extubation [8,9,10,21]. Systematic implementation has produced corresponding improvements. A protocolized cohort had no residual paralysis (0 of 189 patients), with a 95% confidence interval of 0% to 1.9% [48]. Respiratory complications decreased by about 40% in a quality-improvement program involving 35,198 cases [49]. Because measurement noise around 0.9 is appreciable

and devices differ, the useful target is sustained recovery confirmed by repeated measurements rather than a single threshold crossing [16,35].

Estimating the burden requires little time and no cost. Before dosing, consider 5 questions: How much rocuronium was administered in total? Was it given as a single bolus, an infusion, or repeated boluses? How much time has elapsed since the last dose? What is the patient's renal function? Which weight scalar was used for rocuronium and which for sugammadex? The depth of block, measured as either a TOF count or a post-tetanic count, describes the current effect-site state but provides no information about the amount of drug remaining in the peripheral compartment [23,28,31].

The resulting principle is to dose above molar equivalence and add a margin for uncertainty in the estimated burden. Titrating instead to the smallest dose that produces a recovery reading reverses that logic. In practice, this entails choosing the higher dose tier after prolonged or deep block, dosing by actual body weight in patients with obesity, and avoiding doses only slightly above the apparent minimum after infusion [19,20]. For older patients and those with renal impairment, the evidence supports vigilance rather than escalation: standard doses achieve reversal, low doses fail more often, and a larger fixed dose has not been shown to help [17,22,37]. We propose no numerical target multiple because no evidence supports a specific value in high-risk patients.

Observation should be extended when the residual burden is large or the dose is small. Reported adult events occurred from about 15 minutes to more than 90 minutes after sugammadex, and pediatric events occurred within an hour [8,10-13]. As expert opinion rather than a guideline recommendation, we suggest at least 60 minutes of observation, with quantitative measurement where feasible, after prolonged infusion, in severe renal impairment, or whenever a low or ideal-body-weight dose is used. Rescue should be planned beforehand. In the reported cases, additional sugammadex restored function, with airway support provided as needed. Events should also be reported because pharmacovigilance is currently the only source of denominator data [10,22,50].

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Gaps and a research agenda

The principal evidence gap is the lack of a denominator. No prospective study has monitored an unselected high-risk cohort quantitatively for long enough to establish incidence. The cardiac surgical titration study, which continued monitoring into intensive care, comes closest [16]. Deliberate underdosing in frail patients cannot be studied prospectively. Model-based approaches are therefore attractive, but their predictions require validation against clinical data before they can guide dosing [35].

Definitions require harmonization because slope-based and threshold-based criteria cannot be pooled [16-18]. Bedside burden estimation has been shown feasible only in patients with normal organ function and must be extended to renal impairment, advanced age, and obesity; population models themselves disagree about age-related effects on clearance [23,25,27]. No dedicated rocuronium population model exists for severe renal failure, and the available data are partly confounded by assays that cannot distinguish free drug from the complex [33]. Female sex and low body weight recur in case reports but have not been tested as independent covariates. When examined, they were candidate terms in population models based on samples too small to exclude an effect, and both were nonsignificant [8,25,27]. Neither 2023 guideline addresses dosing after prolonged infusion or observation duration after reversal [5,6]. Device-dependent variation in the measured TOF ratio also confounds event detection and definition [18].

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Conclusion

Recurrence of neuromuscular blockade after sugammadex is uncommon but mechanistically explicable: a 1-to-1 binding reaction is dosed against an unmeasured drug quantity. Recurrence concentrates in patients with the largest and least apparent residual burden, including those receiving prolonged infusions or repeated boluses, older patients, those with renal impairment, and those whose sugammadex dose was calculated using a smaller weight scalar than that used for rocuronium. Above molar equivalence, recurrence is mechanistically excluded for as long as free sugammadex remains in excess. The practical priorities are therefore to estimate the burden, dose above equivalence with a margin for uncertainty, and continue measuring until recovery is demonstrably sustained. The evidence needed to translate this principle into a numerical target is not yet available. Prospective cohorts with quantitative monitoring continued well beyond extubation will be needed to generate it.

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Authors' contribution

The sole author performed all work, including conceptualization, the literature search, and writing.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Data availability

Not applicable.

Acknowledgments

A generative artificial intelligence tool (Claude, Anthropic) assisted with literature retrieval, drafting, and language editing. The author reviewed and verified all content, including every cited reference, and accepts full responsibility for the manuscript.

Supplementary materials

None.

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Table 1. Reported events of recurrent neuromuscular blockade after sugammadex

Report	Patient	Rocuronium regimen	Interval from last dose to reversal	Sugammadex dose	Monitoring at reversal	Time to recurrence	Outcome	How recurrence was ascertained
Duvaldestin 2010 (RCT)	Adults, deep block, sevoflurane	Bolus-based	Per protocol	0.5 or 1.0 mg/kg (5 events); none at 2 mg/kg or above	Acceleromyography	17 to 71 min (nadir)	Recovery in 62 to 98 min; 1 patient did not reach 0.9	Quantitative: acceleromyographic TOF ratio fell from 0.9 or higher to below 0.8 (protocol definition); no clinical event or rescue
Le Corre 2011	Woman, 115 kg, body mass index 48	Intermittent boluses to post-tetanic count below 5	40 min	1.74 mg/kg (actual body weight)	Kinemyography, single reading at 5 min	After extubation	Reintubation, further sugammadex	Clinical: respiratory arrest in recovery; 1 twitch on uncalibrated acceleromyography after reintubation; resolved with additional sugammadex
Lorinc 2020 (series)	4 children	Bolus	Varied	Weight-based	Variable	Up to 52 min	Recovery after further therapy	Clinical: weakness or apnea; qualitative TOF counts only; response to additional sugammadex or neostigmine
Sasakawa 2020, case 1	70 yr, chronic renal insufficiency	Repeated boluses, 240 mg total	87 min	Fixed dose of 200 mg	None	After extubation	Rescue sugammadex	Clinical: apnea requiring reintubation; subsequent TOF count of 3; resolved with additional sugammadex (non-peer-reviewed report)
Sasakawa 2020, case 2	80 yr, 61 kg	50 mg then 25 mg every 30 min	50 min	Fixed dose of 200 mg	None	15 min after extubation	Respiratory arrest, 200 mg rescue	Clinical: apnea 15 min after extubation; no monitoring at any point; breathing restored with additional sugammadex (non-peer-reviewed report)
Horrow 2021 (RCT)	Morbid obesity	Bolus	Per protocol	2 mg/kg based on ideal body weight	Acceleromyography	Post-reversal	No recurrence with actual-body-weight dosing	Quantitative: acceleromyographic TOF ratio below 0.9 more than 15 min after reaching 0.9 (protocol definition)
Dubois 2023	41-year-old woman, 47 kg, body mass index 17.9	Infusion for 5 hr 46 min plus boluses, 320 mg (6.8 mg/kg)	Infusion continued until reversal; last bolus 90 min earlier	200 mg vial=4.25 mg/kg, given at TOF count 4	TOF ratio 1.0 confirmed	105 min	400 mg rescue	Clinical desaturation and flaccidity, followed by quantitative findings: no TOF response, post-tetanic count of 3; resolved with sugammadex 400 mg
Bowdle 2023 (titration)	Cardiac surgery, 97 patients	Not detailed	Median 138 min (IQR, 66 to 269)	Titrated	Electromyography, continued in intensive care	5 min (operating room) and 45 min (intensive care)	Recurrent paralysis in 2 of 97	Quantitative: electromyographic TOF ratios of 0.87 and 0.81, without symptoms; corrected with sugammadex 50 mg
Aceto 2025 (RCT)	Older patients, deep block	Bolus	Per protocol	4 or 6 mg/kg	Quantitative	Post-reversal	1 event requiring rescue	Clinical: respiratory arrest in recovery requiring rescue sugammadex; no TOF value reported for the event

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Miura 2026	82 yr, lobectomy	189 mg total, regimen not detailed	Not stated	200 mg	Not stated	35 min afterward transfer	Respiratory arrest, rescue	Clinical: respiratory arrest with normal chest radiograph and head CT; prompt recovery with additional sugammadex
Felix 2026	68 yr, emergency laparotomy	100 mg (2 mg/kg) single dose	64 min	200 mg, TOF above 95% confirmed	Quantitative at extubation	About 60 min after sugammadex, 50 min into recovery-room care	Rescue	Clinical: coma and hypercapnia unresponsive to naloxone; recovery within seconds of sugammadex 200 mg; no TOF value at the event

In the right-hand column, "quantitative" indicates that recurrence was documented by a measured TOF ratio; "clinical" indicates a diagnosis based on signs, with or without a subsequent TOF count, and the response to additional sugammadex. Events identified using these different criteria are not comparable in severity or incidence.

RCT, randomized controlled trial; TOF, train-of-four; IQR, interquartile range; CT, computed tomography.

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Table 2. Determinants of the residual rocuronium burden and of sugammadex elimination

Determinant	Effect on the residual burden or the dose	Key evidence
Single intubating bolus	Most of the dose has undergone distribution and clearance by reversal; small burden, with the weight-based dose comfortably above equivalence	Ploeger 2009; Kleijn 2011
Maintenance infusion, about 0.4 to 0.45 mg/kg/hr	Peripheral depot loaded; prereversal plasma rocuronium in the microgram-per-milliliter range, with wide variability	Rex 2009; Nakanishi 2024
Repeated boluses with a short interval before reversal	Same depot effect as infusion; a short interval since the last dose aggravates the risk	Sasakawa 2020; Le Corre 2011
Advanced age	Rocuronium clearance reduced and tissue uptake increased; distribution volume not increased; sensitivity unchanged	Matteo 1993; Happ 2025
Renal impairment	Sugammadex clearance decreases about 17-fold and half-life increases to about 36 hr; total rocuronium clearance decreases about 4-fold; exposure increases 2.4 to 5.4-fold	Staals 2010; Min 2017
Obesity	Sugammadex pharmacokinetics essentially unaffected by body mass index; exposure reflects the administered dose and thus the weight scalar	Mostoller 2021
High doses	Dose-proportional exposure across 32 to 96 mg/kg, without saturation; tolerated by 12 of 13 healthy volunteers	Peeters 2010
Model prediction	Published models predict train-of-four ratio recovery earlier than it is measured	Carvalho 2023

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Table 3. High-risk populations: mechanism, evidence, and implication

Population	What changes	Evidence	Practical implication
Older adults	Slower disposition and greater tissue uptake; renal function and the speed of spontaneous recovery are the contributing factors	Matteo 1993; McDonagh 2011; Muramatsu 2018; Happ 2025; Aceto 2025	Standard dosing achieves reversal, but recovery is slower and low doses fail more often; a larger fixed dose cannot replace monitoring
Renal impairment	Complex persists for days; margin reduced below molar equivalence; late events underascertained because observation ended at initial recovery	Staals 2010; Min 2017; Oh 2024; Kim 2021; Elkhateb 2025	Standard dosing is effective; extend observation rather than withholding the drug
Obesity	Dose numerator decreases when sugammadex is dosed by ideal body weight after rocuronium was dosed by actual body weight	Horrow 2021; Mostoller 2021	Dose by actual body weight, or increase the milligram dose if ideal body weight is used (Van Lancker 2011; Loupec 2016)
Deep block, prolonged infusion, repeated boluses	Largest and least visible burden	Sparr 2007; Rex 2009; Duvaldestin 2010; Dubois 2023	Higher dose tier; avoid dosing just above the apparent minimum
Low body weight, female sex	Plausible through lower absolute clearance and estimated creatinine clearance; not tested	Dubois 2023; Muramatsu 2018	Hypothesis; heighten vigilance
Children	Events reported up to 52 min after dosing (Lorinc); repeat dosing required at a median of 7 min in infants under 2 yr (Cates)	Lorinc 2020; Cates 2024	Observe for at least 60 min
Magnesium exposure	Reestablishes block after adequate reversal through a nonstoichiometric mechanism	Germano-Filho 2023	Anticipate recurrent block; monitor after magnesium

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Table 4. Dose and recurrence in randomized and titration studies

Study	Population and block depth	Sugammadex dose	Monitoring and duration	Recurrence	Interpretation
Sparr 2007	Profound block, 3 min after rocuronium 0.6 mg/kg	1, 2, 4, 6, 8 mg/kg with plasma concentrations	Acceleromyography, 60 min	None in any arm	1 mg/kg produced inadequate recovery
Duvaldestin 2010	Deep block, sevoflurane	0.5 to 8 mg/kg	Acceleromyography	5 events, all at 0.5 or 1.0 mg/kg	Threshold between 1 and 2 mg/kg
Puhringer 2010	Moderate block, sevoflurane	0.5, 1, 2, 4 mg/kg	Acceleromyography	7 events, 6 at 0.5 mg/kg and 1 at 2.0 mg/kg	Recurrence was not confined to the lowest-dose group
Rex 2009	After an infusion of about 2 hr	4 mg/kg	Acceleromyography until the end of anesthesia; oximetry for 1 hr	None in 51	Evidence supporting dosing after infusion
Horrow 2021	Morbid obesity, moderate and deep block	2 and 4 mg/kg based on ideal versus actual body weight, plus a neostigmine group	Acceleromyography; postrecovery monitoring in 24 of 186	1 event, at 2 mg/kg based on ideal body weight	Dose by actual body weight
Muramatsu 2018	Older versus younger patients, titrated sugammadex infusion	0.76 versus 0.59 mg/kg total	Acceleromyography, at least 30 min	Late decline 35% versus 5%	Renal function and recovery speed contributed, rather than age itself
Bowdle 2023	Cardiac surgery	Titrated	Electromyography continued into intensive care	2 of 97	Individual requirements vary widely
Morita 2025	Normal organ function, 123 patients	4, 6, or 8 times the simulated residual amount	Quantitative; postreversal observation window not defined	None	Burden-based dosing is feasible
Oh 2024	Creatinine clearance below 30 mL/min	2 mg/kg versus cisatracurium with neostigmine	Electromyography, stopped at a train-of-four ratio of 0.9	None detected	Observation window too short to detect late events
Aceto 2025	Older patients, deep block, 33 patients	4 versus 6 mg/kg	Quantitative	1 event; assigned to different groups in the report's results and discussion	A larger fixed dose did not shorten recovery in an underpowered trial
Gao 2025	Mixed	Titration versus labeled dose	Acceleromyography; recovery-room checks every 5 min for at least 60 min	Residual paralysis in recovery 5.4% versus 4.9%; recurrence not an endpoint	Titration reduces the dose without increasing residual paralysis

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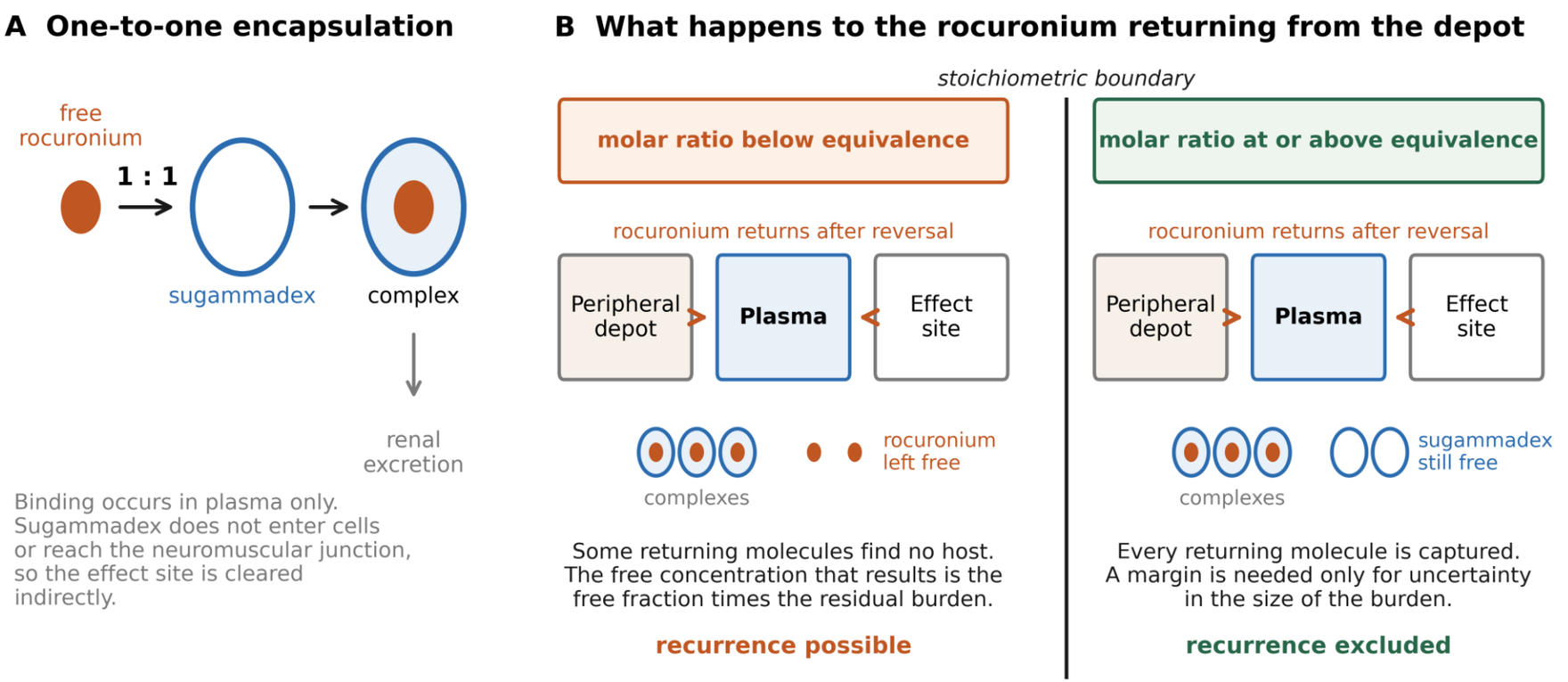


Fig. 1. Stoichiometry of reversal and the origin of recurrence. Panel (A) depicts 1-to-1 encapsulation of rocuronium by sugammadex and renal excretion of the resulting complex. Because binding occurs in plasma, clearance from the effect site and peripheral tissues is indirect, driven by the gradient created by capture. Panel (B) follows rocuronium returning from the peripheral depot after reversal under the 2 stoichiometric conditions. Below molar equivalence, some returning molecules remain uncaptured; the resulting free concentration is the product of the free fraction and the absolute residual burden, making recurrence possible. At or above equivalence, every returning molecule is captured, and recurrence is mechanistically excluded while free sugammadex remains in excess. A margin above equivalence is needed only because the residual burden cannot be estimated precisely at the bedside. The panel has no numerical scale.