

Myasthenia Gravis

Immune-mediated failure of neuromuscular transmission

Mechanism • Thymic associations • Clinical presentation • Diagnosis

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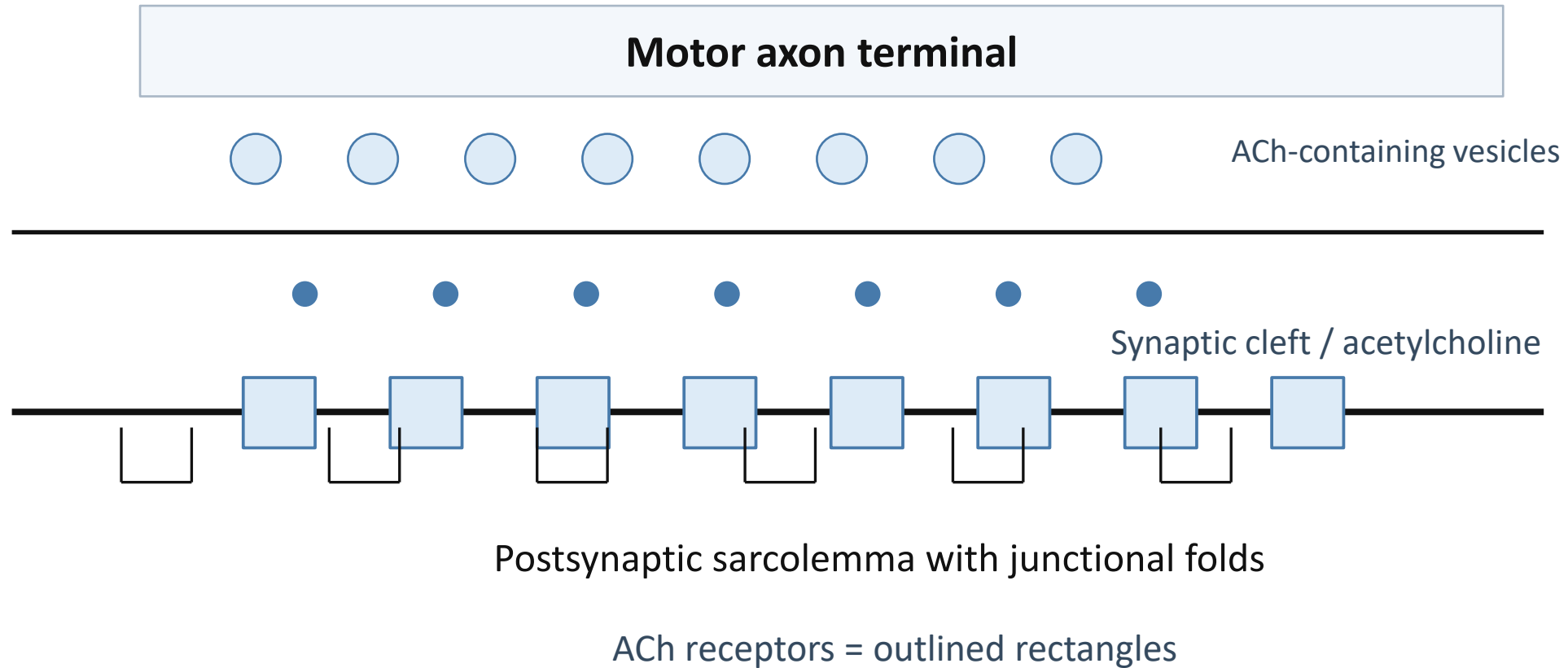
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Learning outcomes

- Localize myasthenia gravis to the postsynaptic neuromuscular junction.
- Contrast anti-AChR and anti-MuSK mechanisms without conflating them.
- Explain the relationship between thymic pathology and autoimmunity.
- Connect ocular, bulbar, and generalized weakness to diagnostic testing.
- Interpret textbook treatment principles and distinguish key mimics.

The neuromuscular junction is a specialized synapse



Schematic: Receptor symbols and spacing are illustrative, not counts or measurements.

Normal neuromuscular transmission: A causal sequence



- Presynaptic boutons face the muscle fiber across a synaptic cleft.
- Postsynaptic ACh receptors initiate the response that leads to contraction.

Postsynaptic specialization increases receptor access

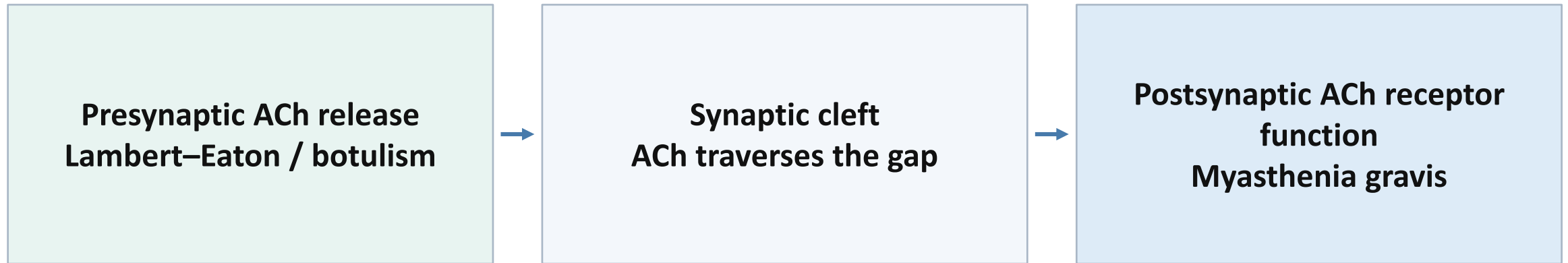
Structural feature

- Complex infoldings of the sarcolemma
- Local clustering of acetylcholine receptors

Functional importance

- Concentrates receptor sites at the end plate
- Supports reliable translation of ACh release into a muscle response

Localize dysfunction before naming a disorder



Different mechanisms can converge on painless weakness.

Myasthenia gravis: Acquired autoimmune disease

Autoantibody-mediated failure of postsynaptic ACh receptor function

The end plate receives nerve-derived ACh, but the resulting muscle response becomes less reliable.

The clinical signal is painless, fatigable weakness

- Neuromuscular-junction disorders typically produce painless weakness.
- Myasthenia gravis produces fluctuating symptoms rather than fixed deficits.
- Weakness often worsens with exertion and during the day.
- Clinical distribution depends partly on the pathogenic autoantibody.

Epidemiology: Prevalence and age distribution

Population frequency

- A prevalence of 150–200 per million.
- This estimate describes MG overall, not an antibody subgroup.

Age pattern

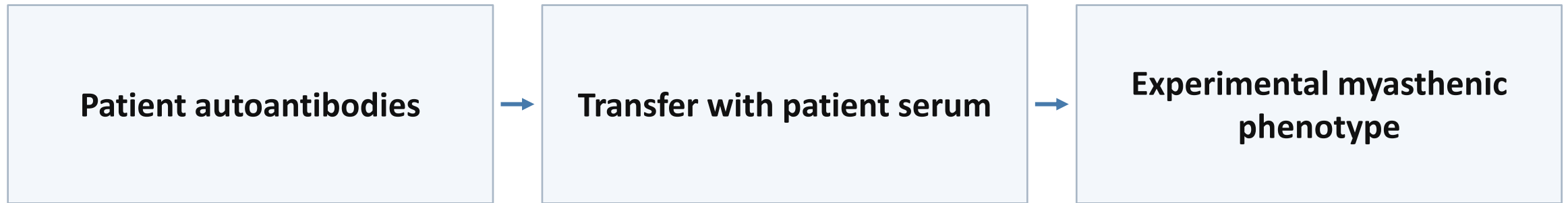
- Age at presentation shows a bimodal distribution.
- Young-adult and older-adult groups differ in sex distribution.

Sex distribution varies with age

Clinical group	Reported pattern	Interpretation
Young adults	Female : male $\approx$ 2 : 1	Female predominance
Older adults	Male predominance	The overall sex ratio is age-dependent

Age-specific pattern as stated in the Robbins source; No age cutoffs are supplied.

Autoantibodies are pathogenic, not merely associated



- Animal transfer experiments support antibody-mediated causation.
- Reducing autoantibody levels is associated with symptomatic improvement.

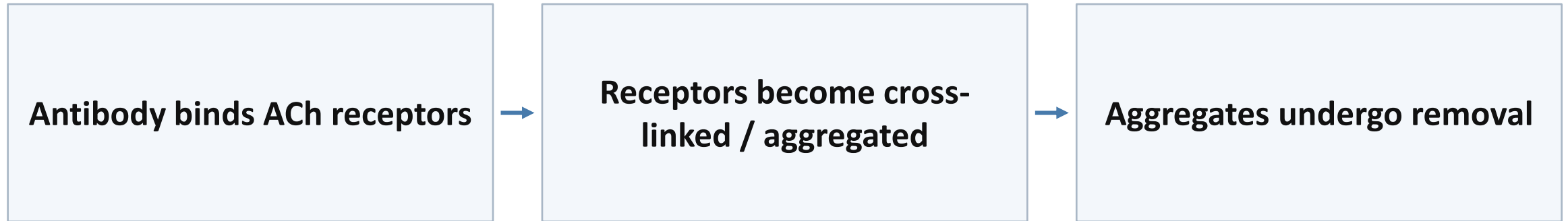
Two antibody mechanisms dominate the textbook account

Target	Site / effect	Important distinction
ACh receptor (AChR)	Postsynaptic receptor depletion + membrane damage	Complement can contribute
Muscle-specific kinase (MuSK)	Disrupted receptor trafficking and clustering	Textbook describes non–complement-fixing antibodies

Anti-AChR antibodies are the major serologic group

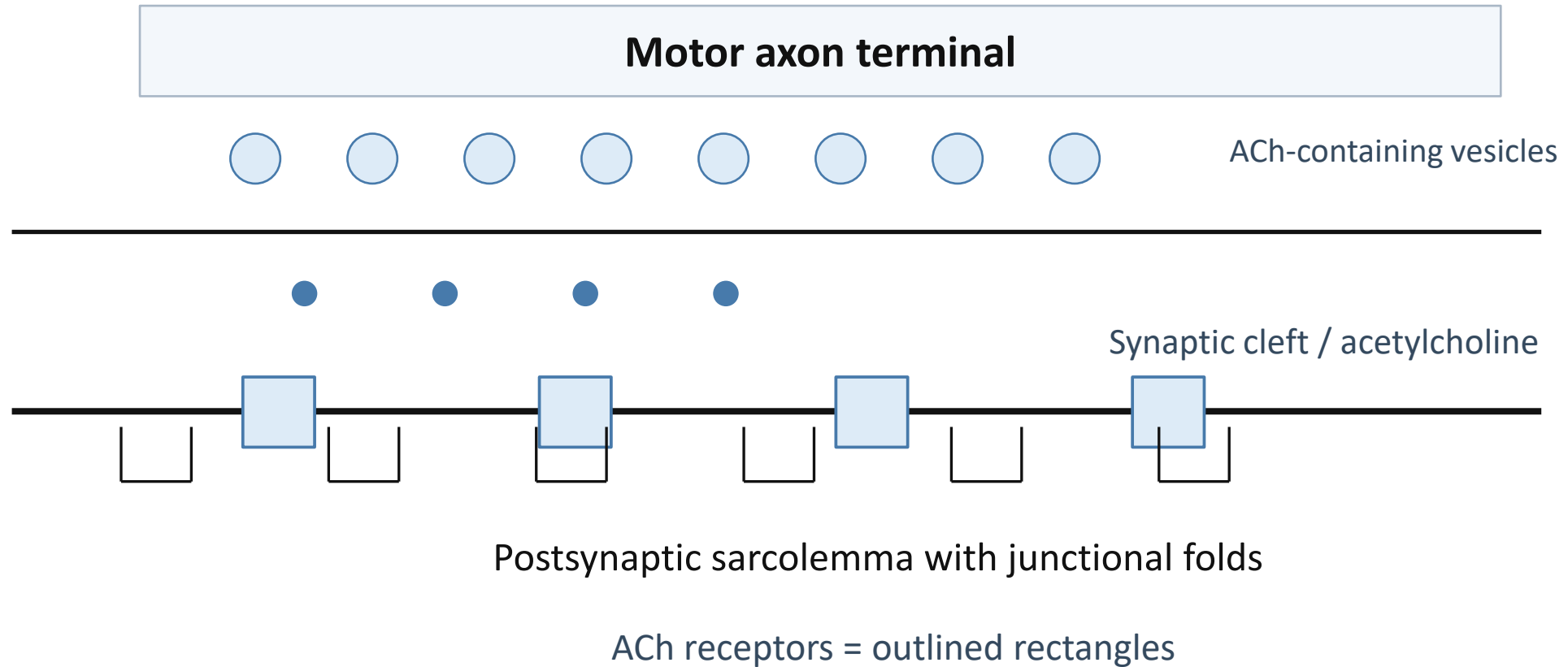
- Anti-AChR antibodies in about 85% of affected patients.
- The target is the acetylcholine receptor on the postsynaptic sarcolemma.
- Receptor-directed autoimmunity reduces effective signaling at the end plate.

Anti-AChR antibodies promote receptor aggregation



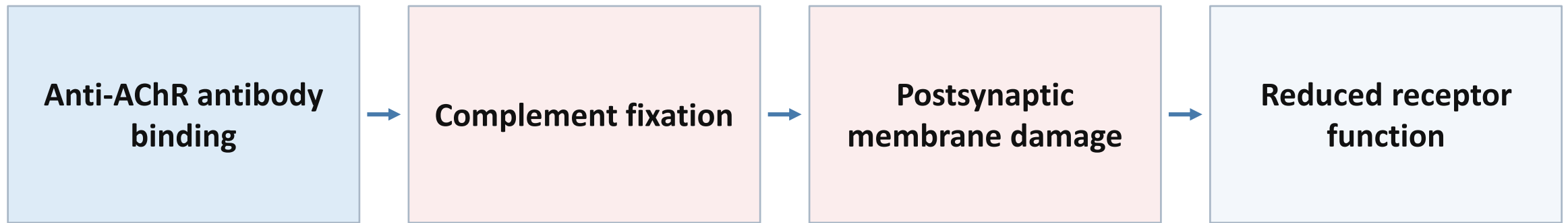
Simplified mechanism — aggregation is one of several pathogenic effects.

Receptor degradation reduces the responsive surface



Schematic: Receptor symbols and spacing are illustrative, not counts or measurements.

Complement-mediated attack injures the end plate



- Membrane injury adds to receptor loss from antibody-driven degradation.

Myasthenic postsynaptic morphology is altered

Normal end plate

- Specialized junctional folds
- Concentrated ACh receptor clusters
- Effective response to nerve-derived ACh

Anti-AChR myasthenia

- Postsynaptic membrane is morphologically altered
- ACh receptors are depleted
- Muscle response to ACh is limited

Two anti-AChR effects converge on reduced transmission



The combined effect is functional, not primary destruction of the motor axon.

Why normal ACh release may produce weakness

Presynaptic event

- Motor nerve terminal releases ACh
- ACh reaches the sarcolemma

Postsynaptic limitation

- Receptors are fewer or poorly organized
- Activation may fail despite ACh availability

Mechanistic inference from the source's receptor-depletion model.

Fatigability follows impaired transmission reliability

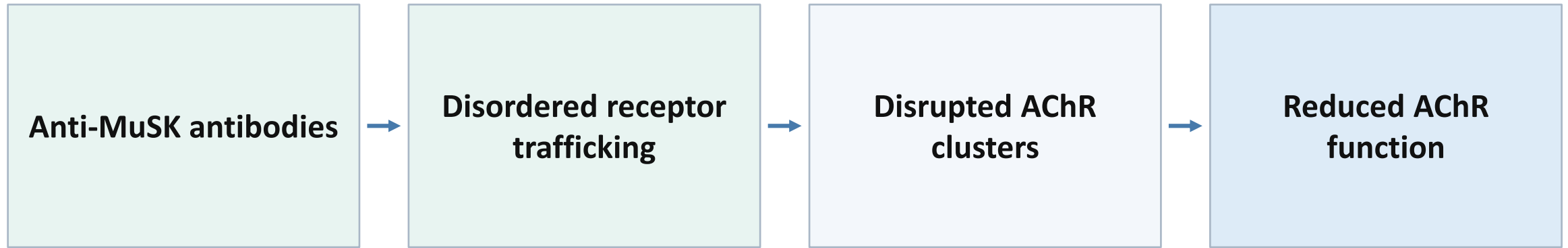


- Symptoms fluctuate and usually worsen with exertion.
- The source describes worsening later in the day as a typical pattern.

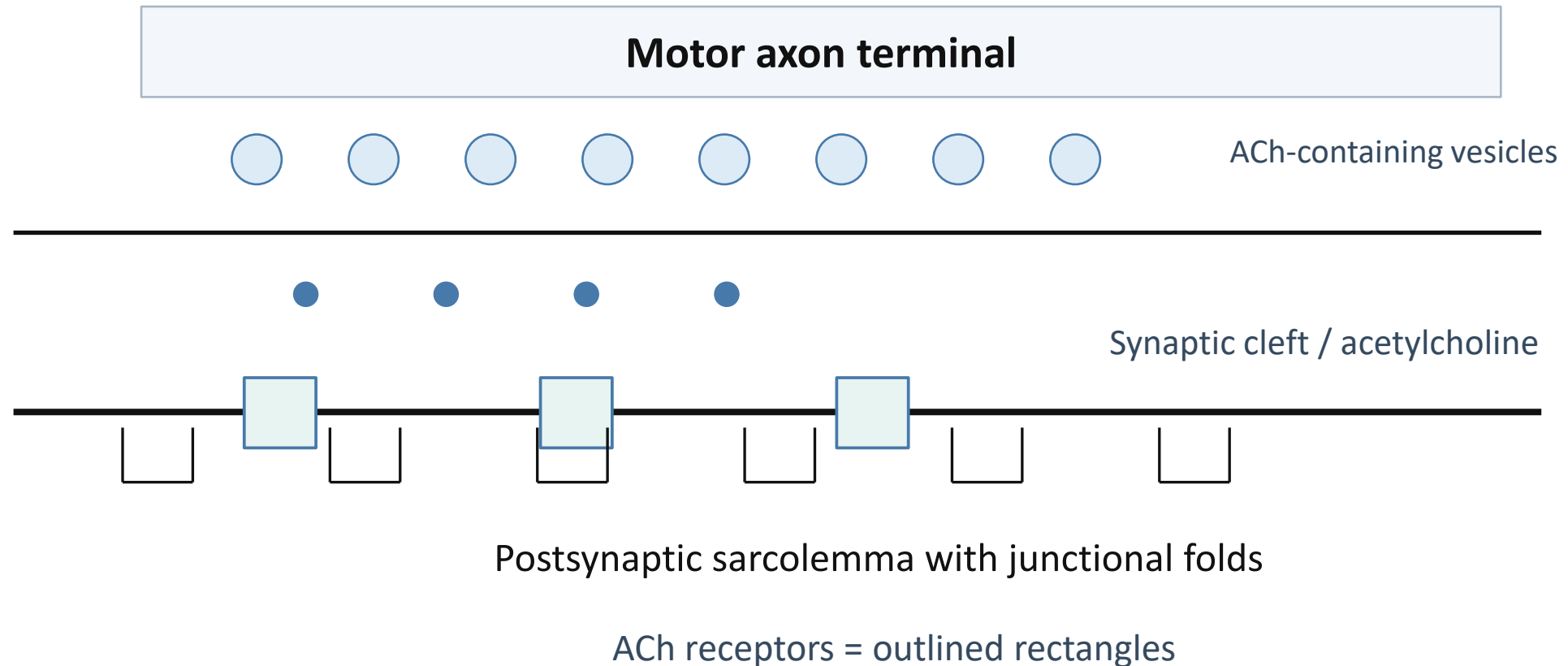
MuSK-related disease disrupts receptor organization

- Muscle-specific receptor tyrosine kinase (MuSK) is a sarcolemmal protein.
- Anti-MuSK antibodies disrupt trafficking and clustering of ACh receptors.
- This pathway impairs function without the complement-fixing mechanism described for anti-AChR MG.

MuSK antibodies: A distinct mechanistic route



Receptor distribution in MuSK-associated disease



Schematic: Receptor symbols and spacing are illustrative, not counts or measurements.

AChR and MuSK myasthenia have different pathways

Feature	Anti-AChR-associated	Anti-MuSK-associated
Primary target	ACh receptor	MuSK
Dominant mechanism	Receptor loss + membrane injury	Impaired receptor organization
Complement (source model)	Contributes to injury	Antibodies do not fix complement
Clinical emphasis	Often ocular involvement	Neck, shoulder, face, bulbar, respiratory

Different antibody targets, shared final pathway

Anti-AChR: Receptor depletion and membrane damage

Anti-MuSK: Disordered receptor clustering

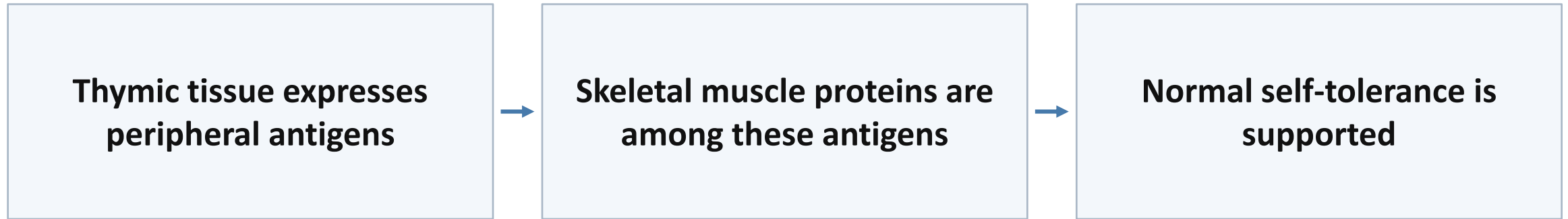
Reduced effective ACh receptor function → weakness

Convergence represents a shared functional endpoint, not identical upstream pathology.

Thymic abnormalities are linked to anti-AChR MG

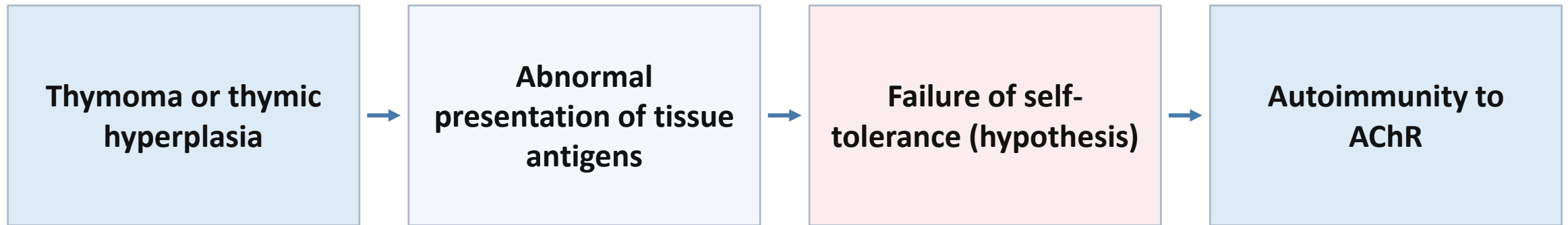
- A strong association with thymic abnormalities in pathogenic anti-AChR myasthenia.
- Two relevant conditions are thymoma and thymic follicular hyperplasia.
- The association motivates a model of impaired thymic self-tolerance.

The thymus normally exposes developing immunity to self



Sequence summarizes the textbook's thymic-tolerance rationale; Immune details are intentionally not extrapolated.

Proposed tolerance failure links thymic disease to MG



Hypothesized mechanism, not proven as a universal sequence.

Thymoma: Epithelial neoplasm associated with MG

Pathologic identity

- Tumor of thymic epithelial cells
- Thymoma in approximately 10% of MG cases

Clinical significance

- A thymic lesion can coexist with an antibody-mediated neuromuscular disorder
- Recognition affects evaluation and treatment planning

Thymic hyperplasia: B-cell follicles are a clue

Source description

- Additional approximately 30% of patients have thymic hyperplasia
- Association is particularly noted in younger patients

Morphologic teaching concept

- B-cell follicles appear in thymic tissue
- Follicular hyperplasia is not equivalent to thymoma

Distinguish thymic neoplasia from follicular hyperplasia

Feature	Thymoma	Thymic hyperplasia
Nature	Thymic epithelial tumor	Reactive follicular abnormality
Illustrative source finding	Neoplastic thymic epithelial cells	B-cell follicles within thymus
MG association in Robbins	About 10%	Additional about 30%
Histologic material in this lecture	No source photomicrograph provided	No source photomicrograph provided

Thymic association depends partly on age

Younger-onset disease

- Thymic hyperplasia is emphasized in younger patients.
- Thymic autoimmunity offers a plausible etiologic model.

Older-onset disease

- Thymic abnormalities are usually absent.
- The basis of autoantibody formation is not known account.

Association is not the same as proven causality

- Thymic changes are strongly associated with anti-AChR disease.
- Robbins frames disrupted self-antigen presentation as a hypothesis.
- The model should not be presented as the proven explanation for every patient.
- Older-onset disease illustrates an unresolved pathogenesis gap.

A clinical syndrome of fluctuating weakness

- Weakness worsens with activity in typical anti-AChR cases.
- Symptoms often intensify over the course of a day.
- Severity and muscle distribution vary between patients.
- Extraocular involvement is diagnostically informative.

Ocular involvement: Ptosis and diplopia

Ptosis

- Weakness affecting eyelid elevation
- A visible sign of ocular myasthenia

Diplopia

- Weakness of extraocular muscles
- Misalignment of ocular movements can produce double vision

Why ocular symptoms are diagnostically valuable



Ocular MG with most myopathies, where extraocular weakness is unusual.

Myasthenia may remain limited to the eyes

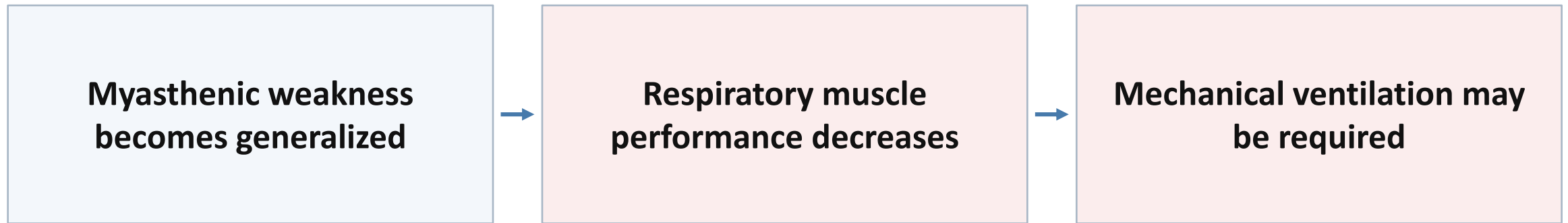
Ocular-predominant presentation

- Symptoms confined to extraocular muscles
- Ptosis and diplopia can dominate

Generalized presentation

- Weakness extends beyond ocular muscles
- Severe cases may involve breathing muscles

Generalized weakness can compromise ventilation



Potential severe consequence, not an inevitable course.

MuSK-associated myasthenia: Focal pattern matters

- MuSK cases may differ from the typical anti-AChR phenotype.
- Neck, shoulder, and facial muscle involvement.
- Bulbar and respiratory muscles are also particularly affected.
- Distribution can therefore guide targeted antibody evaluation.

Match clinical findings to the implicated muscles

Finding	Muscle region	Clinicopathologic meaning
Ptosis	Eyelid elevators	Ocular muscle weakness
Diplopia	Extraocular muscles	Ocular motor imbalance
Bulbar weakness	Bulbar musculature	Potential swallowing/speech difficulties (inference)
Respiratory weakness	Breathing muscles	Risk of ventilatory compromise

Characteristic course: Worsening with exertion



- Fluctuation is more characteristic than continuous, stable loss of power.

Clinical reasoning starts with distribution and timing

Question	Finding supportive of MG
Does strength vary over the day?	Yes: symptoms often worsen later
Is worsening linked to exertion?	Yes: use-dependent fatigability
Are ocular muscles involved?	Ptosis or diplopia is common
Is weakness painless?	Consistent with a neuromuscular-junction process

Diagnosis integrates four information streams



No single one of these elements should be treated as the entire diagnostic assessment.

Serology links phenotype to an immune target

Anti-AChR result

- Supports antibody-mediated postsynaptic MG
- Consistent with the common textbook serologic category

Anti-MuSK result

- Supports a different postsynaptic antibody mechanism
- May match a distinct muscle-distribution pattern

Electrophysiology can demonstrate decrement

Repeated nerve stimulation



Muscle response decreases



**Supports impaired
neuromuscular transmission**

Qualitative description only. No unprovided cutoffs or test sensitivity are asserted.

A decremental response has a mechanistic basis

Normal transmission

- Repetitive stimulation activates the muscle consistently
- Adequate postsynaptic receptor function

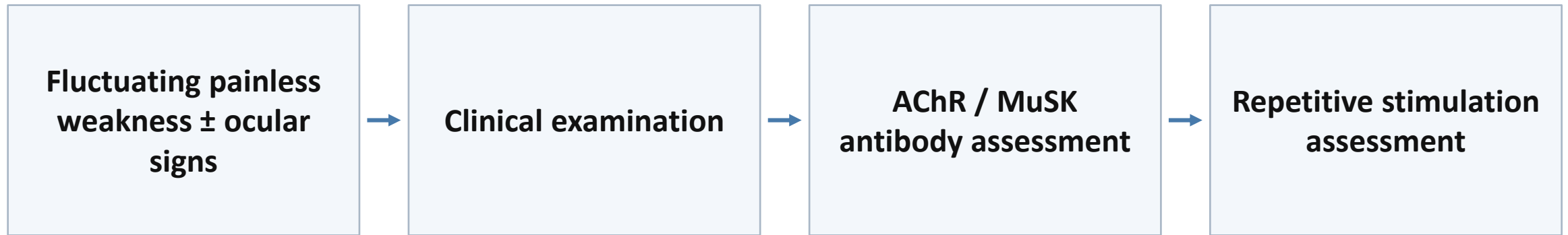
Myasthenia gravis

- The evoked muscle response may diminish with repeated stimulation
- Limited receptor function reduces effective transmission

Avoid interpreting a test without clinical context

- Compatible history suggests the neuromuscular junction.
- Clinical examination determines muscle distribution and severity.
- Autoantibodies can define the target mechanism.
- Electrophysiologic decrement provides physiologic support.

Diagnostic pathway: A source-grounded framework



Teaching framework; Not a validated clinical diagnostic algorithm.

Myasthenia gravis versus Lambert–Eaton syndrome

Discriminating feature	Myasthenia gravis	Lambert–Eaton syndrome
Primary target	Postsynaptic AChR or MuSK	Presynaptic calcium channel
With activity	Weakness tends to worsen	Strength improves after brief activity
Repetitive stimulation	Decremental muscle response	Increment with rapid repeated stimulation
Important association	Thymoma / thymic hyperplasia	Malignancy, often small-cell lung carcinoma

Why LEMS and MG respond differently to activity

Postsynaptic MG

- Fewer effective ACh receptors at the end plate
- Repeated activity exposes weakness

Presynaptic LEMS

- Autoantibodies limit calcium-dependent ACh release
- Brief activity may facilitate strength

Congenital myasthenic syndromes are not autoimmune MG

Acquired autoimmune MG

- Pathogenic AChR- or MuSK-directed antibodies
- Immune-directed treatments are mechanistically relevant

Congenital myasthenic syndromes

- Inherited defects in neuromuscular-junction proteins
- Phenotype and drug response depend on causal mutation

Ocular MG differs from most primary myopathies

Myasthenia gravis

- Ptosis / diplopia are common
- Weakness fluctuates with use
- Primary lesion is at the end plate

Most myopathies

- Extraocular muscle involvement is unusual
- Primary myofiber injury is the defining tissue level
- Clinical phenotypes vary by myopathy

AChE inhibition increases acetylcholine availability



- Acetylcholinesterase inhibitors as first-line treatment.

Immune-directed therapies address antibody production

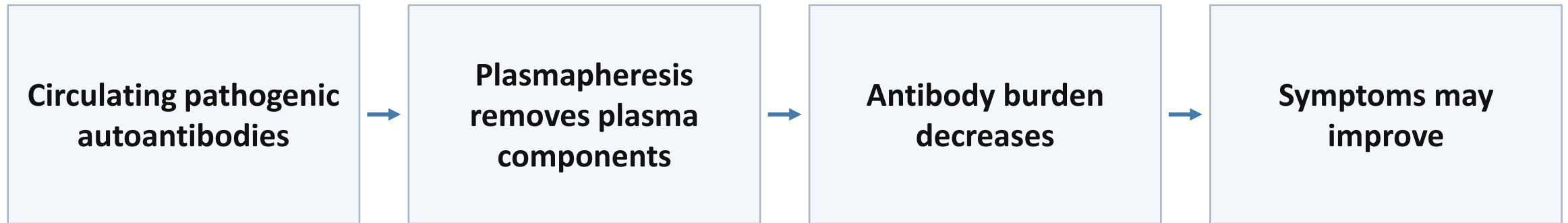
Drug classes

- Glucocorticoids
- Cyclosporine
- Rituximab

Therapeutic rationale

- Immunosuppression / modulation lowers pathogenic immune activity
- Symptom control can follow reduced autoantibody burden

Plasmapheresis directly reduces circulating factors



This is a mechanistic teaching sequence, not a procedure protocol.

Newer pathway-directed therapy follows disease biology

IgG catabolism

- An agent that increases IgG catabolism.
- Lowering IgG can lower circulating pathogenic autoantibodies.

Complement targeting

- Therapies directed at complement.
- The approach fits anti-AChR complement-mediated injury.

Treatments can be mapped to the disease mechanism

Therapeutic strategy	Mechanistic level
Acetylcholinesterase inhibition	Increases lifetime of ACh at the synapse
Plasmapheresis	Reduces circulating antibody-associated factors
Immunosuppressive medication	Reduces pathogenic immune activity
Enhanced IgG catabolism	Accelerates removal of IgG antibodies
Complement pathway blockade	Targets complement-mediated postsynaptic injury

Thymectomy: Preserve the textbook's stated uncertainty

Thymoma-associated MG

- Thymectomy as often effective in patients with thymoma.
- Thymoma itself is a thymic neoplasm.

Without thymoma

- Benefit with hyperplasia or no thymic abnormality as uncertain.
- This is textbook wording, not an updated practice recommendation.

Treatment guidance has evolved and must be verified against current practice guidelines before clinical use.

Outcomes improved as effective therapies emerged

Historical mortality

- Overall mortality above 30% in the 1950s.
- Severe weakness can compromise respiratory function.

Textbook contemporary mortality

- Less than 5% with current therapies.
- These are broad historical estimates, not subgroup predictions.

Case exercise: Painless fluctuation with ocular symptoms

Hypothetical teaching vignette

An adult develops intermittent eyelid drooping and double vision that increase after prolonged activity.

- Which anatomic compartment most plausibly explains the presentation?
- Which additional evidence would support autoimmune MG?

Case interpretation: Localize, then test



- A compatible history alone is not sufficient for etiologic classification.

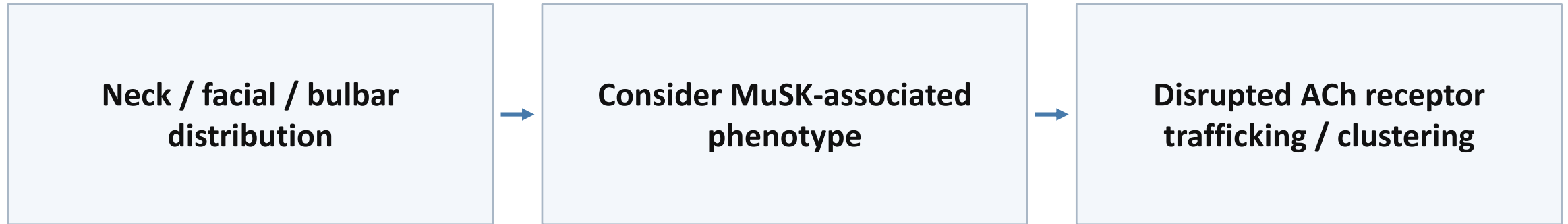
Case exercise: Selective bulbar and neck weakness

Hypothetical teaching vignette

An individual with fluctuating weakness has prominent neck, facial, and bulbar involvement.

- Which antibody subtype is emphasized by this distribution?
- How does its mechanism differ from complement-fixing anti-AChR disease?

Case interpretation: MuSK points to receptor organization



Clinical pattern is suggestive; Confirmation rests on integrated evaluation.

Case exercise: Paradoxical improvement with activity

Hypothetical teaching vignette

An adult reports extremity weakness that improves after several seconds of muscle activity.

- Which alternative NMJ disorder becomes more likely?
- Which presynaptic target and malignancy association should be recognized?

Case interpretation: Presynaptic facilitation suggests LEMS



LEMS is commonly associated with an underlying malignancy in the Robbins source.

Five mechanism-linked points to retain

- MG is an acquired autoimmune postsynaptic transmission disorder.
- AChR antibodies promote receptor loss and complement-mediated membrane injury.
- MuSK antibodies disrupt receptor clustering without complement fixation in the source model.
- Fluctuating, often ocular weakness directs serologic and physiologic evaluation.
- Thymic abnormalities and therapies illuminate—but do not fully resolve—its pathogenesis.

Primary teaching source and scope

Robbins, Cotran & Kumar

Pathologic Basis of Disease, 11th edition (2026)

Myasthenia Gravis; Diseases of the Neuromuscular Junction

Comparative details: adjacent Lambert–Eaton and congenital myasthenic syndrome sections

Treatment information summarizes a pathology textbook and is not a current prescribing guideline.