

Microvillus Inclusion Disease

Cell polarity, brush-border failure, neonatal intestinal disease

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Learning objectives

- Explain how MYO5B-associated vesicular transport maintains epithelial polarity.
- Connect brush-border disruption with neonatal intractable diarrhea and nutritional failure.
- Interpret villin, CD10 and electron-microscopic findings in suspected disease.
- Differentiate MVID from important congenital and acquired enteropathies.

Disease identity and terminology

- Microvillus inclusion disease (MVID) is also called Davidson disease.
- It is a rare inherited disorder of enterocyte membrane trafficking.
- Defective brush-border assembly causes a severe disorder of digestion and transport.
- Intracellular microvillus-bearing profiles give the disorder its name.

Where MVID fits among intestinal disorders

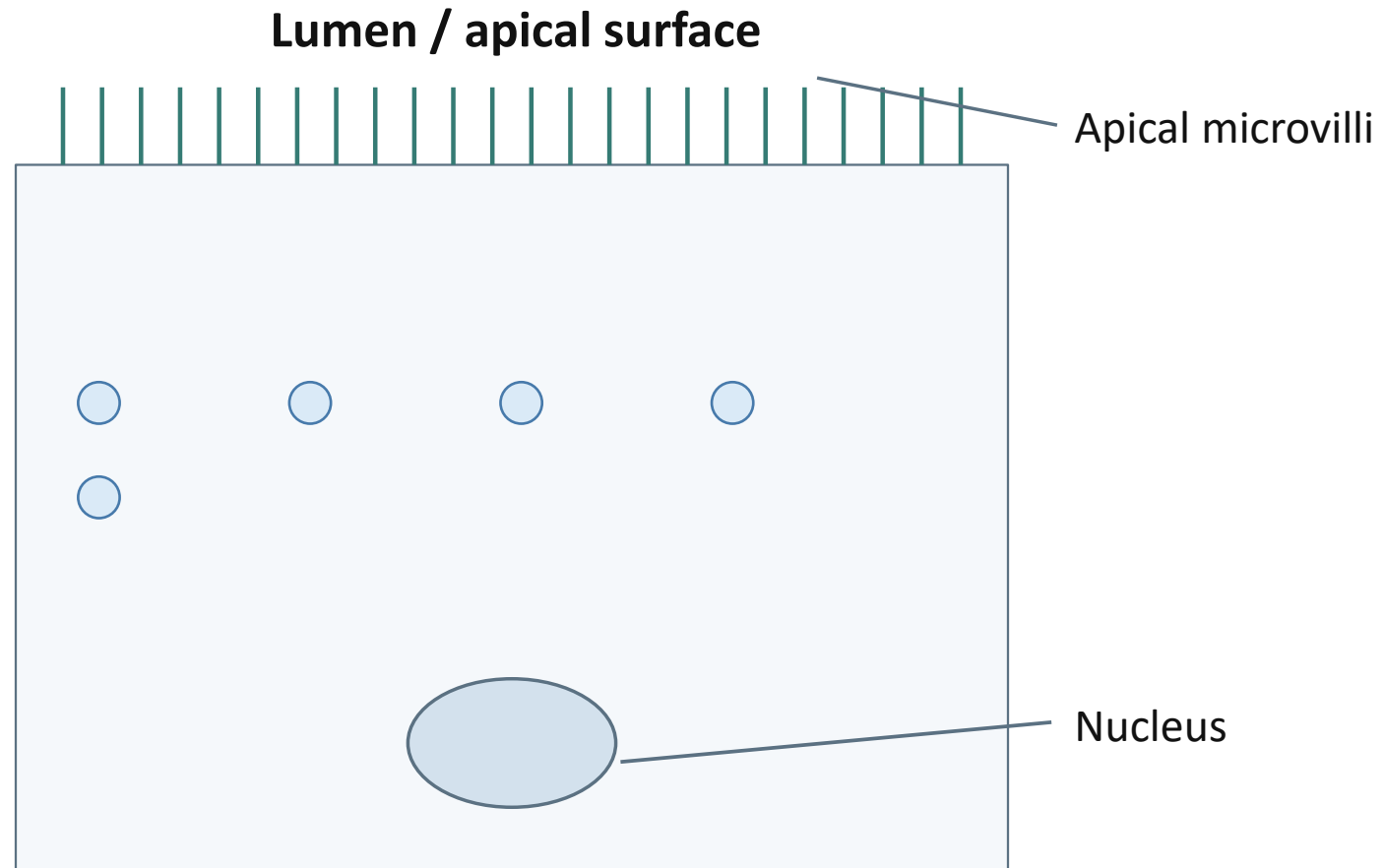
Defects of digestion or absorption

- Disaccharidase deficiency: Failed terminal carbohydrate digestion.
- Abetalipoproteinemia: Defective lipoprotein assembly.
- Celiac disease: Immune-mediated villus injury.

Defects of enterocyte polarity / trafficking

- MVID: Impaired apical membrane delivery and recycling.
- Intestinal epithelial microvilli become abnormal.
- Transport failure can be profound even without brisk inflammation.

Normal enterocyte: Brush-border architecture

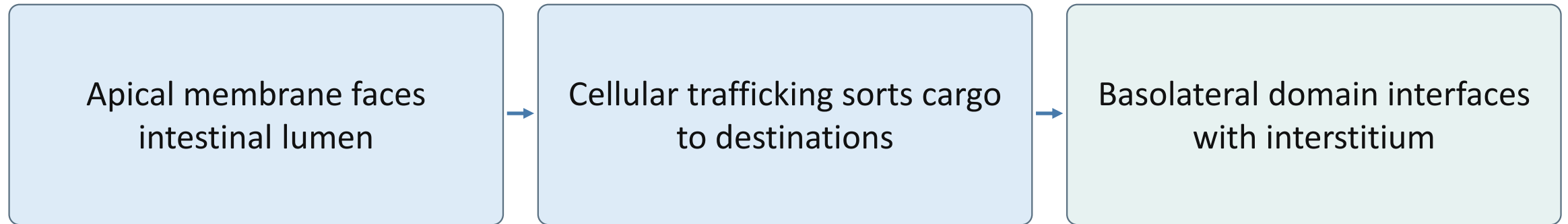


Schematic (not histology or electron microscopy)

What does an intact brush border accomplish?

- Apical microvilli increase the effective membrane surface available to the lumen.
- Membrane-localized enzymes complete terminal digestion.
- Selective transport proteins mediate electrolyte and nutrient flux.
- Microvilli require correct apical delivery and retention of membrane cargo.

A polarized enterocyte separates transport tasks



Correct localization matters as much as the presence of a transport protein.

Membrane organization and intestinal function

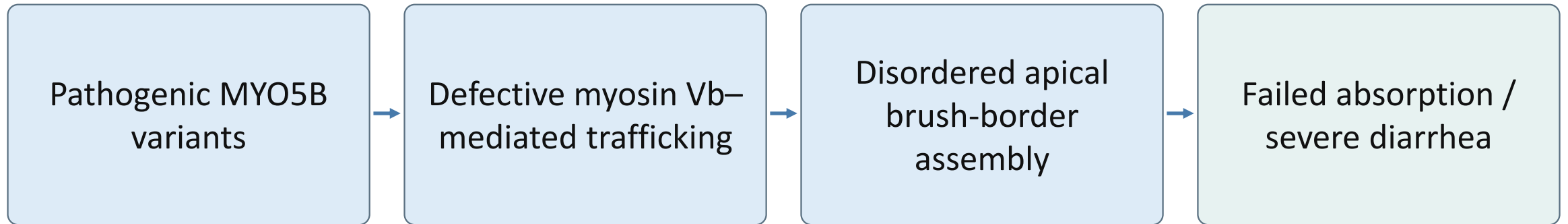
Apical compartment

- Brush border faces digested luminal nutrients.
- Contains specialized transporters and hydrolases.
- Requires continuous trafficking and renewal.

Basolateral compartment

- Supports transfer toward the interstitium.
- Maintains distinct sets of membrane proteins.
- Loss of polarity compromises vectorial transport.

Core disease mechanism

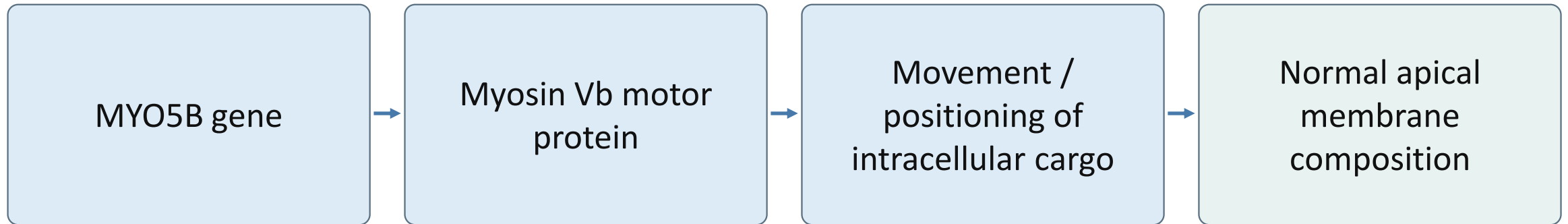


A primary cell-biological defect produces an organ-level intestinal phenotype.

Inheritance: Autosomal recessive pattern

- Classic MYO5B-related MVID follows an autosomal recessive inheritance pattern.
- Affected infants usually harbor pathogenic variants in both MYO5B alleles.
- Parents may be clinically unaffected carriers.
- The molecular diagnosis provides a basis for family counseling.

MYO5B encodes an actin-based motor

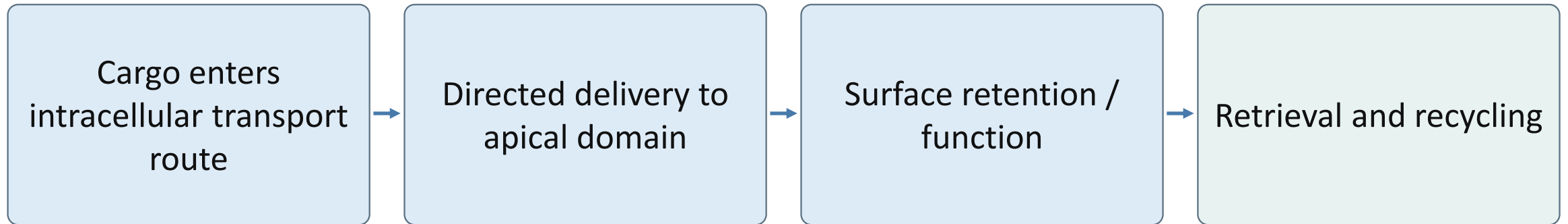


Disease-causing disruption affects membrane delivery and retrieval.

Myosin Vb is more than a structural component

- A molecular motor links membrane-carrying compartments to intracellular movement.
- Apical cargo must arrive at the correct membrane surface.
- Recycling restores or replaces membrane components after internalization.
- MYO5B disruption changes where epithelial proteins reside.

A simplified apical trafficking cycle



This diagram is conceptual; Individual vesicle routes are not drawn to scale.

RAB-associated apical trafficking context

- Experimental literature links myosin Vb with RAB8A and RAB11A transport machinery.
- This network helps coordinate delivery of selected apical membrane cargo.
- Loss of productive coupling can reproduce features of MVID in models.
- These details extend beyond the short Robbins disease paragraph.

Transport protein synthesis versus localization

Protein made but mislocalized

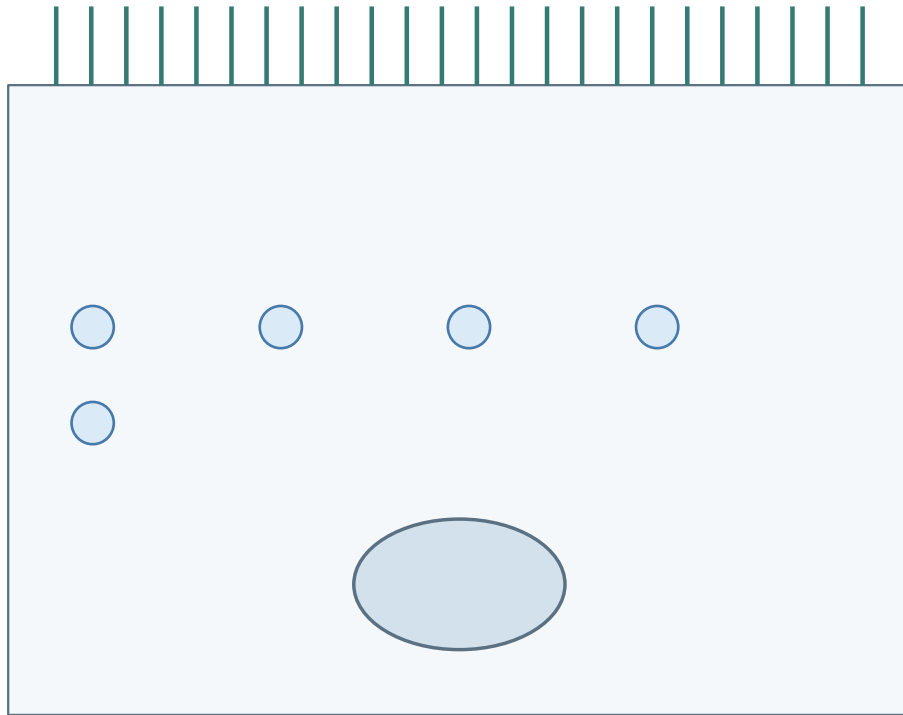
- An enterocyte may still express a transporter.
- The protein may accumulate in inappropriate compartments.
- Surface function is lost despite residual cellular expression.

Protein localized correctly

- Apical sorting delivers cargo to its functional domain.
- Vectorial electrolyte and nutrient transport can proceed.
- Organization and polarity support the epithelial barrier.

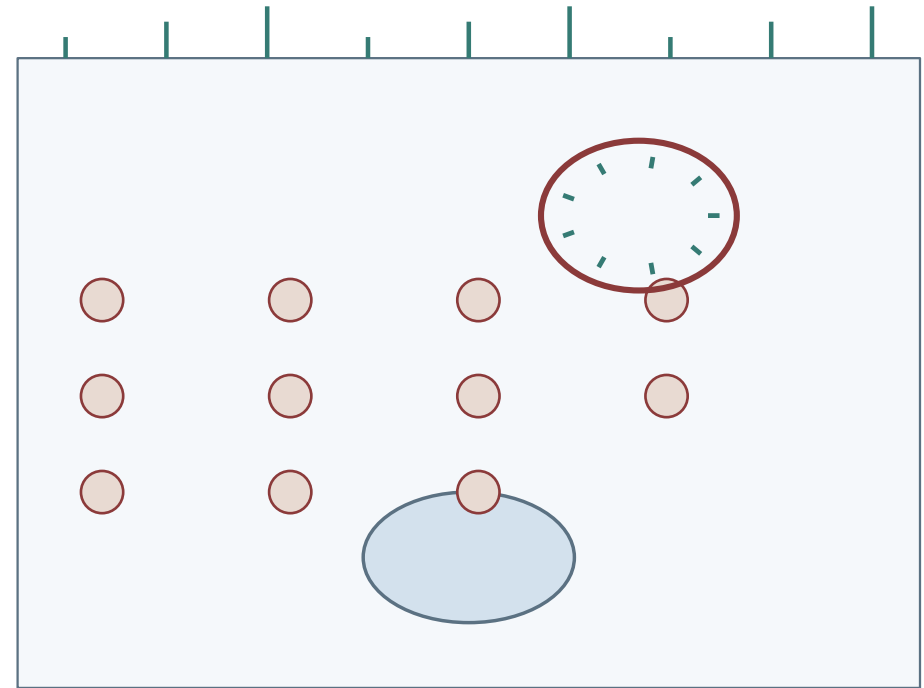
Brush-border assembly: Normal versus abnormal

Normal polarized enterocyte



Continuous apical brush border

MVID enterocyte



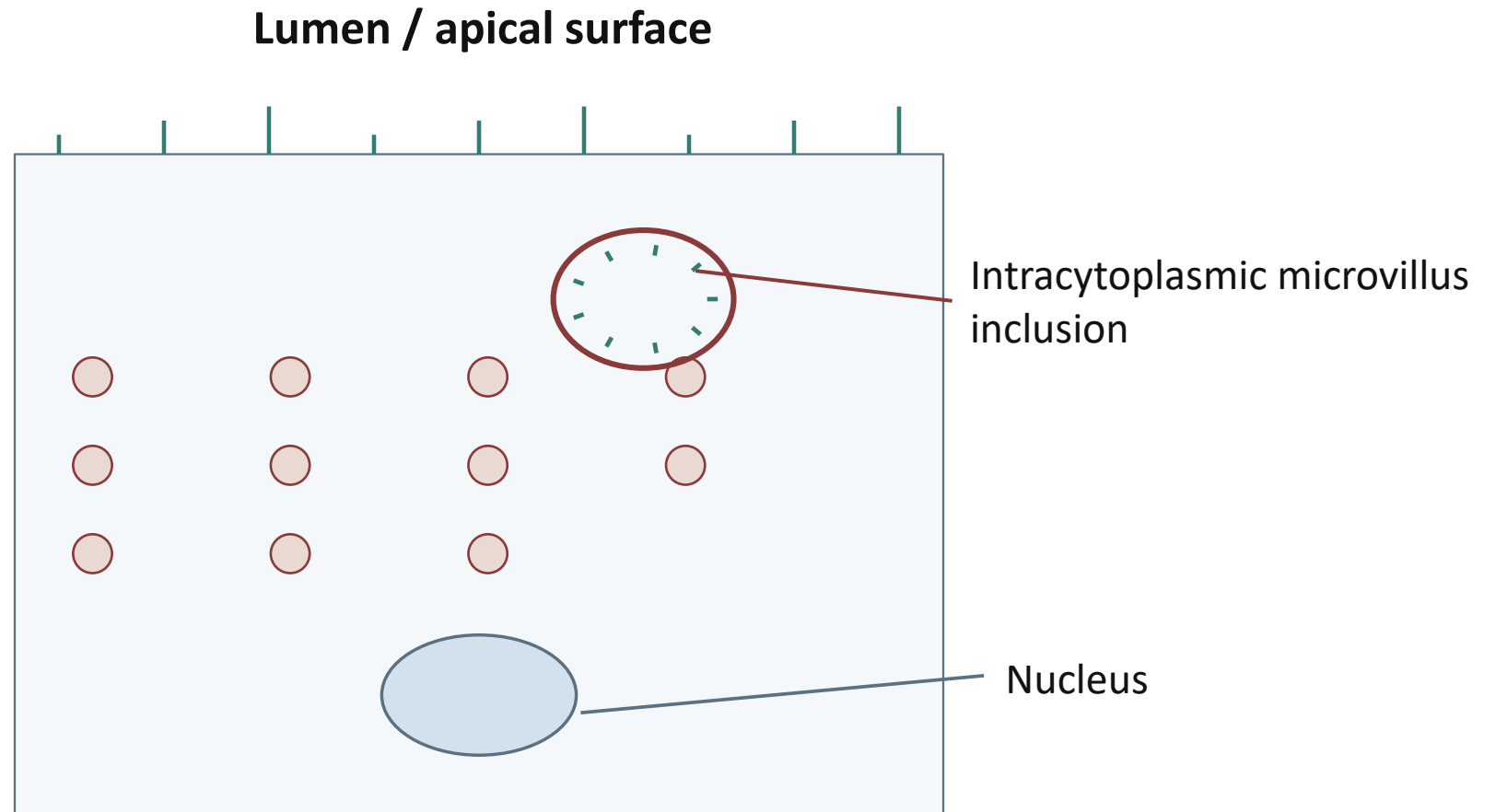
Shortened brush border + intracellular inclusion

Schematic (not histology or electron microscopy)

What does “microvillus inclusion” mean?

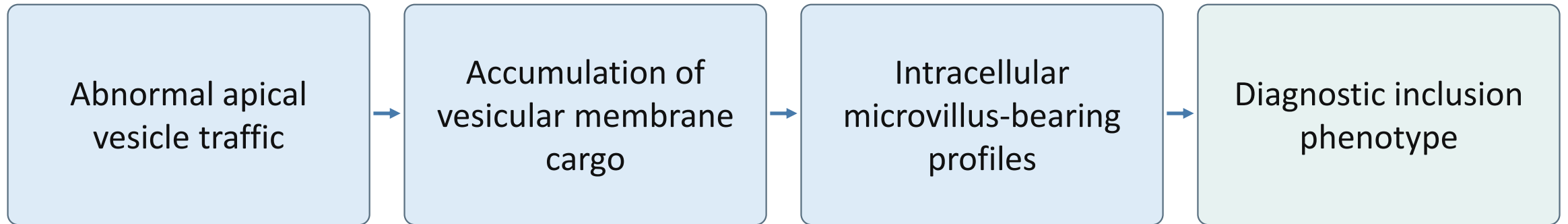
- Microvilli or microvillus-like membranes are present inside epithelial cytoplasmic profiles.
- These profiles are distinct from an intact luminal brush border.
- The source links their accumulation to defective plasma-membrane trafficking.
- Electron microscopy demonstrates their diagnostic ultrastructure.

Conceptual microvillus inclusion in an enterocyte



Schematic (not histology or electron microscopy)

From trafficking failure to inclusion formation



A mechanistic synthesis: The precise cellular origins of inclusions are complex.

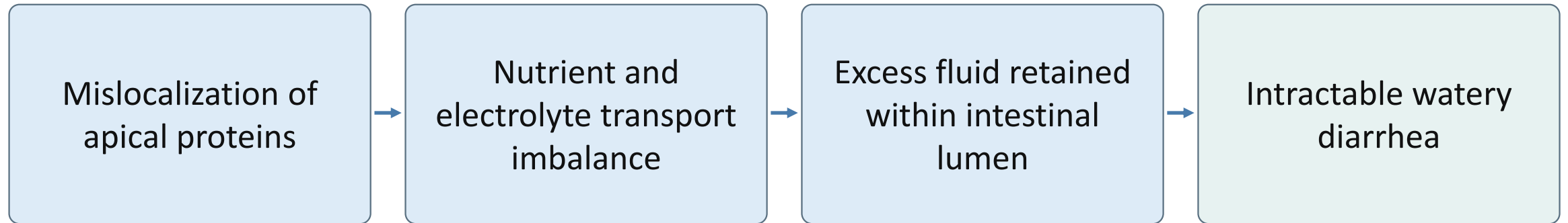
Why terminal digestion is impaired

- Brush-border membrane enzymes depend on correct apical organization.
- Disorganized microvilli diminish the functional digestive interface.
- Digestion products may not be generated or handled normally at the surface.
- Defective terminal digestion as one contributor to diarrhea.

Why transepithelial transport is impaired

- Electrolyte and nutrient handling requires properly localized membrane transporters.
- MYO5B-related trafficking disturbances alter the apical transport apparatus.
- Reduced absorptive capacity can coexist with ongoing epithelial secretory processes.
- Net intestinal water balance shifts toward severe luminal fluid loss.

Linking cell biology to diarrhea



The hallmark symptom is the physiological consequence of failed absorption/transport.

Malabsorptive and secretory features may coexist

Malabsorptive component

- Brush-border digestion and transport are deficient.
- Nutrient assimilation is inadequate.
- Growth and nutritional status are threatened.

Secretory / electrolyte component

- High-volume watery stool may persist despite restricted enteral intake.
- Ion and water transport become unbalanced.
- Severe sodium and fluid losses may occur.

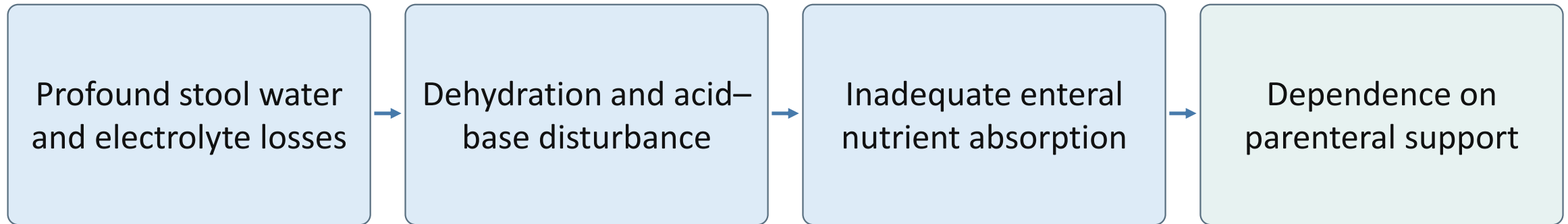
Age at onset is diagnostically informative

- Severe diarrhea before three months of age.
- Manifestations often begin within the first days of life.
- Such early onset supports investigation of congenital epithelial disorders.
- Age alone is not sufficient for a definitive diagnosis.

A typical presenting clinical pattern

- Intractable, high-volume watery diarrhea in early infancy.
- Dehydration can develop rapidly because intestinal fluid losses are continuous.
- Feeding intolerance and inability to maintain hydration/nutrition are prominent.
- The apparent severity is disproportionate to nonspecific mucosal inflammation.

Immediate consequences of intestinal failure



Clinical priorities derive directly from the physiologic deficits.

Metabolic complications: Mechanisms, not cutoffs

- Ongoing gastrointestinal losses can deplete total-body water and electrolytes.
- Metabolic acidosis is reported with severe neonatal MVID.
- Failure to establish adequate enteral nutrition threatens growth.
- Individual fluid and electrolyte management requires measured patient data.

Growth and nutritional consequences

- Severe epithelial dysfunction prevents reliable intestinal nutrient delivery.
- Failure to thrive may accompany the persistent diarrhea.
- Intravenous nutrition can maintain intake but does not repair the epithelial defect.
- Clinical care must assess hydration, nutrition and line-related complications.

Extraintestinal findings require careful attribution

- MYO5B variants can be associated with low-GGT cholestatic liver disease.
- Parenteral nutrition can independently contribute to hepatobiliary complications.
- Hepatic manifestations should not automatically be labeled treatment-induced.
- Broader genotype–phenotype relationships are evolving.

Intestinal and hepatobiliary manifestations

Enterocyte disease

- Apical trafficking disorder with microvillus inclusions.
- Profound diarrhea and malabsorption.
- Dependence on fluid and nutrition replacement.

Associated hepatobiliary disease

- Some genotypes alter canalicular transport localization.
- Cholestasis may occur independently of parenteral nutrition.
- Management requires separating genetic and treatment effects.

What routine histology may suggest

- A small-intestinal biopsy may show villus blunting or atrophy.
- Apical enterocyte cytoplasm can be vacuolated or granular.
- Surface brush-border attenuation may be patchy.
- These light-microscopic features alone are not disease-specific.

Architecture versus cell-level lesion

Mucosal architecture

- Villus shortening can accompany many enteropathies.
- Inflammatory changes and crypt responses vary.
- Overall villus morphology cannot identify MVID by itself.

Enterocyte brush-border phenotype

- Loss of normal sharp apical membrane line.
- Subapical cytoplasmic staining/vesicles.
- Internalized microvillus-containing structures.

Periodic acid–Schiff: An explanatory adjunct

- Normal apical brush-border staining tends to form a narrow luminal line.
- MVID may produce abnormal apical/subapical PAS-positive material.
- An expanded cytoplasmic band or granules can prompt closer evaluation.
- PAS cannot replace ultrastructural and molecular correlation.

Normal and MVID PAS staining patterns

Expected normal pattern

- Relatively continuous, narrow apical staining.
- Localization follows the enterocyte–lumen interface.
- No characteristic intracellular microvillus-containing band.

Abnormal MVID pattern

- Attenuated or disrupted apical line.
- Subapical/apical cytoplasmic PAS-positive accumulations.
- Pattern should trigger CD10/villin or EM correlation.

CD10 immunohistochemistry in MVID

- CD10 ordinarily accentuates the intestinal brush-border surface.
- In MVID, intracytoplasmic/apical subapical CD10-positive structures may appear.
- A broadened, irregular or misplaced CD10 pattern supports a trafficking disorder.
- CD10 is an adjunctive morphological marker, not a genotype test.

CD10: Normal distribution versus MVID

Normal enterocyte

- Fine linear surface labeling of the brush border.
- Emphasizes the luminal enterocyte margin.
- No characteristic internalized staining pattern.

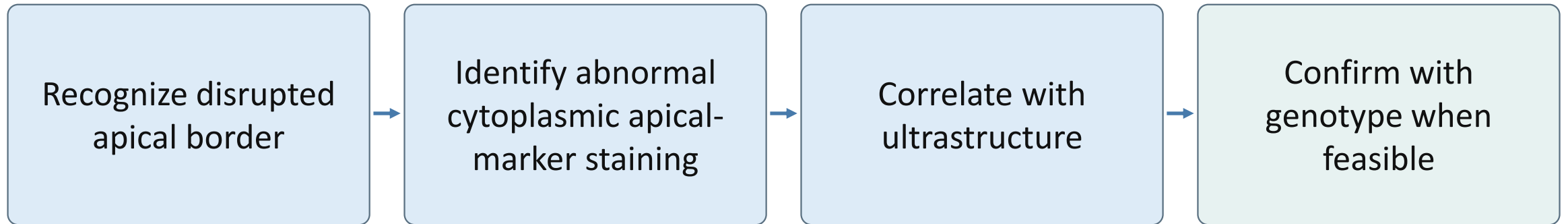
MVID enterocyte

- Abnormal apical cytoplasmic or vesicular labeling.
- Microvillus inclusion-related structures may stain.
- Distribution is interpreted with morphology and clinical context.

Villin highlights microvillus-related structures

- Villin is a brush-border-associated protein.
- Villin immunostaining can reveal abnormal internalized apical components.
- Loss of the expected crisp apical surface distribution is informative.
- The staining pattern complements CD10 and ultrastructural assessment.

Reasoning from immunostaining to diagnosis



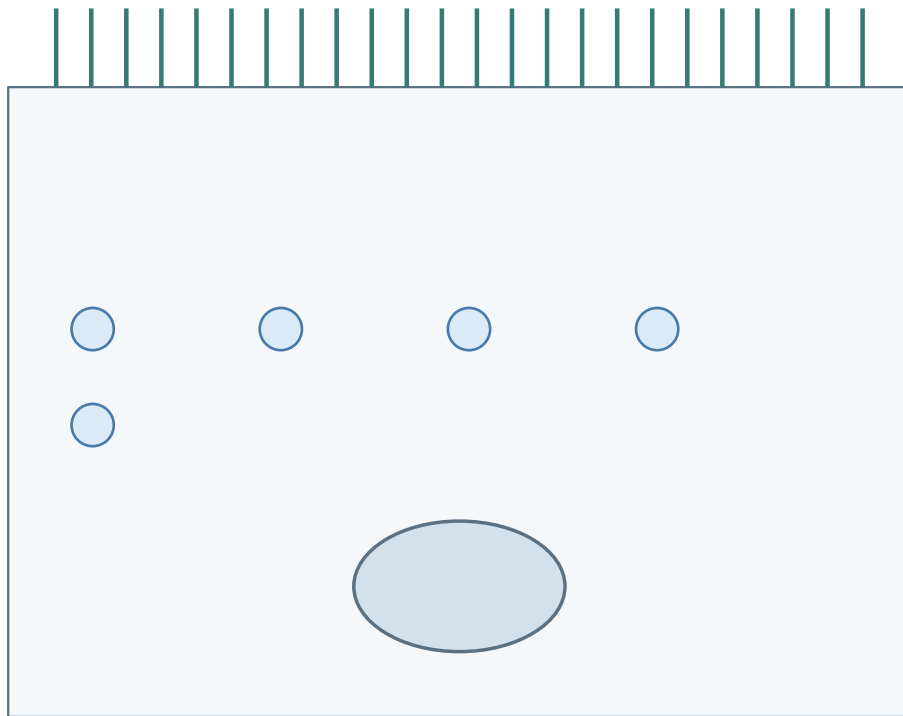
A single stained structure is not sufficient without correlation.

Electron microscopy: Defining lesion

- Enterocytes may have shortened, sparse or absent luminal microvilli.
- Intracytoplasmic inclusions are lined by microvilli.
- Abnormal apical vesicular and tubulovesicular profiles may accumulate.
- EM demonstrates topology that routine H&E cannot resolve.

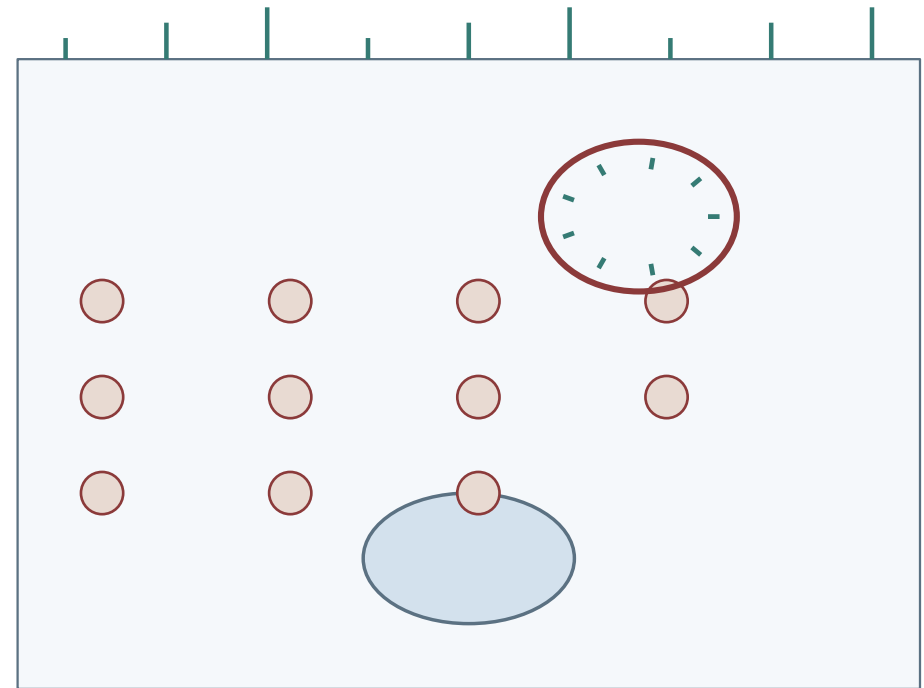
EM interpretation: Schematic ultrastructural correlate

Normal polarized enterocyte



Continuous apical brush border

MVID enterocyte



Shortened brush border + intracellular inclusion

Schematic (not histology or electron microscopy)

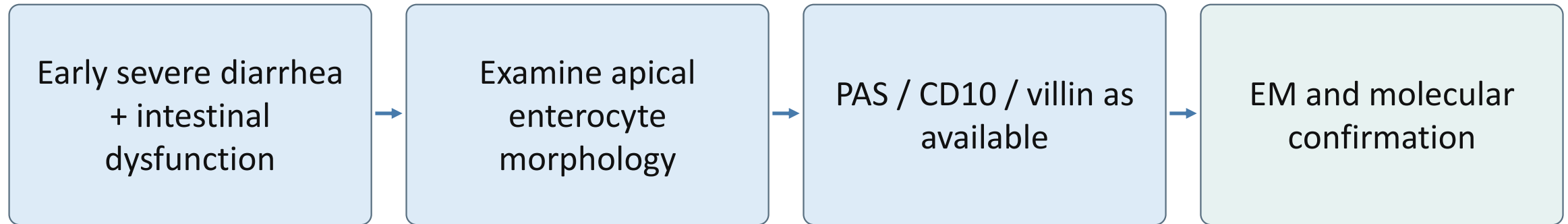
Do not confuse an inclusion with surface microvilli

- Normal microvilli project from the apical membrane into the intestinal lumen.
- An inclusion is bounded within the cytoplasm of an enterocyte.
- EM helps establish the position and orientation of the membrane structures.
- The accompanying reduced brush border strengthens interpretation.

Sampling effects and diagnostic pitfalls

- An abnormal phenotype can be more conspicuous in mature villus enterocytes.
- Microvillus inclusions and staining changes may be focal or heterogeneous.
- A normal-looking field does not establish absence of disease.
- Sampling, fixation and method availability should inform diagnostic confidence.

Biopsy-based diagnostic reasoning



This is a teaching pathway, not a clinical-practice guideline.

Genetic confirmation and its limits

- Biallelic pathogenic MYO5B variants support classic MVID.
- Genetic testing can resolve a difficult phenotypic differential.
- Variant classification requires appropriate pathogenicity evidence.
- A negative or uncertain result should be integrated with histology and clinical data.

Molecular heterogeneity beyond classic MYO5B

- Subsequent research identifies STX3 and STXBP2-related MVID phenotypes.
- UNC45A-associated disorders can produce MVID-like enterocyte abnormalities.
- The genes converge on epithelial polarity, myosin-related function or apical traffic.
- These additional genes are supplementary literature, not part of Robbins' short paragraph.

Classical gene and broader differential genes

Classic textbook locus

- MYO5B → myosin Vb motor.
- Core problem: Apical membrane trafficking.
- Autosomal recessive disease with early severe diarrhea.

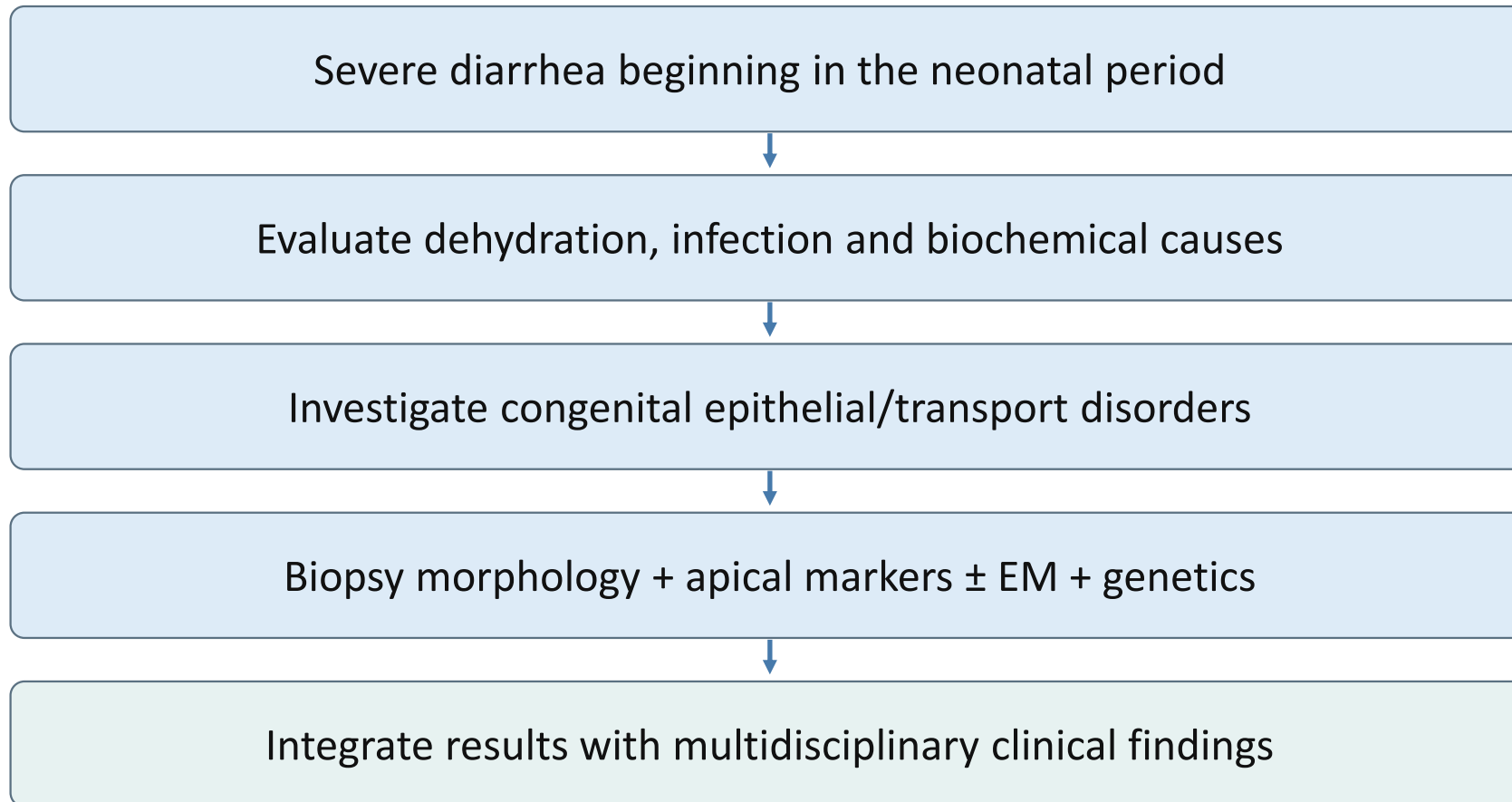
Broader literature-associated loci

- STX3 → apical membrane fusion machinery.
- STXBP2 → vesicle fusion machinery; Systemic disease context.
- UNC45A → myosin folding/function; MVID-like phenotypes.

A molecular result is not automatically causal

- Assess allele configuration and inheritance for recessive disease.
- Distinguish pathogenic / likely pathogenic variants from uncertain significance.
- Review whether the phenotype matches a known gene-associated syndrome.
- Report concordance and residual uncertainty rather than assigning a diagnosis from a VUS.

A rational neonatal diagnostic pathway



MVID versus lactase deficiency

MVID

- Primary inherited membrane trafficking disorder.
- Severe neonatal intractable diarrhea.
- Abnormal apical vesicles and brush-border organization.
- Intracellular microvillus inclusions are diagnostic clues.

Lactase deficiency

- Disaccharidase defect at brush border.
- Osmotic symptoms linked to lactose exposure.
- Histology usually unremarkable in isolated deficiency.
- Symptoms in congenital cases abate with lactose exclusion.

MVID versus abetalipoproteinemia

MVID

- MYO5B-linked trafficking defect in classic disease.
- Severe early watery diarrhea and brush-border lesions.
- Subapical inclusions on EM; CD10/villin anomalies.

Abetalipoproteinemia

- MTTP-linked failure to assemble apoB lipoproteins.
- Infant diarrhea, steatorrhea and nutritional deficits.
- Lipid-laden vacuolated enterocytes; Acanthocytes may appear.

MVID versus celiac disease

MVID

- Often manifests within days of birth.
- Apical trafficking defect; Inclusions can be detected.
- Villus atrophy is possible but not defining in isolation.

Celiac disease

- Immune-mediated gluten-associated enteropathy.
- Typical villous atrophy with increased intraepithelial lymphocytes.
- Diagnosis requires suitable serologic–clinical–histologic correlation.

MVID versus autoimmune enteropathy

MVID

- Genetic apical membrane trafficking disorder.
- Internalized microvillus structures support its diagnosis.
- Severe diarrhea can occur without prominent immune injury.

Autoimmune enteropathy

- Immune dysregulation may be associated with IPEX/FOXP3.
- Other autoimmunity and epithelial immune damage occur.
- Mucosal inflammatory patterns and systemic findings differ.

MVID versus tufting enteropathy

MVID

- Abnormal apical brush border and intracellular inclusions.
- Vesicular trafficking/polarity disease.
- EM and apical-marker immunostains help confirmation.

Tufting enteropathy

- Another congenital epithelial enteropathy.
- Focal epithelial surface tufts are a distinctive clue.
- EPCAM variants are associated with many cases.

High-yield congenital diarrhea discrimination

Condition	Biological defect	Most useful discriminator
MVID	Apical trafficking / polarity	Microvillus inclusions; CD10/villin
Congenital lactase deficiency	Lactose hydrolysis	Milk-triggered osmotic diarrhea
Abetalipoproteinemia	ApoB lipoprotein assembly	Enterocyte lipid vacuoles
Tufting enteropathy	Epithelial adhesion	Surface epithelial tufts
Congenital ion transporter defects	Electrolyte absorption/flux	Characteristic stool chemistry/genetics

Avoid diagnosing from villous atrophy alone

- Shortened villi have many different possible etiologies.
- Enterocyte-level abnormalities can be more specific than global villus architecture.
- Clinical age of onset and mucosal inflammation guide prioritization.
- Confirm MVID through a compatible cellular/ultrastructural and/or molecular pattern.

Case application: Neonatal intractable diarrhea

A newborn develops profuse watery diarrhea in the first postnatal week.

- Fluid loss continues despite careful nutritional adjustments.
- Small-bowel biopsy demonstrates abnormal subapical CD10 staining.
- No alternative acquired cause adequately explains the severity.

What diagnosis and confirmatory examinations are most appropriate?

Case interpretation: Integrate phenotype and tissue

- MVID should be prioritized among congenital epithelial diarrheal disorders.
- Subapical CD10 labeling suggests mislocalized brush-border components.
- Look for microvillus inclusions on electron microscopy.
- Seek a compatible pathogenic genotype; Do not rely on one stain alone.

Case application: Interpreting electron microscopy

Biopsy from an infant with persistent severe diarrhea is examined ultrastructurally.

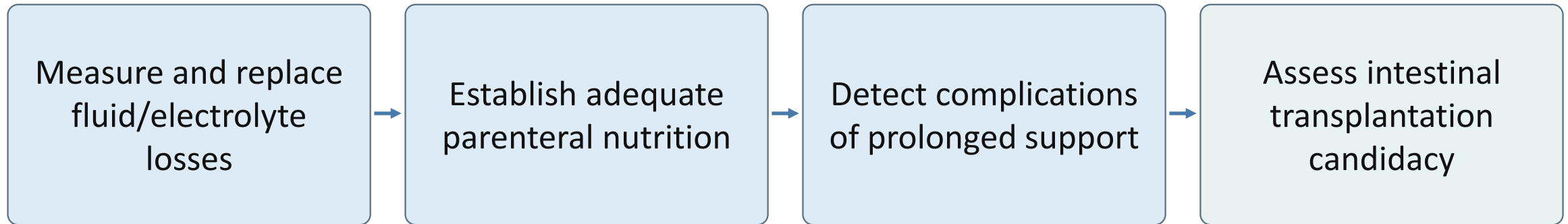
- Surface microvilli are sparse and shortened.
- A membrane-bounded cytoplasmic compartment is lined by microvilli.
- Subapical vesicular structures are increased.

Which abnormality best distinguishes this from nonspecific villous injury?

EM case answer: Location defines the lesion

- An intracytoplasmic microvillus-lined inclusion is characteristic of MVID.
- Shortened surface microvilli are important supporting evidence.
- Correlate the EM phenotype with apical immunostaining and genetics.
- Absence of a visible inclusion in one field does not exclude disease.

Management goals follow the causal pathway



Treatment supports physiology; It does not restore normal myosin Vb function.

Parenteral nutrition: Rationale and limits

- Severe mucosal dysfunction may prevent adequate enteral fluid/nutrient uptake.
- Total parenteral nutrition (TPN) bypasses intestinal absorptive failure.
- TPN does not correct the defective brush border or eliminate diarrheal losses.
- Long-term care requires specialist monitoring for vascular-access and liver complications.

Intestinal transplantation in severe MVID

- Small-bowel transplantation is a recognized option for profound intestinal failure.
- It can provide functioning absorptive intestinal epithelium.
- Recipient selection must balance benefit with major surgical and immunologic risks.
- Associated liver disease may influence transplant planning.

Two support strategies have different goals

Total parenteral nutrition

- Supplies fluid, electrolytes and nutrients intravenously.
- Maintains growth while bypassing ineffective intestinal absorption.
- Prolonged therapy carries infection, access and hepatobiliary risks.

Intestinal transplantation

- Aims to restore functional intestinal absorption.
- May reduce reliance on lifelong parenteral support.
- Carries rejection, immunosuppression and procedure-related risk.

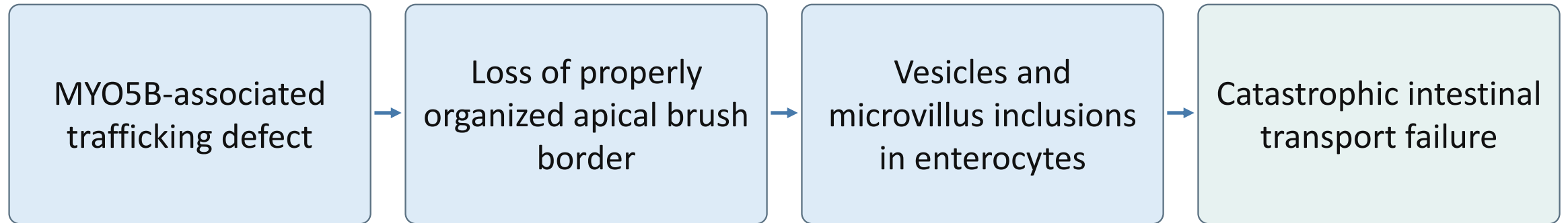
The high-burden complications must be monitored

- Recurrent dehydration and electrolyte disturbances from ongoing diarrhea.
- Central venous catheter-related complications during TPN.
- Nutrition-associated and/or genotype-associated cholestasis.
- Growth and developmental outcomes over a prolonged disease course.

Experimental strategies are not established cures

- Cell and animal models clarify myosin Vb-dependent epithelial trafficking.
- Research explores ways to restore transporter localization or reduce fluid loss.
- Preclinical mechanistic observations are not equivalent to effective infant therapy.
- TPN and transplantation remain central clinical approaches in the cited literature.

Core causal chain to retain



Microvillus inclusion disease links molecular cell polarity to a neonatal phenotype.

Five diagnostic principles

- Suspect a congenital epithelial disorder in severe diarrhea beginning within days of birth.
- Findings relate to apical enterocyte membrane trafficking—not inflammation alone.
- CD10 and villin can disclose internalized brush-border components.
- Electron microscopy demonstrates the defining intracellular inclusions.
- Interpret pathogenic genotypes in conjunction with phenotype and tissue.

Final challenge: The misleading biopsy

An infant with watery diarrhea has duodenal villus blunting but little inflammation.

- The differential includes congenital epithelial defects and several non-MVID disorders.
- A pathologist is asked whether villus atrophy proves MVID.
- Only routine H&E sections have been reviewed.

Which additional evidence is needed before a confident MVID diagnosis?

Final challenge: Expected reasoning

- Villus blunting is nonspecific and cannot diagnose MVID.
- Interrogate the apical enterocyte phenotype with PAS, CD10 and/or villin.
- Seek intracytoplasmic microvillus inclusions by electron microscopy when feasible.
- Combine findings with age, course, biochemical workup and molecular testing.

References: Primary textbook and diagnosis

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