

ADVANCED AND PIONEER RESEARCH IN HEALTH SCIENCES



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*ADVANCED AND
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Editor

Assoc. Prof. Dr. DURMUŞ HATİPOĞLU





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Circadian Regulation of Neurocortical Exercise Adaptations

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ABSTRACT

Physical exercise supports neuroplasticity through neurotrophic signaling, synaptic adaptation, and changes in cognitive and motor function. However, these responses occur within a biological context shaped by circadian rhythms, chronotype, sleep history, and fatigue. This narrative review examines how circadian regulation may influence adaptations to neurocortical exercise, defined here as training that integrates sensory processing, cognitive control, and motor output. It synthesizes evidence on circadian organization, exercise-induced neuroplasticity, cognitive-motor interference, motor learning, and rehabilitation to develop a conceptual framework linking circadian timing, cognitive load, and exercise type. Available evidence supports time-of-day variation in attention, executive function, cortical excitability, and neuromuscular performance, while selected motor-learning studies suggest that practice timing can influence subsequent consolidation. Nevertheless, direct evidence that circadian alignment improves long-term neuroplastic adaptations to neurocortical exercise remains limited.

Accordingly, the proposed framework emphasizes matching task demands to individual readiness and distinguishing immediate performance from acquisition, consolidation, retention, and transfer. Potential applications include neurological rehabilitation, balance training in older adults, and return-to-sport rehabilitation, where sleep, medication effects, and fatigue may interact with biological timing. Wearable monitoring, adaptive virtual environments, and neural feedback may eventually support individualized timing decisions, but require validation. Circadian timing should therefore be considered a potentially relevant component of exercise prescription rather than a basis for universal morning-versus-evening recommendations. Future studies should distinguish endogenous circadian phase from clock time and evaluate both immediate and delayed functional outcomes.

Keywords – Circadian rhythms; Neuroplasticity; Neurocortical exercise; Cognitive-motor integration; Motor learning; Rehabilitation

INTRODUCTION

Physical exercise is increasingly conceptualized not merely as a peripheral musculoskeletal stimulus but as a brain-driven adaptive process involving central motor command, sensory integration, and higher-order neural regulation (Basso & Suzuki, 2016; Morgan et al., 2015). This perspective is supported by evidence demonstrating that exercise induces widespread neurobiological changes, including alterations in neurotransmitter systems, synaptic plasticity, and regional brain activation patterns (Basso & Suzuki, 2016).

Within this framework, neuroplasticity refers to the capacity of the nervous system to reorganize structurally and functionally in response to internal and external stimuli (Kolb & Gibb, 2011). Exercise-induced neuroplasticity has been consistently associated with increases in neurotrophic factors such as brain-derived neurotrophic factor (BDNF), as well as with enhanced synaptic efficacy, neurogenesis, and angiogenesis (Cotman et al., 2007; Voss et al., 2013). Meta-analytic evidence further indicates that both acute and chronic exercise significantly elevate circulating BDNF levels in healthy individuals, supporting its role as a key mediator of exercise-related brain adaptation (Szuhany et al., 2015).

Despite these advances, a critical limitation in literature is the implicit assumption that exercise-induced neurobiological effects are time-independent. In contrast, a large body of research in chronobiology demonstrates that physiological and cognitive processes are regulated by endogenous circadian rhythms, which organize biological function across the 24-hour day (Czeisler & Buxton, 2017). These rhythms influence hormonal secretion, metabolic activity, and neural excitability, all of which are central to adaptive responses to exercise (Wolff & Esser, 2019).

Importantly, exercise itself may act as a *zeitgeber*, capable of modulating circadian timing, while simultaneously being influenced by circadian phase (Lewis et al., 2018). This bidirectional relationship suggests that the outcomes of exercise are not solely determined by intensity, duration, or modality, but also by the time of day at which exercise is performed (Wolff & Esser, 2019).

The relevance of circadian timing becomes even more pronounced when considering cognitive and neurocortical processes. Cognitive performance, including attention, executive function, and reaction time, exhibits significant diurnal variation, often peaking later in the day depending on chronotype (Schmidt et al., 2007; Valdez, 2019). Since these cognitive domains are integral to motor learning and neurocortical training paradigms, fluctuations in brain state across the day may directly influence the effectiveness of such interventions (Robertson et al., 2004).

Furthermore, emerging evidence suggests that synaptic plasticity itself is under circadian control, with oscillations in molecular pathways involved in long-term potentiation and memory formation (Frank, 2016). Sleep, which is tightly regulated by circadian processes, plays a crucial role in synaptic homeostasis and memory consolidation, further linking time-of-day biology to neuroplastic adaptation (Tononi & Cirelli, 2014).

Taken together, these findings highlight a significant conceptual gap: while exercise neuroscience has established robust links between physical activity and neuroplasticity, it has largely overlooked the temporal structure of brain function as a determinant of adaptive outcomes. This gap is particularly relevant for neurocortical exercise paradigms, which rely heavily on attention, perception, and cognitive-motor integration.

Based on this framework, the present review proposes the following hypothesis: neuroplastic adaptations to exercise are modulated by circadian rhythms, and neurocortical exercise interventions may be optimized when aligned with time-of-day-dependent fluctuations in brain function and cognitive capacity.

1. CIRCADIAN SYSTEM AND THE BRAIN

1.1 Central and Peripheral Clocks

The circadian system in mammals is hierarchically organized, with the suprachiasmatic nucleus (SCN) of the hypothalamus functioning as the master pacemaker that synchronizes physiological and behavioral rhythms to the external light–dark cycle (Hastings et al., 2018; Takahashi et al., 2008). The SCN receives direct photic input from intrinsically photosensitive retinal ganglion cells via the retinohypothalamic tract, allowing environmental light to entrain endogenous rhythms (Hastings et al., 2018).

Beyond the SCN, peripheral clocks are present in nearly all tissues, including skeletal muscle, liver, and multiple brain regions (Mohawk et al., 2012). These clocks are driven by cell-autonomous transcription–translation feedback loops involving core clock genes such as *CLOCK*, *BMAL1*, *PER*, and *CRY* (Takahashi et al., 2008). Importantly, peripheral clocks can be entrained not only by the SCN but also by non-photic cues such as feeding and physical activity, suggesting a distributed and flexible circadian network (Mohawk et al., 2012; Wolff & Esser, 2019).

Exercise has been identified as a potential zeitgeber capable of modulating circadian phase, particularly in peripheral tissues such as skeletal muscle, where it can influence the expression of clock genes and metabolic regulators (H.-K. Kim et al., 2023; Wolff & Esser, 2019). This indicates that physical activity is not only regulated by circadian rhythms but may also actively participate in their modulation.

1.2 Circadian Regulation of Neuroplasticity

Circadian rhythms exert a profound influence on molecular pathways underlying neuroplasticity, including neurotrophin signaling, synaptic transmission, and gene expression (Frank, 2016). One of the most well-characterized factors is brain-derived neurotrophic factor (BDNF), which exhibits diurnal variation and plays a central role in synaptic plasticity, long-term potentiation (LTP), and neuronal survival (Begliuomini et al., 2008). Fluctuations in BDNF availability across the day may therefore influence the brain's capacity for plastic adaptation.

Hormonal oscillations further contribute to circadian modulation of brain function. Cortisol, which peaks in the early morning, enhances arousal and modulates memory encoding processes, although excessive levels may impair plasticity (Czeisler & Buxton, 2017). Similarly, dopaminergic activity, which is critical for reward-based learning and motor control, displays

circadian variation and is regulated in part by clock gene expression (Hood & Amir, 2017).

At the synaptic level, circadian mechanisms regulate processes such as LTP and long-term depression (LTD), suggesting that synaptic efficacy is time-of-day dependent (Frank, 2016). Additionally, sleep—under strong circadian control—facilitates synaptic homeostasis and memory consolidation, reinforcing the link between circadian biology and neuroplastic outcomes (Tononi & Cirelli, 2014).

1.3 Diurnal Variation in Cognitive Performance

Cognitive performance is not constant throughout the day but instead follows predictable circadian patterns, influenced by both endogenous rhythms and individual chronotype (Schmidt et al., 2007). Executive functions, including working memory, inhibitory control, and cognitive flexibility, often demonstrate improved performance later in the day in young adults, although this pattern may vary depending on chronotype alignment (Valdez, 2019).

Reaction time and attentional processes also exhibit diurnal variation, generally improving from morning to afternoon as core body temperature and cortical arousal increase (Schmidt et al., 2007). These fluctuations are thought to reflect underlying changes in neural efficiency, particularly within prefrontal and attentional networks.

Importantly, the concept of synchrony effects suggests that cognitive performance is optimized when task demands align with an individual's circadian preference (i.e., morningness vs. eveningness) (May & Hasher, 1998). This has significant implications for neurocortical training and motor learning, as the effectiveness of cognitively demanding tasks may depend on both time of day and individual chronotype.

2. EXERCISE AND NEUROPLASTICITY

Physical exercise is widely recognized as a potent modulator of neuroplasticity, exerting effects across molecular, cellular, and system-level processes within the central nervous system. These adaptations are mediated through coordinated changes in neurotrophic signaling, synaptic function, neurogenesis, and neuroimmune interactions, which together support improvements in cognitive and motor performance (Cotman et al., 2007; Voss et al., 2010).

Among the molecular mediators of exercise-induced neuroplasticity, brain-derived neurotrophic factor (BDNF) is the most extensively studied. BDNF plays a critical role in synaptic plasticity, neuronal survival, and long-term potentiation (LTP), which are essential for learning and memory processes (Cotman et al., 2007). Both acute and chronic exercise have been shown to significantly increase circulating BDNF levels in humans, as demonstrated in meta-analytic findings (Szuhany et al., 2015).

In addition to BDNF, exercise stimulates the release of insulin-like growth factor-1 (IGF-1), which contributes to neuroplasticity by promoting neuronal growth and survival. Experimental studies have shown that circulating IGF-1 can cross the blood–brain barrier and mediate exercise-induced increases in hippocampal neurogenesis (Trejo et al., 2001). Similarly, vascular endothelial growth factor (VEGF) has been identified as a key regulator of exercise-induced angiogenesis and neurogenesis, supporting increased cerebral perfusion and metabolic capacity (Fabel et al., 2003).

Importantly, several of these molecular pathways operate within a broader physiological context influenced by circadian biology. For example, hormonal regulators such as cortisol and systemic metabolic factors exhibit diurnal variation, which may shape the internal environment in which these neurotrophic responses occur (Czeisler & Buxton, 2017). While direct evidence linking time-of-day to exercise-induced neurotrophin responses remains limited, these interactions suggest a potential modulatory role of circadian timing.

2.1 Synaptic Plasticity, Neurogenesis, and Sleep Interaction

Exercise has been shown to enhance synaptic plasticity, particularly within the hippocampus, by increasing synaptic strength and facilitating long-term potentiation (Voss et al., 2013). Animal studies demonstrate that voluntary physical activity increases dendritic spine density and improves synaptic efficacy, which are associated with enhanced learning capacity (Cotman et al., 2007).

In parallel, exercise promotes adult neurogenesis, especially in the dentate gyrus of the hippocampus. Seminal work has demonstrated that voluntary running significantly increases the proliferation of neural progenitor cells and their integration into functional neural circuits (van Praag et al., 1999). These newly generated neurons contribute to memory formation and cognitive flexibility.

The interaction between exercise and neuroplasticity is closely linked to sleep-dependent processes. Sleep plays a fundamental role in memory consolidation and synaptic homeostasis, allowing for the stabilization and integration of newly formed neural connections (Tononi & Cirelli, 2014). Since sleep is regulated by circadian rhythms, the consolidation of exercise-induced neuroplastic changes is likely influenced by the temporal organization of sleep–wake cycles (M. G. Frank & Cantero, 2014).

2.2 Neuroinflammation and Immune Modulation

Exercise also modulates neuroinflammatory processes, which are increasingly recognized as key regulators of neuroplasticity. Regular physical activity has been associated with reduced levels of pro-inflammatory cytokines and enhanced anti-inflammatory signaling, contributing to a neural environment that supports plastic adaptation (Gleeson et al., 2011).

At the same time, the immune system is subject to circadian regulation, with fluctuations in immune cell trafficking and cytokine production observed across the day (Scheiermann et al., 2013). Although direct evidence linking exercise timing, inflammation, and neuroplasticity remains limited, these findings suggest that the inflammatory context in which exercise occurs may vary depending on time of day, potentially influencing adaptive outcomes.

2.3 Exercise Timing and Neuroplastic Outcomes

Emerging evidence suggests that the timing of exercise may influence neuroplastic outcomes by interacting with time-of-day-dependent changes in physiology and brain function. Variations in hormonal levels, core body temperature, and neural excitability across the day may alter responsiveness to training stimuli (Wolff & Esser, 2019).

In addition, research on motor learning indicates that the acquisition and retention of new skills can be influenced by factors such as sleep and time-of-day-dependent cognitive states, which are themselves regulated by circadian processes (Robertson et al., 2004). While direct experimental evidence specifically linking exercise timing to neuroplastic adaptation is still developing, these findings support the idea that identical exercise interventions may produce different outcomes depending on when they are performed.

3. NEUROCORTICAL EXERCISES AND NEURAL BASIS OF NEUROCORTICAL TRAINING

Neurocortical exercises refer to training paradigms that explicitly target the integration of sensory processing, cognitive control, and motor output, rather than focusing solely on peripheral physiological adaptations such as strength or endurance (Seidler et al., 2010). These exercises are characterized by their reliance on higher-order brain functions, including attention, perception, decision-making, and sensorimotor integration, which are primarily mediated by cortical and subcortical networks (Leisman et al., 2016).

Motor behavior is increasingly understood as the product of distributed neural networks involving the primary motor cortex, premotor cortex, supplementary motor area, cerebellum, basal ganglia, and prefrontal cortex (Kandel et al., 2021). Within this framework, neurocortical exercises aim to enhance the efficiency and adaptability of these networks by imposing task demands that require continuous integration of sensory input and motor planning.

The prefrontal cortex (PFC) plays a central role in these processes by supporting executive functions such as working memory, attentional control, and decision-making (Miller & Cohen, 2001). During complex motor tasks, increased PFC activation reflects the cognitive demands associated with planning and adapting behavior in dynamic environments (Seidler et al., 2010).

This is particularly evident in tasks that require rapid adjustments to unpredictable stimuli, where top-down control mechanisms are essential.

3.1 Types of Neurocortical Exercises

Neurocortical training encompasses a broad range of modalities designed to challenge different aspects of brain function:

Visual training: Exercises targeting visual processing, tracking, and anticipation have been shown to improve perceptual-cognitive skills and reaction time in both athletes and clinical populations (Appelbaum & Erickson, 2018).

Vestibular and balance training: Vestibular stimulation enhances postural control and spatial orientation through integration of sensory inputs within brainstem and cerebellar circuits (Horak, 2006).

Proprioceptive training: Exercises involving joint position sense and kinesthetic awareness improve sensorimotor integration and motor accuracy (Riemann & Lephart, 2002).

Reaction and decision-making training: Tasks that require rapid responses to external stimuli engage cortical networks involved in attention and executive control, contributing to improved cognitive-motor performance (Voss et al., 2010).

These modalities share a common feature: they impose cognitive and sensory demands that extend beyond simple motor execution, thereby engaging neurocortical mechanisms of adaptation.

3.2 Neuroplastic Adaptations to Neurocortical Training

Neurocortical exercises induce experience-dependent plasticity within brain networks, leading to functional and structural changes associated with improved performance. Neuroimaging studies have demonstrated that motor skill learning is associated with changes in cortical activation patterns, including both increased efficiency (reduced activation) and recruitment of additional neural resources depending on task complexity and learning stage (Dayan & Cohen, 2011).

Furthermore, repeated engagement in cognitively demanding motor tasks promotes functional connectivity changes between cortical and subcortical regions, facilitating more efficient sensorimotor integration (Bassett et al., 2015). These adaptations are not limited to motor areas but extend to cognitive networks, reflecting the integrative nature of neurocortical training.

Importantly, the degree of neuroplastic adaptation appears to depend on the level of task complexity and cognitive engagement, with more demanding tasks eliciting greater cortical involvement and potentially stronger adaptive responses (Guadagnoli & Lee, 2004). This suggests that neurocortical exercises may be particularly effective in driving plastic changes due to their inherently high cognitive load.

3.3 Circadian Sensitivity of Neurocortical Processes

Neurocortical exercises are inherently dependent on cognitive functions such as attention, executive control, and sensory processing, all of which are subject to circadian modulation. Functional neuroimaging studies have shown that brain activity in regions such as the prefrontal cortex varies across the day, with corresponding changes in cognitive performance (Schmidt et al., 2015).

Attention and executive function, which are critical for neurocortical training, exhibit time-of-day-dependent fluctuations, influenced by both circadian phase and homeostatic sleep pressure (Valdez, 2019). These fluctuations affect not only performance outcomes but also the efficiency of neural processing, which may in turn influence the effectiveness of training-induced plasticity.

Additionally, sensory processing, including visual and vestibular integration—has been shown to vary across the day, potentially due to changes in cortical excitability and neuromodulatory systems (Ly et al., 2016). Given that neurocortical exercises rely heavily on these processes, it is reasonable to propose that their effectiveness may be time-dependent, even if direct experimental evidence remains limited.

4. DUAL-TASK AND CIRCADIAN COGNITIVE LOAD INTERACTION

Neurocortical exercises frequently require the simultaneous integration of motor execution, sensory processing, attention, and decision-making. For this reason, many neurocortical training paradigms resemble dual-task conditions rather than isolated motor tasks. In dual-task situations, individuals must perform a motor task while simultaneously managing an additional cognitive or perceptual demand, such as maintaining balance while responding to visual stimuli or walking while performing a mental calculation. These conditions are highly relevant to neurocortical exercise because they reveal how motor control depends on limited attentional and executive resources (Woollacott & Shumway-Cook, 2002; Yogev-Seligmann et al., 2008).

Dual-task performance often produces cognitive-motor interference, defined as a decline in motor performance, cognitive performance, or both when two tasks are performed concurrently rather than separately (Al-Yahya et al., 2011; Leone et al., 2017). This interference has been observed in gait, balance, postural control, and complex movement tasks, indicating that motor behavior is not always automatic but may require substantial cognitive supervision (Woollacott & Shumway-Cook, 2002). In the context of neurocortical exercise, however, cognitive-motor interference should not be viewed only as a limitation. When appropriately controlled, it may also

function as a useful training stimulus that challenges the nervous system to coordinate cognitive and motor demands more efficiently.

4.1 Cognitive Load as a Training Variable

Cognitive load refers to the amount of information-processing demand imposed on the central nervous system during task execution. In neurocortical exercise, cognitive load may increase when the task involves multiple stimuli, rapid response selection, unpredictable environmental cues, divided attention, or complex decision-making. As cognitive load increases, the nervous system must distribute limited processing resources between motor control and cognitive operations (Pashler, 1994; Tombu & Jolicœur, 2003).

From a motor-learning perspective, cognitive load may be considered a dose-like variable. If the task is too simple, it may not provide enough neural challenge to promote adaptation. If the task is too complex, excessive cognitive load may impair movement quality, reduce accuracy, and limit learning. This principle is consistent with the challenge point framework, which proposes that optimal learning occurs when task difficulty is matched to the learner's skill level and available information-processing capacity (Guadagnoli & Lee, 2004). Therefore, neurocortical exercise prescription should consider not only physical intensity and motor complexity but also the cognitive demands imposed by the task.

This is particularly important because neurocortical training aims to improve more than peripheral movement output. It targets attentional control, sensory integration, response selection, and flexible motor adaptation. These processes depend strongly on prefrontal and frontoparietal networks that support executive control and goal-directed behavior (Miller & Cohen, 2001). Thus, the cognitive load embedded within a neurocortical exercise may influence both immediate performance and the quality of long-term adaptation.

4.2 Central Capacity and Cognitive-Motor Interference

Cognitive-motor interference can be explained partly by central capacity models. According to these models, the central nervous system has a limited capacity for processing concurrent tasks; when combined motor and cognitive demands exceed this capacity, performance deterioration occurs (Pashler, 1994; Tombu & Jolicœur, 2003). For example, a low-demand balance task

paired with a simple visual response may produce minimal interference, whereas a complex balance task combined with rapid decision-making may exceed available cognitive resources and disrupt both motor and cognitive performance.

Evidence from dual-task studies supports this interpretation. Systematic reviews show that dual-task walking commonly alters gait parameters, particularly gait speed, and that the degree of interference depends on task complexity, cognitive task type, and participant characteristics (Al-

Yahya et al., 2011). Neural evidence also indicates that dual-task performance involves distributed brain regions, including prefrontal, parietal, supplementary motor, and cerebellar networks (Leone et al., 2017). These findings suggest that dual-task neurocortical exercise should be progressed carefully: the aim is to create an adaptive challenge without overwhelming the individual's processing capacity.

4.3 Circadian Variation in Executive Capacity

The interaction between dual-task performance and circadian timing becomes important because attention, working memory, alertness, and executive control vary across the day. Human cognitive performance is regulated by both circadian rhythms and homeostatic sleep pressure, producing time-of-day-dependent changes in sustained attention, inhibitory control, and working memory (Schmidt et al., 2007; Valdez, 2019). Since dual-task neurocortical exercises rely heavily on these functions, the same exercise may impose different levels of cognitive difficulty at different times of day.

The prefrontal cortex plays a central role in executive control, task coordination, and attentional allocation (Miller & Cohen, 2001). Functional neuroimaging studies suggest that prefrontal and thalamic activity during working memory tasks is influenced by chronotype and time of day (Schmidt et al., 2015). This means that a dual-task drill performed during an individual's non-optimal circadian phase may require greater effort or produce stronger interference than the same drill performed during a more favorable cognitive window.

Therefore, cognitive load should not be understood as a fixed property of the exercise alone. It emerges from the interaction between task demands and the individual's current neurocognitive state. A task that is appropriately challenging in the afternoon may be excessive in the early morning for some individuals, particularly if alertness or working memory capacity is reduced. Conversely, a task that is demanding in the morning may be better tolerated later in the day when arousal and executive performance are higher (Schmidt et al., 2007; Valdez, 2019).

4.4 Practical Implications for Neurocortical Exercise Timing

A circadian approach to dual-task neurocortical exercise suggests that training load should be adjusted according to motor complexity, cognitive demand, time of day, and individual chronotype. Morning sessions may be more appropriate for lower-complexity cognitive-motor tasks when the goal is to reinforce movement quality, postural control, or basic sensorimotor accuracy. This may be particularly useful for individuals who experience reduced alertness or slower cognitive processing early in the day. However, this pattern should not be generalized to all individuals, because morning-type chronotypes may perform better earlier than evening-type chronotypes (Schmidt et al., 2015).

Late afternoon or evening sessions may offer a more favorable window for higher-load dual-task paradigms in some individuals, especially when the goal is to challenge reaction speed, decision-making, attentional flexibility, and cognitive-motor integration. At these times, improved alertness and executive efficiency may allow more complex neurocortical tasks to be tolerated without excessive performance breakdown (Schmidt et al., 2007; Valdez et al., 2012). Nevertheless, evening training is not universally superior, because accumulated fatigue, sleep debt, psychological stress, and prior physical load may reduce cognitive capacity later in the day. Overall, dual-task neurocortical exercise should be considered a time-sensitive intervention. Cognitive load is shaped not only by task complexity but also by circadian fluctuations in attention, executive control, and processing capacity. When cognitive load is aligned with the individual's time-dependent brain state, dual-task training may provide an optimal adaptive stimulus. When it is poorly aligned, the same task may become excessive and interfere with movement quality or learning. This perspective provides a bridge between cognitive-motor interference, circadian biology, and neurocortical exercise prescription, supporting the broader hypothesis that exercise-induced neuroplasticity may be optimized by considering not only what type of exercise is performed, but also when it is performed.

5. EXERCISE TYPE × TIME OF DAY: A CORTICAL ADAPTATION MATRIX

The interaction between circadian timing and neurocortical adaptation should not be interpreted as a single universal rule suggesting that one time of day is optimal for all forms of exercise. Different exercise modalities rely on different combinations of physiological, cognitive, and cortical mechanisms. Aerobic exercise, resistance training, motor learning, and dual-task neurocortical training do not impose identical demands on the nervous system; therefore, their sensitivity to time of day may also differ.

Circadian rhythms influence several variables that are relevant to exercise adaptation, including core body temperature, hormonal secretion, neuromuscular performance, alertness, cognitive efficiency, and sleep–wake regulation (Chtourou & Souissi, 2012; Schmidt et al., 2007; Valdez, 2019). At the same time, exercise itself may act as a non-photic zeitgeber, capable of influencing circadian timing and peripheral clock function (Wolff & Esser, 2019). This bidirectional relationship suggests that exercise prescription should consider not only intensity, duration, frequency, and modality, but also the timing of the training stimulus.

Aerobic exercise may be particularly relevant as a neuroplastic priming strategy. Acute endurance exercise has been shown to increase circulating brain-derived neurotrophic factor (BDNF), a key mediator of synaptic plasticity and learning-related adaptation, although the magnitude of this response varies according to exercise protocol and individual factors

(Liang et al., 2023). Morning aerobic exercise may therefore be useful when the aim is to increase arousal, stabilize daily activity rhythms, or prepare the brain for later cognitive or motor tasks. However, current evidence does not justify the claim that morning aerobic exercise is universally superior for neuroplasticity. Rather, it should be considered a plausible timing strategy when the target is neurotrophic priming or circadian entrainment.

Resistance and high-intensity exercise appear to be more closely linked to time-of-day variation in neuromuscular performance. Strength, power, and anaerobic output often show lower values in the morning and higher values later in the day, possibly due to daily changes in body temperature, neuromuscular efficiency, and hormonal environment (Chtourou & Souissi, 2012). From a neurocortical perspective, later-day resistance or power training may provide a more favorable context for maximal motor unit recruitment, rapid force production, and complex motor output. Nevertheless, these effects are not fixed. Training at a specific time of day may improve performance at that same time, suggesting that temporal specificity should be considered when the goal is preparation for a particular competition, therapy session, or daily functional demand (Chtourou & Souissi, 2012; Kūusmaa et al., 2016).

Motor learning requires a different interpretation because the primary outcome is not simply immediate performance, but the acquisition, stabilization, and later retrieval of a motor skill. Evidence suggests that time of day may influence motor skill consolidation, with some findings indicating stronger consolidation after afternoon practice compared with morning practice (Truong et al., 2022). This does not mean that motor learning should always occur later in the day. Morning sessions may be appropriate for low-pressure acquisition, movement awareness, and technical refinement, whereas later-day sessions may be useful when the goal is performance expression, complex coordination, or consolidation-sensitive learning. Thus, the timing of motor-learning practice should be matched to the specific learning objective.

Dual-task and neurocortical exercises place the greatest demand on attentional control, sensory integration, working memory, and decision-making. Since these cognitive functions fluctuate across the day, the same task may impose different levels of difficulty depending on circadian phase, chronotype, sleep quality, and fatigue (Schmidt et al., 2007; Valdez, 2019). Morning dual-task training may be more appropriate when cognitive load is low to moderate, such as simple visual tracking, controlled balance tasks, or low-speed reaction drills. More complex tasks, including rapid decision-making, unpredictable stimuli, or sport-specific cognitive-motor challenges, may be better tolerated later in the day in some individuals. However, this pattern should remain individualized, because morning chronotypes may tolerate cognitive load earlier, while accumulated fatigue may reduce evening performance.

Overall, the exercise type $\times$ time-of-day matrix supports a more precise approach to neurocortical exercise prescription. The central question is not whether morning or evening exercise is universally superior, but whether the timing of the exercise matches the dominant adaptive target. By aligning exercise modality with time-dependent physiological and cognitive states, clinicians and trainers may improve the likelihood that a given exercise stimulus produces the intended cortical, motor, or performance-related adaptation.

6. TRANSFER OF NEUROCORTICAL EXERCISES TO PERFORMANCE: THE TEMPORAL DIMENSION

Neurocortical training seeks to improve reaction speed, perceptual accuracy, decision-making, balance, and movement adaptability beyond the practiced task. Transfer may be sensitive to the conditions under which a skill is learned and later expressed. Attention and reaction time vary with circadian phase, sleep pressure, and chronotype; consequently, practice and assessment at different times may capture different levels of readiness rather than equivalent learning outcomes (Schmidt et al., 2007; Valdez, 2019).

Acquisition, consolidation, retention, and performance expression should therefore be evaluated separately. Sleep-dependent and offline processes help stabilize motor memories (Robertson et al., 2004). In a finger-tapping study, afternoon physical and mental practice produced better consolidation than morning practice, although acquisition improved at both times (Truong et al., 2022). This finding supports a task-specific temporal interpretation, rather than a general recommendation that all motor learning should occur later in the day.

For practical assessment, reaction drills should be interpreted alongside sleep history, fatigue, chronotype, and testing time. Slower responses during reduced alertness may reflect temporary state effects. Once a skill is established, graded practice under varied conditions may support transfer to functional or sport-specific demands; however, the benefit of deliberately varying neurocortical practice time remains a hypothesis requiring direct testing.

Fatigue and reduced attentional capacity may compromise movement quality during demanding tasks (Halsen, 2014; Schmidt et al., 2007). Training should therefore progress toward the physical and cognitive demands of performance without abrupt load increases or persistent technical deterioration. General training-load principles support developing tolerance while managing fatigue (Gabbett, 2016), but do not establish a circadian injury-prevention protocol. The proposed implication is to distinguish favorable conditions for initial learning from the variable conditions required for transfer, while monitoring errors, compensatory movement, and recovery.

7. CLINICAL AND REHABILITATION IMPLICATIONS: A CHRONOBIOLOGICAL APPROACH

The temporal framework developed in the previous chapters has important implications for clinical rehabilitation. If neurocortical exercise adaptation is influenced by circadian phase, cognitive readiness, sleep pressure, and chronotype, then rehabilitation outcomes may depend not only on the content of therapy but also on the timing of therapy. This does not mean that a single time of day should be prescribed for all patients. Rather, it suggests that rehabilitation planning may benefit from a chronobiological perspective in which therapy timing is aligned with the patient's physiological state, cognitive capacity, fatigue level, and functional goals.

This approach may be particularly relevant in neurological rehabilitation, where motor recovery depends on neuroplasticity, attention, repetition, feedback processing, and motor learning. After stroke, rehabilitation aims to promote functional reorganization and improve the use of impaired motor systems. Sleep and circadian regulation are important in this context because motor learning and memory consolidation are partly supported by sleep-dependent processes (Gudberg & Johan-sen-Berg, 2015). In addition, circadian disruption, poor sleep quality, fatigue, and altered rest–activity rhythms are common after stroke and may influence participation in therapy, learning capacity, and recovery trajectories (Korostovtseva & Kolomeichuk, 2023). Therefore, the timing of rehabilitation sessions may be relevant when the goal is to maximize attention, engagement, and consolidation of newly practiced motor skills.

In practical terms, stroke rehabilitation may require a distinction between therapy for acquisition and therapy for transfer. Sessions focused on introducing new motor patterns, improving movement awareness, or practicing precise upper-extremity control may be more effective when the patient is alert and cognitively engaged. In contrast, once a skill has been acquired, selected practice under more variable daily conditions may help transfer the skill to real-life contexts. However, this should be done carefully, because excessive fatigue or low alertness may reduce movement quality and promote compensatory strategies rather than adaptive recovery.

Parkinson's disease represents another condition in which a chronobiological perspective may be clinically meaningful. Parkinson's disease is associated not only with dopaminergic motor dysfunction but also with sleep disturbances, circadian rhythm disruption, autonomic symptoms, and fluctuations in motor and non-motor function (Smilowska et al., 2023). Dopaminergic activity is closely involved in motor control, reward-based learning, motivation, and movement initiation; therefore, variations in medication response, alertness, and daily symptom fluctuations may alter the patient's readiness for neurocortical exercise. For individuals with Parkinson's disease, rehabilitation timing may need to consider the interaction

between circadian state, medication “on–off” periods, fatigue, and cognitive-motor demand.

This does not imply that therapy should be limited to a single optimal window. Instead, timing may be adjusted according to the therapeutic aim. When the goal is to learn a new movement strategy, practice may be scheduled during periods of better motor control and cognitive readiness. When the goal is functional robustness, selected tasks may later be practiced under more realistic conditions, including dual-task walking, turning, obstacle negotiation, or reactive balance tasks. In this way, chronobiological planning may help distinguish between the best time for learning and the necessary conditions for functional transfer.

The chronobiological approach is also relevant in musculoskeletal rehabilitation, particularly after anterior cruciate ligament injury or reconstruction. ACL injury is increasingly understood not only as a peripheral ligament injury but also as a sensorimotor and neurocognitive challenge involving altered proprioception, motor control, attentional demand, and movement decision-making (Mou et al., 2026). Return-to-sport rehabilitation often requires the athlete to perform under conditions of speed, fatigue, visual distraction, opponent pressure, and unpredictable movement demands. These requirements overlap strongly with the neurocortical principles discussed in earlier chapters.

For ACL rehabilitation, the potential role of timing should be interpreted through its interaction with movement quality, fatigue, attention, and cognitive-motor load rather than as a direct circadian prescription. Because ACL injury and reconstruction are associated with sensorimotor and neurocognitive demands, early-stage rehabilitation may prioritize controlled movement quality and proprioceptive accuracy, whereas later stages may progressively incorporate dual-task demands, visual perturbations, reactive drills, and sport-specific decision-making when movement quality is sufficiently stable (Mou et al., 2026). This progression should be presented as a clinically derived implication rather than as a direct time-of-day protocol, because direct evidence on circadian timing in ACL rehabilitation remains limited.

Geriatric balance rehabilitation provides another important example. Balance control in older adults is strongly affected by attention, executive function, sensory integration, and dual-task capacity. Dual-task balance training has been shown to improve balance-related outcomes in older adults, but its effectiveness depends on the appropriate progression of motor and cognitive demands (Khan et al., 2022). Since older adults may also experience greater variability in sleep quality, fatigue, medication effects, and circadian rhythm stability, the timing of balance and dual-task training may influence safety, engagement, and learning quality.

In line with the dual-task and cognitive-load principles discussed earlier, cognitively demanding balance tasks may be most appropriate when

alertness is sufficient and fatigue is low (Khan et al., 2022; Schmidt et al., 2007). For some individuals, this may occur earlier in the day; for others, it may occur later depending on chronotype, daily routine, medication timing, and sleep quality. Simple balance tasks, gait training, and low-load sensory integration exercises may be used during lower-capacity periods, whereas more complex dual-task or perturbation-based exercises may be reserved for periods of better cognitive-motor readiness. The clinical goal is not to avoid challenge, but to place challenge at a time when it is adaptive rather than destabilizing.

8. INTEGRATIVE MODEL PROPOSAL

The proposed Circadian Timing $\times$ Cognitive Load $\times$ Exercise Type framework brings together the biological context of practice, its information-processing demands, and its adaptive objective. Circadian rhythms influence cognition and physiological readiness, while exercise can interact with circadian organization (Cajochen & Schmidt, 2025; Schmidt et al., 2007; Wolff & Esser, 2019). The framework proposes that their interaction may help explain why an identical exercise produces different immediate demands across individuals and sessions.

Circadian timing refers to endogenous phase and its relationship with chronotype and external clock time. Sleep pressure, recent sleep, fatigue, medication effects, and daily routines are related contextual influences and should be assessed separately rather than treated as measures of circadian phase. Both circadian and sleep-dependent processes influence attention, working memory, and executive control (Schmidt et al., 2007; Valdez, 2019; Cajochen & Schmidt, 2025). A balance task with visual decisions may therefore be tolerable during adequate alertness but excessive after poor sleep or accumulated fatigue.

Cognitive load describes the attentional, perceptual, inhibitory, memory, and decision-making demands embedded in movement. Concurrent motor and cognitive tasks can produce interference (Leone et al., 2017). Appropriately graded difficulty may create a useful learning challenge, but increasing load does not necessarily strengthen adaptation. Consistent with the challenge point framework, task difficulty should be matched to the learner's skill and processing capacity (Guadagnoli & Lee, 2004).

Exercise type identifies the dominant adaptive target. Aerobic exercise may support arousal and neurotrophic priming; resistance or high-intensity exercise may prioritize force production; motor practice targets skill acquisition and consolidation; and dual-task training emphasizes cognitive-motor integration. Their different demands imply that any useful timing strategy should be specific to the intended outcome, rather than based on a universal morning-versus-evening rule.

The model's central assumption is that a useful adaptive window emerges when task demands match current physical and cognitive capacity.

Insufficient challenge may provide a limited stimulus, whereas excessive interference may impair movement quality or learning. Immediate task success alone cannot establish that this window has been optimized: delayed retention and transfer are also required. Selected evidence that practice time influences consolidation supports this distinction (Truong et al., 2022).

Clinically, the framework suggests adjusting task complexity when alertness or fatigue changes, considering medication response and chronotype, and accounting for the time at which functional or competitive performance is required. It remains a conceptual proposal rather than a validated prescription algorithm. Trials should test whether matching timing, cognitive load, and modality improves retention and transfer compared with usual scheduling, while distinguishing true circadian effects from sleep, fatigue, and behavioral influences.

9. FUTURE PERSPECTIVES

Future research should establish whether exercise timing modifies the magnitude or durability of neurocortical adaptation. Personalized prescription already recognizes variation associated with age, sex, health, exercise dose, sleep, medication, diet, and circadian factors (Noone et al., 2024). Exercise may also act as a non-photic time cue, but its effects depend on timing, protocol, and the physiological outcome measured (Lewis et al., 2018). These observations justify testing individualized timing strategies without assuming that their clinical superiority has been established.

Wearables may support this work by tracking sleep-wake patterns, activity, heart rate, skin temperature, and light exposure. Their use requires validated devices, transparent algorithms, and attention to artifacts and population-specific accuracy (de Zambotti et al., 2024). Modeling approaches that combine wearable signals with circadian models offer potential estimates of biological phase (Kim et al., 2024). Such estimates should be distinguished from direct phase measurements and validated before they guide rehabilitation scheduling.

Artificial intelligence could combine these measurements with movement quality, reaction time, fatigue, adherence, and patient-reported outcomes to support timing and progression decisions. AI applications in virtual rehabilitation include assessment, prediction, feedback, and monitoring, but current evidence is heterogeneous (Abedi et al., 2024). Proposed chrono-neurocortical applications should therefore complement clinical reasoning and patient preferences, with professional supervision and clear explanations of recommendations.

Virtual reality offers controlled adjustment of stimulus speed, distractors, spatial demands, feedback, and task uncertainty. Reviews emphasize adaptive difficulty and engagement while identifying the need for stronger conceptual frameworks and outcome evidence (Guzmán et al., 2024). Technology-assisted dual-task interventions have also been studied in

Parkinson's disease and cognitive impairment, targeting gait, balance, cognition, and dual-task performance (Tuena et al., 2023). These platforms could test whether adapting cognitive load to biological readiness improves durable outcomes rather than session performance alone.

EEG-based closed-loop brain-computer interfaces provide another potential source of feedback on motor intention and neural engagement (Jin et al., 2024). Combining neural feedback with wearable monitoring and adaptive environments could support individualized training, but visible movement, measured brain activity, and beneficial plasticity should not be treated as interchangeable outcomes. The value added by neural feedback must be compared with conventional behavioral monitoring.

Future trials should separate endogenous circadian phase from clock time, account for chronotype and sleep-wake history, and assess acquisition, consolidation, retention, and transfer. They should determine whether wearable phase estimates are sufficiently accurate, whether adaptive digital systems produce lasting functional gains, and whether neural feedback improves outcomes beyond standard rehabilitation. Studies in neurological and athletic populations are needed before the proposed integrated systems can support routine prescription.

Implementation also requires privacy protection, informed consent, clear data ownership, algorithmic transparency, and equitable access. Automatic changes in cognitive demand must remain compatible with movement quality and safety. These systems should be clinically supervised and evaluated across diverse populations, with the proposed benefits of circadian alignment treated as research questions until direct evidence is available.

10. CONCLUSION

Exercise-induced neuroplasticity should not be considered a temporally uniform process. The neural and cognitive state in which exercise is performed varies across the day as a function of circadian timing, sleep-wake history, chronotype, fatigue, and other behavioral and physiological influences. These fluctuations are particularly relevant to neurocortical exercise paradigms, in which successful performance depends on the coordinated engagement of attention, executive control, sensory integration, decision-making, and motor planning. Consequently, an identical exercise task may represent a different cognitive and neural challenge depending on when and under what physiological conditions it is performed.

Current evidence is strongest for time-of-day and circadian modulation of cognitive performance, cortical excitability, neuromuscular function, and selected aspects of motor learning. In contrast, direct evidence demonstrating that exercise performed at a particular circadian phase produces superior long-term neuroplastic adaptation remains limited. This distinction is essential. Improved performance during a training session does not

necessarily indicate enhanced learning, and enhanced acquisition does not necessarily predict superior consolidation, retention, or transfer. Exercise timing should therefore be interpreted in relation to the specific adaptive objective rather than according to a universal morning-versus-evening prescription.

Within this context, the proposed Circadian Timing $\times$ Cognitive Load $\times$ Exercise Type framework provides a conceptual basis for integrating biological timing into neurocortical exercise prescription. The optimal training condition is likely to emerge from the interaction between the individual's biological state, the cognitive demands of the task, and the intended adaptive target. Such an approach may be particularly relevant in rehabilitation and performance settings, where the temporal requirements for skill acquisition, consolidation, and real-world performance may differ.

The transition from this conceptual framework to evidence-based chrono-neurocortical exercise prescription will require studies that distinguish endogenous circadian phase from external clock time, account for chronotype and sleep–wake history, and evaluate both immediate and delayed outcomes of training. Wearable monitoring, adaptive digital environments, and neural assessment technologies may eventually facilitate this transition by allowing exercise to be matched more closely to biological rather than clock time. Until such evidence becomes available, circadian timing should be viewed not as a rigid determinant of exercise effectiveness, but as a potentially important and individualized component of the broader physiological context in which neurocortical adaptation occurs.

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Safe Medication Management in The Neonatal Intensive Care Unit

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ABSTRACT

Medication safety in neonatal intensive care units (NICUs) is a fundamental component of medications. The physiological immaturity, low body weight, rapid developmental changes, and polypharmacy associated with neonates complicate the treatment process and increase the risk of errors.

This book chapter provides a comprehensive examination of medication safety in the NICU. It begins by explaining the concept of medication safety, the fundamental characteristics of neonatal pharmacology, and the classification of medication errors; it then evaluates in detail the risk factors encountered in medication management, dose calculation methods, medication preparation processes, and principles of safe administration.

The chapter addresses safety approaches regarding medication administration via intravenous, oral, intramuscular, subcutaneous, topical, and inhalation routes, while focusing on therapeutic drug monitoring, the assessment of adverse drug reactions, and pharmacovigilance practices. Additionally, the responsibilities of nurses regarding order verification, medication preparation, administration, patient monitoring, documentation, and error reporting are outlined.

In light of current literature, safety-enhancing practices—such as electronic prescribing systems, barcode technologies, smart infusion pumps, standardized drug concentrations, clinical decision support systems, and the involvement of clinical pharmacists—have been evaluated. Additionally, the contributions of simulation-based training, quality improvement projects, and a multidisciplinary team approach to reducing medication errors have been addressed.

In conclusion, medication safety in the Neonatal Intensive Care Unit (NICU) is a multidimensional process requiring the integration of healthcare professionals' knowledge and skills, an organizational safety culture, technological support systems, and evidence-based practices. Ensuring safe medication management is critically important for reducing preventable errors and improving neonatal patient outcomes.

Keywords: Neonatal intensive care unit, medication safety, medication errors, nursing, pharmacovigilance, therapeutic drug monitoring, patient safety, dose calculation.

INTRODUCTION

Neonatal intensive care units (NICUs) are specialized clinical settings where premature infants, those with low birth weight, and those with various medical conditions requiring critical care during the first days of life receive treatment. Care processes in these units involve the use of advanced

technology, multidisciplinary teamwork, and intensive pharmacological treatment regimens (Lu and Rosenbaum, 2014; Stark et al., 2022). Medication administration carries a high risk due to the fact that neonatal organ systems are not yet fully developed, pharmacokinetic and pharmacodynamic characteristics differ significantly from those of adults, and dosages are often based on individual calculations (Besunder et al., 1988; Vooght-Johnson, 2019).

Medication safety is a multidimensional aspect of patient safety that encompasses administering the right medication to the right patient, at the right dose, at the right time, via the right route, and using the correct documentation system (World Health Organization, 2017). In the NICU, medication errors can occur at any stage—including prescribing, order interpretation, dose calculation, preparation, administration, and monitoring—and can lead to serious morbidity and mortality (Alghamdi et al., 2019; Stavroudis et al., 2010).

The literature indicates that newborns are among the patient groups most affected by medication errors. Factors increasing the risk of error include the adaptation of adult medication formulations for use in premature infants, the necessity of preparing very small doses, and the frequent need for intravenous administration (Clark et al., 2006; Mørk et al., 2022). Additionally, workload in the intensive care setting, communication issues, knowledge gaps, distractions, and systemic inadequacies contribute to the occurrence of errors (Bacon and Hoffman, 2020; Michalek and Carson, 2020).

In recent years, numerous strategies aimed at enhancing medication safety have been developed in line with advancements in patient safety. These strategies include the use of electronic prescribing systems, barcode technologies, smart infusion pumps, clinical decision support systems, and standardized medication concentrations (Kuitunen et al., 2022; Schnock et al., 2024). Furthermore, the integration of clinical pharmacists into care teams, double-check procedures, and simulation-based training programs also contribute to reducing medication errors (Henry Basil et al., 2025; Canales-Siguero et al., 2025).

Nurses play a central role in ensuring medication safety in the Neonatal Intensive Care Unit (NICU). They are actively involved in every stage of the process, including order verification, dose calculation, medication preparation, administration, monitoring, documentation, and error reporting. Consequently, nurses' pharmacological knowledge, clinical experience, and skills in safe medication administration directly influence patient outcomes (Alghamdi et al., 2019; Henry Basil et al., 2025).

This book chapter provides a comprehensive overview of medication safety in the NICU. It begins by defining the concept of medication safety and explaining the pharmacological characteristics specific to newborns; it then examines in detail the causes of medication errors, dose calculation processes, routes of administration, therapeutic drug monitoring, and nursing

responsibilities. Furthermore, by evaluating current technological advancements, evidence-based practices, and strategies to enhance medication safety, the chapter presents a holistic perspective on safe medication management in neonatal care.

1. THE IMPORTANCE AND CHALLENGES OF MEDICATION MANAGEMENT IN NEONATAL INTENSIVE CARE UNITS

Neonatal intensive care units (NICUs) are high-risk clinical settings where premature and critically ill infants requiring advanced medical care during the first days of life are treated. Pharmacological therapies administered in these units play a decisive role in reducing mortality and morbidity rates. However, the fact that the physiological and pharmacological characteristics of neonates differ from those of adults and older children complicates the planning and administration of drug therapy (Besunder et al., 1988; Lu and Rosenbaum, 2014; Vooght-Johnson, 2019).

The immaturity of organ systems leads to significant alterations in the processes of drug absorption, distribution, metabolism, and elimination. In particular, the incomplete development of hepatic enzyme systems and renal functions in premature infants results in marked differences in pharmacokinetic properties. This situation limits the safety of standard dosing approaches and necessitates individualized dose calculations (Butranova et al., 2023; Mørk et al., 2022; Vooght-Johnson, 2019).

Medication use is highly prevalent in NICUs, with the vast majority of patients exposed to multiple drugs simultaneously. Large-scale studies indicate that antibiotics, cardiovascular drugs, respiratory system agents, analgesics, and parenteral nutrition products are among the most frequently used therapeutic options (Clark et al., 2006; Hsieh et al., 2014; Stark et al., 2022; Wang et al., 2025). The use of multiple medications, however, entails additional risks regarding drug interactions and administration errors.

Medication errors are considered one of the most significant threats to patient safety in neonatal intensive care units (NICUs). Errors occurring at any stage—prescribing, preparation, dispensing, administration, or monitoring—can lead to serious adverse events. The narrow therapeutic range in neonates and the fact that doses are typically calculated on a per-kilogram basis mean that even minor calculation errors can result in clinically critical consequences (Stavroudis et al., 2010; Alghamdi et al., 2019; Henry Basil et al., 2025). Research indicates that medication errors occur more frequently in pediatric and neonatal intensive care settings compared to adult intensive care units. Dose calculation errors, incorrect concentration preparation, and inaccuracies in infusion rates are among the most commonly reported types of errors (Alghamdi et al., 2019; Stavroudis et al., 2010). In premature and low-birth-weight infants, the consequences of these errors can be more severe and may

lead to long-term complications (Butranova et al., 2023; Henry Basil et al., 2025).

While technological advancements contribute to enhancing medication safety, they are not sufficient on their own. Electronic prescribing systems, barcode-assisted medication administration, and smart infusion pumps are considered effective tools for reducing errors. However, the effectiveness of these systems relies on the training of healthcare professionals, the establishment of standard protocols, and the cultivation of a strong culture of patient safety (Bacon & Hoffman, 2020; Kuitunen et al., 2022; Erdfelder et al., 2023; Borrelli et al., 2025).

In the Neonatal Intensive Care Unit (NICU), medication management is a multi-stage process that encompasses not only the administration of the correct medication but also its preparation at the appropriate dosage, administration at the right time, monitoring of effects, and early identification of potential adverse events. Effective collaboration among nurses, physicians, and clinical pharmacists at every step of this process is critical for patient safety (Canales-Siguero et al., 2025; Michalek & Carson, 2020).

This chapter addresses the fundamental principles of safe medication management in neonatal intensive care units, the characteristics of neonatal pharmacology, the causes of medication errors, and prevention strategies in light of current literature. Additionally, the responsibilities of nurses regarding medication safety, the contributions of technological applications, and quality improvement approaches will be examined in detail.

2. FUNDAMENTALS OF NEONATAL PHARMACOLOGY

Conducting drug therapy safely and effectively in newborns requires an understanding of the fundamental principles of developmental pharmacology. This period is characterized by rapid physiological changes and the ongoing functional maturation of organ systems. Consequently, the pharmacokinetic and pharmacodynamic properties of drugs differ significantly from those in adults. These differences are particularly pronounced in premature newborns, necessitating specialized approaches regarding dosage determination, administration frequency, and therapeutic monitoring (Besunder et al., 1988; Lu and Rosenbaum, 2014; Vooght-Johnson, 2019).

2.1. Pharmacokinetic Properties in the Newborn

Pharmacokinetics encompasses the processes of drug absorption, distribution, metabolism, and excretion within the organism. Since these four processes operate differently in newborns compared to adults, the efficacy and toxicity risk of a given drug may vary according to age (Lu and Rosenbaum, 2014; Mørk et al., 2022).

2.1.1. Absorption

The immature characteristics of the gastrointestinal system directly affect drug absorption. Delayed gastric emptying, elevated gastric pH, and

underdeveloped intestinal motility can alter the bioavailability of oral medications. Therapeutic levels may increase for some drugs while remaining lower than expected for others (Besunder et al., 1988; Vooght-Johnson, 2019). In premature infants, the immature structure of the intestinal mucosa and variability in perfusion can lead to unpredictable outcomes. Therefore, it is recommended to carefully monitor the clinical response during oral treatments and, if necessary, check serum drug levels (Lu and Rosenbaum, 2014; Butranova et al., 2023).

2.1.2. Distribution

The proportion of total body water is higher in newborns than in adults; in premature infants, this ratio can reach 80–90%. This increases the volume of distribution for water-soluble drugs and necessitates higher doses per kilogram (Besunder et al., 1988; Lu and Rosenbaum, 2014). Low adipose tissue content limits the distribution of lipophilic drugs. Conversely, low plasma protein levels increase the free fraction of protein-bound drugs, thereby raising the risk of toxicity. Competition for binding sites between drugs and bilirubin can have clinically critical consequences, particularly in premature infants (Besunder et al., 1988; Vooght-Johnson, 2019).

2.1.3. Metabolism

Hepatic enzyme systems are not fully developed in newborns. Age-related changes in cytochrome P450 activity influence the metabolic rate of many drugs. This can lead to drugs remaining in the body for longer periods and reaching toxic levels (Mørk et al., 2022; Butranova et al., 2023). Due to the limited metabolic capacity in premature infants, dosages of antibiotics, opioids, and sedatives must be carefully adjusted. Rapid changes in liver function during the postnatal period can result in varying dosage requirements for the same patient within a span of a few weeks (Vooght-Johnson, 2019; Butranova et al., 2023).

2.1.4. Excretion

Since renal function is not fully developed in newborns, drug elimination is slower compared to adults. Glomerular filtration rate is low at birth and increases progressively during the first few weeks of life. Consequently, the half-life of renally excreted drugs is prolonged, creating a risk of accumulation (Lu and Rosenbaum, 2014; Mørk et al., 2022). The elimination of aminoglycosides depends on renal function; therapeutic drug monitoring for drugs such as gentamicin and amikacin is important for ensuring efficacy and reducing the risk of nephrotoxicity (Butranova et al., 2023).

2.2. Impact of Gestational Age and Birth Weight on Drug Dosing

Chronological age alone is insufficient for determining drug doses in newborns. Gestational age, postnatal age, birth weight, and current body weight must be evaluated together. Since there are pharmacokinetic differences between preterm and term newborns, standard dosing practices can lead to serious errors (Stavroudis et al., 2010; Vooght-Johnson, 2019).

Calculation errors can easily occur in very low birth weight infants because doses are administered in small volumes. Therefore, independent verification of doses and the use of electronic support systems are recommended (Alghamdi et al., 2019; Henry Basil et al., 2025).

2.3. Pharmacodynamic Characteristics in Newborns

Pharmacodynamics examines the effects of drugs on target organs and systems. Receptor sensitivity and cellular response mechanisms in newborns differ from those in adults; consequently, the same serum concentration may result in different clinical effects (Lu and Rosenbaum, 2014; Vooght-Johnson, 2019). Sensitivity to opioids, sedatives, and cardiovascular drugs may be increased due to the immaturity of the central nervous system, as well as the cardiovascular and respiratory systems. Dosing without considering these differences can lead to serious adverse events (Besunder et al., 1988; Mørk et al., 2022).

2.4. The Issue of Newborn-Specific Drug Formulations

Most drugs used in the NICU are administered by adapting preparations originally manufactured for adults or older children. This situation necessitates additional dilution procedures and increases the risk of error (Clark et al., 2006; Hsieh et al., 2014). Furthermore, pharmacokinetic and safety data regarding the use of many drugs in newborns are limited. Consequently, "off-label" use is common. Studies indicate that a significant proportion of drugs used in the NICU are administered off-label (Clark et al., 2006; Stark et al., 2022; Al-Turkait et al., 2022).

2.5. Importance for Clinical Practice

Understanding the fundamental principles of neonatal pharmacology plays a critical role in ensuring medication safety. Accurate dose calculations, appropriate determination of administration frequencies, monitoring of drug levels, and early detection of adverse effects all depend on pharmacological knowledge. Therefore, it is a fundamental component of patient safety for physicians, nurses, and clinical pharmacists working in the Neonatal Intensive Care Unit (NICU) to possess up-to-date knowledge regarding developmental pharmacology (Alghamdi et al., 2019; Henry Basil et al., 2025; Canales-Siguero et al., 2025).

In conclusion, the pharmacokinetic and pharmacodynamic properties of drugs in neonates differ significantly from those in adults. Taking these differences into account is essential for developing individualized treatment plans and preventing medication errors. A pharmacological approach based on neonatal developmental physiology forms the foundation of safe medication management in the NICU.

3. MEDICATION ERRORS IN THE NICU: TYPES, CAUSES, AND RISK FACTORS

Neonatal Intensive Care Units (NICUs) are among the clinical settings with the highest rates of medication use and are considered high-risk environments regarding medication safety. The physiological vulnerability of newborns, their low body weight, rapid clinical changes, and the simultaneous use of multiple medications increase the likelihood of medication errors. Therefore, understanding the causes and risk factors associated with medication errors is considered a fundamental requirement for ensuring patient safety (Stavroudis et al., 2010; Alghamdi et al., 2019).

A medication error is defined as any preventable event that has the potential to cause harm to the patient and occurs during the prescribing, preparation, dispensing, administration, or monitoring of medication. Medication errors in the NICU not only compromise treatment success but can also lead to serious morbidity and mortality. Consequently, medication safety is a priority objective in international patient safety programs (Alghamdi et al., 2019; Henry Basil et al., 2025).

3.1. Classification of Medication Errors

Medication errors are classified according to the stages of the treatment process in which they occur. This classification facilitates the identification of error sources and the development of preventive strategies (Stavroudis et al., 2010).

3.1.1. Prescribing Errors

Incorrect drug selection, erroneous dosage determination, inappropriate route of administration, and incomplete orders are among the types of prescribing errors. Since dosages for newborns must be calculated based on body weight, even minor calculation errors can lead to serious clinical consequences (Alghamdi et al., 2019; Canales-Siguero et al., 2025). Medication orders for premature infants that fail to account for gestational age are a significant cause of errors. Although electronic prescribing systems have reduced these errors, they have not eliminated them entirely (Canales-Siguero et al., 2025).

3.1.2. Medication Preparation Errors

Preparing the wrong concentration, inappropriate dilution, or incorrect medication preparation falls into this category. Preparing doses in small volumes for newborns complicates the process (Stavroudis et al., 2010; Henry Basil et al., 2025). Dilutions performed because commercial preparations are unavailable in appropriate dosages increase the risk of error (Clark et al., 2006; Stark et al., 2022).

3.1.3. Distribution Errors

Sending the wrong medication or a product with the wrong concentration to the clinical unit is classified as a distribution error.

Similarities in packaging and names are significant causes of these errors (Alghamdi et al., 2019; Stavroudis et al., 2010).

3.1.4. Administration Errors

Medication administration involving the wrong patient, wrong dose, wrong time, or wrong route of administration falls into this category. It is one of the most frequently reported types of errors in neonatal intensive care (Alghamdi et al., 2019; Henry Basil et al., 2025). Incorrect programming of infusion pumps poses a serious risk, particularly with vasoactive medications and parenteral nutrition products (Schnock et al., 2024; Borrelli et al., 2025).

3.1.5. Monitoring Errors

Failure to adequately assess the effects and side effects of a medication is defined as a monitoring error. Inadequate monitoring of drugs with a narrow therapeutic range—such as aminoglycosides, vancomycin, and antiepileptics—can lead to toxicity (Butranova et al., 2023).

3.2. Most Common Medication Error in the NICU: Dosage Errors

Dosage errors are the most frequently reported type of error in neonatal intensive care. This category comprises miscalculations, concentration errors, or inaccuracies in infusion rates (Alghamdi et al., 2019; Henry Basil et al., 2025). Incorrect use of decimal points can lead to dosage errors of 10-fold or even 100-fold (Stavroudis et al., 2010). Rapid weight fluctuations in premature infants are also a significant factor contributing to the occurrence of dosage errors.

3.3. Risk Factors Contributing to Medication Errors

- **Calculation difficulties:** Complex dosage calculations mean that even minor errors can lead to serious consequences (Alghamdi et al., 2019).

- **Lack of knowledge:** Insufficient knowledge regarding pharmacokinetic properties and administration protocols increases the risk of error (Henry Basil et al., 2025).

- **Workload and staffing shortages:** A high-intensity work pace and fatigue increase the risk of error (Stavroudis et al., 2010; Henry Basil et al., 2025).

- **Communication problems:** Misunderstandings during verbal orders and the incomplete transfer of information lead to errors (Alghamdi et al., 2019; Canales-Siguero et al., 2025).

- **Issues with similar names and packaging:** Similarities in drug names and packaging can lead to the administration of the wrong medication (Stavroudis et al., 2010; Erdfelder et al., 2023).

3.4. Clinical Consequences of Medication Errors

Medication errors in newborns can lead to complications such as hypoglycemia, hypotension, respiratory depression, nephrotoxicity, and neurotoxicity (Alghamdi et al., 2019). Furthermore, they prolong the length of hospital stay, increase costs, and place an additional burden on the healthcare system (Henry Basil et al., 2025; Borrelli et al., 2025).

3.5. Evaluation of the Section

Medication errors in the NICU have a multifactorial nature and can occur at all stages of the treatment process. Dosage errors, in particular, are the most frequently encountered type of error in the neonatal patient population. Calculation difficulties, workload, communication gaps, and system-related issues are key factors that increase the risk of error. Therefore, to ensure safe medication management, preventive strategies must be developed at both individual and institutional levels. The next section will discuss in detail the principles of safe medication management and evidence-based practices aimed at reducing medication errors in the NICU.

4. PRINCIPLES AND STRATEGIES OF SAFE MEDICATION MANAGEMENT

Medication safety in neonatal intensive care units is considered one of the most critical components of patient safety. Due to the physiological fragility of newborns, the necessity of calculating dosages based on individual characteristics, and the prevalence of polypharmacy, even the slightest error in medication management processes can lead to serious clinical consequences. Therefore, safe medication management relies not only on individual attentiveness and experience but also on standardized processes, technological support systems, and a strong safety culture (Alghamdi et al., 2019; Henry Basil et al., 2025).

System-based approaches have been developed globally within patient safety initiatives to reduce medication errors. Today, safe medication management extends beyond the principles of the right patient, right medication, right dose, right route, and right time to encompass multidisciplinary teamwork, technological solutions, and continuous quality improvement activities (Michalek and Carson, 2020; Canales-Siguero et al., 2025).

4.1. Fundamental Principles of Safe Medication Management

In the nursing and patient safety literature, the approach forming the foundation of safe medication practices is defined as the "Rights" principles. These principles aim to reduce the risk of error by establishing a systematic control mechanism within the medication administration process (Alghamdi et al., 2019).

- **Right Patient:** The identity verification process is of critical importance. Given that newborns cannot communicate verbally, verification using identification wristbands and at least two identifiers is recommended (Erdfelder et al., 2023).

- **Right Medication:** Labels must be checked carefully to prevent confusion between medications with similar names or packaging (Stavroudis et al., 2010; Erdfelder et al., 2023).

- **Right Dose:** Dosage should be calculated based on current body weight and gestational age, and a double-check system should be employed

for medications administered at the microgram level (Alghamdi et al., 2019; Henry Basil et al., 2025).

- **Right Route:** The prescribed route of administration must be followed correctly, as errors in the route can lead to serious complications (Vooght-Johnson, 2019).

- **Right Time:** Timing errors regarding antibiotics and continuous infusion medications can result in therapeutic failure (Butranova et al., 2023).

- **Right Approach and Documentation:** Administration in accordance with standard procedures and a comprehensive documentation system contribute to quality improvement efforts (Canales-Siguero et al., 2025).

- **Right Information and Assessment:** Monitoring the response to treatment and keeping parents informed are essential components of family-centered care (Michalek and Carson, 2020).

4.2. Electronic Prescribing and Clinical Decision Support Systems

Electronic prescribing systems (CPOE) enable medication orders to be generated digitally. These systems reduce errors caused by illegible handwriting and provide automated dose-checking mechanisms (Canales-Siguero et al., 2025). Modern systems can provide age- and weight-appropriate dosage recommendations, monitor maximum dosage limits, and issue alerts regarding drug interactions. Clinical decision support systems enhance safety, particularly with high-risk medications; however, their effectiveness depends on user training and the level of integration (Michalek and Carson, 2020).

4.3. Barcode Medication Administration Systems

Barcode systems enable the matching of the patient's identity with the medication. Scanning the patient's wristband and the medication barcode verifies the correct patient-correct medication match (Erdfelder et al., 2023). Research indicates that these systems reduce errors involving the wrong patient and wrong medication. Furthermore, the electronic monitoring of administration times contributes to quality improvement processes (Michalek and Carson, 2020; Erdfelder et al., 2023). Although implementing barcode systems in the Neonatal Intensive Care Unit (NICU) requires specific adjustments, they are widely recommended due to the safety benefits they offer.

4.4. Smart Infusion Pumps

Intravenous medication administration is one of the highest-risk processes in neonatal intensive care. Consequently, the use of smart infusion pumps is becoming increasingly widespread. Smart pumps prevent programming errors through the use of drug libraries and predefined dose limits (Kuitunen et al., 2022). Dose Error Reduction Systems (DERS) alert users when infusion rates or dose limits are exceeded. These systems enhance safety, particularly regarding vasopressors, opioids, and high-risk intravenous medications (Kuitunen et al., 2022; Schnock et al., 2024). Systematic reviews demonstrate that smart pumps are effective in reducing medication errors;

however, device updates, the standardization of drug libraries, and ongoing user training are essential (Borrelli et al., 2025; Schnock et al., 2024).

4.5. Standardization Strategies

Standardization plays a critical role in enhancing medication safety. This approach aims to establish common practice processes among various healthcare professionals and to reduce variability (Bacon and Hoffman, 2020).

- **Standard concentrations:** The use of standard concentrations, particularly for medications administered via continuous infusion, reduces errors arising from differing preparation methods (Kuitunen et al., 2022).

- **Standardization of abbreviations:** It is recommended to avoid abbreviations that could be misinterpreted and to write out dosage units clearly. For instance, using "mcg" or "microgram" instead of symbols that might be misread reduces the risk of error (Bacon and Hoffman, 2020).

- **Color-coding systems:** Marking high-risk medications with distinctive colors draws the attention of healthcare professionals and reduces the likelihood of mix-ups (Erdfelder et al., 2023).

4.6. Double-Check and Team Approach

Double-checking procedures for high-risk medications constitute a key method for enhancing safety. Having a second healthcare professional verify the medication dose, concentration, and administration rate reduces the risk of error (Alghamdi et al., 2019).

Furthermore, a multidisciplinary team approach is a fundamental component of safe medication management. Collaboration among physicians, nurses, and clinical pharmacists enhances safety at every stage of the treatment process. The active participation of clinical pharmacists has been found effective in reducing medication errors (Michalek and Carson, 2020).

4.7. Safety Culture and Error Reporting Systems

A patient safety culture refers to an environment in which healthcare professionals can report errors without fear of punishment. Error reporting should be viewed as a means to identify system deficiencies rather than to assign individual blame (Bacon and Hoffman, 2020).

Through error reporting systems, institutions can identify recurring issues and develop corrective measures. This approach contributes to the sustainable improvement of medication safety (Alghamdi et al., 2019).

4.8. Evaluation of the Section

Safe medication management in the NICU is a systematic process involving multi-layered safety barriers, rather than one relying solely on individual diligence and experience. Principles of correct administration, electronic prescribing systems, barcode technologies, smart infusion pumps, standardization efforts, and a team-based approach play a significant role in reducing medication errors. However, ensuring the sustainability of safe medication management requires the establishment of a strong patient safety culture throughout the institution.

5. DOSE CALCULATION AND PREPARATION PROCESSES

One of the most critical stages in ensuring medication safety in neonatal intensive care units is the execution of accurate dose calculation and appropriate medication preparation processes. Due to the physiological characteristics, low body weights, and developmental pharmacokinetic differences of newborns, standard dosing approaches used for adults cannot be applied to this patient group. Therefore, the use of individualized calculation methods during the treatment process is essential (Besunder et al., 1988; Lu and Rosenbaum, 2014).

Dose calculation errors account for a significant portion of medication errors observed in the NICU. Incorrect dose calculations can lead to serious adverse events in premature and extremely low birth weight infants. Consequently, systematic safety measures must be implemented during the processes of dose calculation, preparation, and administration (Alghamdi et al., 2019; Henry Basil et al., 2025).

5.1. Principles of Dose Calculation in Neonates

Doses are generally calculated based on weight in kilograms (mg/kg, mcg/kg, or units/kg). In certain special cases, methods based on body surface area may be used. During the calculation process, current body weight, gestational age, postnatal age, organ function, and clinical status must be evaluated together (Vooght-Johnson, 2019; Butranova et al., 2023).

Due to rapid weight fluctuations in premature infants, doses require regular recalculation. Outdated weight data increase the risk of overdose or underdosing (Stavroutis et al., 2010). Additionally, concentration, total volume, and infusion duration must be accurately determined (Alghamdi et al., 2019).

5.2. Dose Calculation Based on Kilograms

The most common method is calculating the dose per kilogram. For example, administering a drug with a recommended dose of 5 mg/kg to a neonate weighing 2 kg:

$$\text{Total dose} = 5 \text{ mg/kg} \times 2 \text{ kg} = 10 \text{ mg}$$

This method is frequently used for antibiotics, analgesics, and cardiovascular drugs (Butranova et al., 2023). However, errors involving decimal places pose a serious risk for drugs dosed in the microgram range. Therefore, it is recommended that calculations be verified through an independent double-check (Stavroutis et al., 2010; Henry Basil et al., 2025).

5.3. Dose Calculation Based on Body Surface Area

Some drugs are dosed based on body surface area (BSA). The Mosteller formula is the most commonly used method:

$$\text{BSA (m}^2\text{)} = \sqrt{[(\text{Height (cm)} \times \text{Weight (kg)}) / 3600]}$$

Although less preferred for neonates, this method is important for certain oncological and specialized treatments. Verification of calculations using electronic systems is recommended (Lu and Rosenbaum, 2014).

5.4. High-Risk Medications and Dosage Errors

Dopamine, dobutamine, fentanyl, morphine, insulin, heparin, and TPN products are among the high-risk medications (Alghamdi et al., 2019). The literature reports that the most serious errors involve 10-fold or 100-fold overdoses (Stavroudis et al., 2010). Confusing microgram and milligram units can lead to life-threatening consequences. Therefore, it is recommended that dosage units be clearly written out (Bacon and Hoffman, 2020). Double-checking, standard concentrations, and smart pumps reduce error rates (Kuitunen et al., 2022; Schnock et al., 2024).

5.5. Medication Preparation Processes

The preparation phase involves converting the medication into a form suitable for administration. Most medications used in neonates are adapted from adult preparations, which complicates the process (Clark et al., 2006; Stark et al., 2022). Correct concentration, appropriate diluents, and aseptic techniques are of critical importance (Henry Basil et al., 2025). Preparation procedures should be performed in environments free from distracting stimuli (Bacon and Hoffman, 2020).

5.6. Dilution Procedures and Safety Precautions

Medications require dilution due to the small doses administered to neonates. Incorrect dilution procedures can lead to medication ineffectiveness or toxicity. Therefore, standardized dilution charts should be used (Bacon and Hoffman, 2020). Verification by a second person is recommended for high-risk medications (Kuitunen et al., 2022).

5.7. Infusion Preparation and Programming Process

Intravenous infusions are common in the NICU. Setting the infusion rate correctly is just as important as ensuring the correct concentration. Incorrect programming increases the risk of overdose or underdose. Smart infusion pumps are recommended to mitigate these risks (Kuitunen et al., 2022; Borrelli et al., 2025).

5.8. Assessment of Medication Compatibility and Incompatibilities

Administering multiple intravenous medications through the same venous access site increases the risk of incompatibility. Issues such as precipitate formation, discoloration, or loss of active ingredient may occur (Vooght-Johnson, 2019). Compatibility checks for medications administered alongside TPN are of critical importance (Butranova et al., 2023). Clinical pharmacist support is effective in mitigating these risks (Michalek and Carson, 2020).

5.9. Evaluation of the Section

Dose calculation and medication preparation processes are fundamental components of medication safety in the NICU. Weight-based dosing, accurate dilution, double-checking of high-risk medications, and compatibility assessments reduce error rates. Technological support systems and standardized protocols strengthen safe medication management. The next

section will discuss medication administration routes and safe administration approaches in neonates in detail.

6. ROUTES OF DRUG ADMINISTRATION AND SAFE ADMINISTRATION

Ensuring medication safety in neonatal intensive care units is not limited solely to determining the correct drug and dosage. Administering the drug via the appropriate route is critical for ensuring pharmacological efficacy and preventing adverse effects. Due to the anatomical and physiological characteristics of newborns, routes of administration differ from those used for adults, and each method carries its own specific advantages and risks (Vooght-Johnson, 2019; Lu and Rosenbaum, 2014).

Medication administration errors are among the most frequently reported types of errors in neonatal intensive care. Selecting the wrong route of administration, errors in infusion rates, or deficiencies in administration technique can reduce treatment efficacy and lead to serious complications. Therefore, the administration process must be carried out in accordance with standard protocols (Alghamdi et al., 2019; Henry Basil et al., 2025).

6.1. Intravenous Drug Administration

Intravenous (IV) administration is the most commonly used method in the NICU. Delivering the drug directly into the circulation ensures a rapid onset of action and eliminates bioavailability issues. In critically ill newborns, antibiotics, vasoactive agents, analgesics, and TPN products are predominantly administered via the IV route (Clark et al., 2006; Stark et al., 2022).

However, IV administration is one of the highest-risk methods. Errors during preparation or administration can quickly lead to serious consequences. Consequently, the use of standard concentrations, double-check systems, and electronic verification methods is recommended (Alghamdi et al., 2019; Bacon and Hoffman, 2020).

6.1.1. Use of Infusion Pumps

Infusion pumps provide high accuracy at low volumes. Pump technologies offer advantages because even small changes in volume can affect clinical outcomes in premature infants (Kuitunen et al., 2022). Smart pumps alert users and reduce errors through the use of dose limits and drug libraries (Schnock et al., 2024; Borrelli et al., 2025).

6.1.2. Safety Precautions

It is necessary to check the patency of the intravenous access, evaluate drug compatibility, and verify infusion rates. Early detection of extravasation and catheter-related complications is important (Michalek and Carson, 2020). Double-checking is recommended for high-risk medications (Alghamdi et al., 2019).

6.2. Oral Medication Administration

Oral administration is non-invasive and easy. However, absorption in newborns differs from that in adults due to the immature nature of the gastrointestinal system (Besunder et al., 1988; Lu and Rosenbaum, 2014). Bioavailability can be more variable in premature infants; therefore, clinical response must be monitored carefully (Vooght-Johnson, 2019).

6.2.1. Safety Principles

The use of accurate measuring devices is important. Oral syringes improve dose accuracy, whereas household spoons can lead to errors (Alghamdi et al., 2019). Tube placement must be verified during nasogastric tube administration (Vooght-Johnson, 2019).

6.3. Intramuscular Medication Administration

Intramuscular (IM) administration is used to a limited extent due to insufficient muscle mass and pain. However, they may be preferred for vaccines, vitamins, and certain medications (Vooght-Johnson, 2019). Careful selection of the appropriate anatomical site and adherence to volume limits are required (Lu and Rosenbaum, 2014).

6.4. Subcutaneous Drug Administration

Subcutaneous administration is used for insulin and certain biological agents. Due to the limited amount of subcutaneous adipose tissue, the technique requires care (Lu and Rosenbaum, 2014). Rotating the injection site and monitoring for local reactions is recommended (Vooght-Johnson, 2019).

6.5. Topical Drug Administration

Topical administration involves application to the skin or mucous membranes. In newborns, systemic absorption is higher than in adults because the epidermal barrier is not fully developed, thereby increasing the risk of toxicity (Besunder et al., 1988). Antiseptics, antifungals, and dermatological preparations are frequently used; however, their safety profiles must be considered (Vooght-Johnson, 2019).

6.6. Inhalation Drug Administration

Inhalation administration is used for respiratory system treatments. Bronchodilators and surfactant therapies play a significant role in neonatal intensive care (Clark et al., 2006; Stark et al., 2022). Systemic side effects are reduced because the drug reaches the target organ directly. However, efficacy depends on the type of device and the administration technique (Vooght-Johnson, 2019).

6.7. Post-Administration Monitoring and Safety

Therapeutic efficacy and adverse effects must be monitored following drug administration. Close monitoring of vital signs is particularly necessary for IV administration (Butranova et al., 2023). Allergic reactions, hemodynamic changes, and respiratory problems must be recognized early (Alghamdi et al., 2019). Regular observation and documentation facilitate the planning of subsequent doses (Butranova et al., 2023).

6.8. Section Overview

In the PICU, routes of medication administration are selected based on the patient's clinical condition and the characteristics of the drug. Intravenous administration is the most common method; however, oral, intramuscular, subcutaneous, topical, and inhalation routes also have specific indications. Since each method carries its own inherent risks, standard protocols, technological support systems, and careful monitoring play a fundamental role in ensuring safety. The next section will address medication monitoring, therapeutic drug level tracking, and error reporting processes in detail.

7. DRUG MONITORING AND EVALUATION

Safe medication management in neonatal intensive care units is not limited to administering the right drug at the right dose. Systematic drug monitoring must be conducted to evaluate treatment efficacy, detect adverse effects early, and prevent complications. Due to the physiological immaturity and pharmacokinetic variability of neonates, drug responses differ from those of adults; this necessitates close clinical monitoring throughout the course of treatment (Besunder et al., 1988; Vooght-Johnson, 2019).

Drug monitoring is a dynamic process that encompasses evaluating therapeutic efficacy, identifying adverse effects, and adjusting the treatment plan as necessary. Collaboration among physicians, nurses, and clinical pharmacists during this process enhances patient safety (Michalek and Carson, 2020; Canales-Siguero et al., 2025).

7.1. Clinical Evaluation of Drug Efficacy

The initial post-treatment evaluation focuses on whether the targeted clinical effect has been achieved. Expectations include the resolution of signs of infection with antibiotics, the achievement of hemodynamic stability with vasoactive drugs, and effective pain control with analgesics (Butranova et al., 2023).

Clinical evaluation should not rely solely on laboratory results. Vital signs, behavioral changes, feeding tolerance, and urine output are important indicators of treatment efficacy (Vooght-Johnson, 2019). Systematic evaluation at regular intervals is recommended, given that responses develop more slowly in premature infants (Lu and Rosenbaum, 2014).

7.2. Therapeutic Drug Monitoring (TDM)

TDM is based on measuring the serum concentrations of specific drugs and adjusting treatment according to these results. Due to the high degree of pharmacokinetic variability in newborns, TDM is a crucial component of patient safety (Butranova et al., 2023).

The objective is to ensure the drug remains within the effective concentration range and to prevent toxicity. Low serum levels can lead to treatment failure, while high levels may result in adverse effects (Mørk et al., 2022).

7.3. Drugs Requiring TDM

- **Gentamicin:** Due to its narrow therapeutic range, regular monitoring of serum levels is required. High levels increase the risk of nephrotoxicity and ototoxicity (Butranova et al., 2023).

- **Vancomycin:** Used for MRSA infections. High serum levels can lead to nephrotoxicity, while low levels can result in treatment failure (Mørk et al., 2022).

- **Anticonvulsants:** Monitoring serum concentrations of drugs such as phenobarbital and phenytoin is important regarding clinical efficacy and toxicity (Vooght-Johnson, 2019).

7.4. Monitoring Adverse Drug Reactions

Adverse drug reactions occur more frequently and are more severe in newborns. Respiratory depression, hypotension, tachycardia, nephrotoxicity, and hepatotoxicity may be observed (Vooght-Johnson, 2019). Close monitoring is essential, particularly when using opioids, sedatives, and aminoglycosides. Nursing observations play a critical role in the early recognition of these complications (Henry Basil et al., 2025).

7.5. Laboratory Monitoring

Renal and hepatic function tests, complete blood counts, and electrolyte levels should be evaluated regularly (Mørk et al., 2022). Monitoring serum creatinine during aminoglycoside therapy and performing liver function tests for drugs undergoing hepatic metabolism are important (Butranova et al., 2023). Findings should be interpreted in conjunction with clinical data (Vooght-Johnson, 2019).

7.6. Pharmacovigilance and Medication Safety

Pharmacovigilance encompasses activities aimed at identifying and preventing adverse effects associated with medication use. Documenting adverse events in newborns is of great importance (Alghamdi et al., 2019; Stark et al., 2022). Through these practices, new adverse effects can be identified, and guidelines updated (Al-Turkait et al., 2022).

7.7. Medication Error Reporting Systems

Medication error reporting systems facilitate the documentation of actual or potential errors. The objective is not to assign individual blame but to identify system-related issues (Bacon and Hoffman, 2020). Regular analyses reveal common error types and contribute to the development of preventive strategies (Stavroudis et al., 2010). A robust reporting culture should be supported by non-punitive approaches (Michalek and Carson, 2020).

7.8. The Nurse's Role in Medication Monitoring

Nurses are the professionals who spend the most time with the patient following medication administration. Assessing vital signs, identifying adverse effects, and documenting findings are core nursing responsibilities (Henry Basil et al., 2025). Up-to-date pharmacological knowledge and continuous education programs support this process (Alghamdi et al., 2019).

7.9. Evaluation of the Section

Medication monitoring and evaluation processes are integral to safe medication management in the NICU. Therapeutic drug monitoring, early identification of adverse reactions, laboratory assessments, and pharmacovigilance practices enhance patient safety. Nurses' clinical observation skills and active participation in error reporting systems play a significant role in the sustainable improvement of medication safety. The next section will address in detail the nurse's responsibilities in medication administration, training requirements, and the development of professional competencies.

8. NURSING RESPONSIBILITIES AND EDUCATION

Nurses play a central role in the safe administration of medication in neonatal intensive care units (NICUs). They are actively involved in every stage of the process, from verifying medication orders and preparing the medication to administering it and monitoring its effects. Consequently, nurses' knowledge, skills, and decision-making processes are directly linked to patient safety (Alghamdi et al., 2019; Henry Basil et al., 2025).

Due to the physiological characteristics of newborns and their heightened sensitivity to medications, nurses working in the NICU must possess advanced pharmacological knowledge. Care provided to premature and extremely low birth weight infants demands a high level of vigilance and expertise (Vooght-Johnson, 2019; Lu and Rosenbaum, 2014).

International standards emphasize that nurses assume roles not only as administrators but also as evaluators, educators, and patient advocates. Therefore, nursing responsibilities require a comprehensive professional approach that extends beyond technical procedures (Michalek and Carson, 2020).

8.1. Verification of Medication Orders

Nurses must thoroughly review medication orders, checking the drug name, dosage, route, timing, and frequency. Any ambiguous orders must be clarified prior to administration (Alghamdi et al., 2019). Verifying that dosages correspond to the infant's current weight is of critical importance (Stavroudis et al., 2010). Even when electronic systems are utilized, the final check remains the responsibility of healthcare professionals (Canales-Siguero et al., 2025).

8.2. Responsibilities During the Medication Preparation Process

During preparation, the expiration date, concentration, and storage conditions of the medications must be evaluated (Clark et al., 2006; Stark et al., 2022). Procedures should be performed in environments free from distractions (Bacon and Hoffman, 2020). Independent double-checking is recommended for high-risk medications (Kuitunen et al., 2022).

8.3. Responsibility for Safe Medication Administration

The "rights" of medication administration must be strictly adhered to during the administration phase (Alghamdi et al., 2019). Patient identification is of particular importance in the NICU (Erdfelder et al., 2023). For intravenous administrations, checking pump settings and verifying the patency of the venous access site are among the nurse's responsibilities (Schnock et al., 2024).

8.4. Post-Administration Monitoring and Evaluation

Treatment efficacy and adverse effects must be monitored following medication administration. Vital signs, oxygen saturation, and laboratory results should be tracked regularly (Vooght-Johnson, 2019; Butranova et al., 2023). Unexpected effects must be documented and reported to the team (Henry Basil et al., 2025).

8.5. Responsibility for Recording and Documentation

Accurate and complete record-keeping is a fundamental element of medication safety (Canales-Siguero et al., 2025). Incomplete records negatively affect the continuity of care. Although electronic systems enhance traceability, the responsibility for accuracy rests with the nurse (Michalek and Carson, 2020).

8.6. The Nurse's Role in Preventing Medication Errors

Nurses are among the most critical safety barriers in the prevention of medication errors (Alghamdi et al., 2019). Adherence to standard protocols, double-checking, and the effective use of barcode systems and smart pumps are recommended (Erdfelder et al., 2023; Kuitunen et al., 2022). Error reporting should be conducted with the aim of system improvement (Bacon and Hoffman, 2020).

8.7. Role in Family Education and Counseling

Nurses should inform parents about the purpose, effects, and administration process of medications (Michalek & Carson, 2020). Education regarding home medication administration must be provided prior to discharge (Vooght-Johnson, 2019). Increasing the families' level of knowledge strengthens treatment adherence (Lu & Rosenbaum, 2014).

8.8. Continuing Professional Education and Competence Development

NICU nurses must keep abreast of current scientific developments and participate in continuing education programs (Henry Basil et al., 2025). Pharmacology, dosage calculation, smart pump usage, and compatibility assessments form the foundation of these training programs (Kuitunen et al., 2022). Simulation-based training reduces error rates (Bacon and Hoffman, 2020). Professional competence must be maintained through regular knowledge updates (Michalek and Carson, 2020).

8.9. Evaluation of the Section

NICU nurses assume critical responsibilities at every stage of medication management. Order verification, preparation, safe administration,

monitoring, documentation, and error prevention activities are fundamental components of nursing care. Family education and continuing professional development processes contribute to the sustainable improvement of medication safety. Therefore, equipping NICU nurses with up-to-date knowledge and skills is of strategic importance for patient safety.

9. EVIDENCE-BASED PRACTICES AND CURRENT APPROACHES TO ENHANCING MEDICATION SAFETY IN NEONATAL INTENSIVE CARE UNITS

Improving medication safety in neonatal intensive care units has become a priority area in patient safety initiatives in recent years. Due to the physiological vulnerability of neonates, the complexity of drug therapy, and the potential for medication errors to result in serious consequences, it is essential to develop safety practices based on scientific evidence. Current initiatives aimed at enhancing medication safety are moving beyond individual practices to target system-level improvements (Alghamdi et al., 2019; Canales-Siguero et al., 2025).

Evidence-based practices refer to approaches developed by integrating clinical experience with current scientific evidence. Studies conducted in neonatal intensive care units (NICUs) demonstrate that standardized processes and technology-supported practices significantly reduce error rates (Michalek and Carson, 2020).

9.1. World Health Organization and International Patient Safety Initiatives

The WHO's "Medication Without Harm" program aims to reduce medication-related harm (World Health Organization, 2017). Organizations such as the ISMP and JCI recommend the widespread adoption of high-risk medication management, barcode systems, and electronic verification processes (Bacon and Hoffman, 2020). These guidelines emphasize that medication errors are predominantly system-related (Michalek and Carson, 2020).

9.2. The Role of the Clinical Pharmacist in Medication Safety

Integrating clinical pharmacists into PICU teams contributes to the reduction of medication errors. They play an active role in prescription verification, dose calculation, compatibility assessment, and TDM processes (Michalek and Carson, 2020). This contribution is particularly significant regarding high-risk medications (Al-Turkait et al., 2022). Lower rates of adverse events are reported in multidisciplinary care models (Michalek and Carson, 2020).

9.3. Standard Concentration Practices

The use of standard concentrations reduces errors arising from varying preparation methods (Kuitunen et al., 2022). This practice decreases dosing errors, particularly with vasoactive medications. Safety is further enhanced

when used in conjunction with smart pumps (Schnock et al., 2024). Studies indicate that standard protocols lower error rates (Borrelli et al., 2025).

9.4. Smart Technologies and Digital Transformation

Electronic prescribing systems, barcode-assisted administration, and smart pumps are key technological components of medication safety in the PICU (Canales-Siguero et al., 2025). Electronic systems provide support for dose calculation; barcode systems reduce errors related to patient identification and medication administration (Erdfelder et al., 2023). Meanwhile, smart pumps prevent programming errors through dose error reduction software (Kuitunen et al., 2022; Schnock et al., 2024).

9.5. Simulation-Based Training Programs

Simulation training enables the development of clinical skills in a safe environment. It has been reported that the use of simulation in neonatal intensive care units (NICUs) reduces error rates (Bacon and Hoffman, 2020). These training programs incorporate scenarios involving high-risk medications and emergency procedures. Regular simulation training enhances nurses' knowledge and skills (Henry Basil et al., 2025).

9.6. Quality Improvement Projects

Quality improvement projects are conducted to reduce medication errors and standardize processes (Alghamdi et al., 2019). The PDCA (Plan-Do-Check-Act) cycle is a frequently used method in these projects (Michalek and Carson, 2020). Multidisciplinary teamwork contributes to strengthening the safety culture (Canales-Siguero et al., 2025).

9.7. Artificial Intelligence and Future Applications

Artificial intelligence-based systems can predict medication errors and provide clinical decision support to clinicians (Canales-Siguero et al., 2025). Machine learning algorithms can identify interactions and personalize dosage recommendations (Borrelli et al., 2025). However, further research is needed regarding data quality and ethical dimensions.

9.8. Evidence-Based Nursing Practices

Evidence-based nursing refers to supporting care decisions with scientific data. Dosage calculation checklists, double-check procedures, and standardized recording systems are methods used in nursing (Alghamdi et al., 2019). It has been shown that error rates decrease in clinical settings where these practices are widely implemented (Michalek and Carson, 2020; Henry Basil et al., 2025).

9.9. Evaluation of the Chapter

Enhancing medication safety in the NICU is a multifaceted process. International initiatives, clinical pharmacist support, standard concentrations, smart technologies, simulation training, and quality projects are key components of this process. Current evidence indicates that system-based approaches and multidisciplinary collaboration are effective in reducing medication errors. In the future, with the widespread adoption of AI-powered

decision-making systems and digital technologies, medication safety will be elevated to a higher level.

10. CONCLUSION AND RECOMMENDATIONS

Medication management in neonatal intensive care units (NICUs) is one of the most critical components of patient safety. Due to the physiological immaturity, low body weight, rapid developmental changes, and polypharmacy associated with neonates, treatment processes are inherently prone to errors. Therefore, ensuring medication safety requires not only individual vigilance but also system-based approaches, standardized practices, and a robust safety culture. The potential for medication errors to result in serious morbidity and mortality further underscores the importance of safety practices.

This section has examined in detail the conceptual foundations of medication safety, neonatal pharmacology, the causes of medication errors, principles of safe medication management, dose calculation processes, routes of administration, medication monitoring, and the responsibilities of nurses. The literature indicates that errors can occur at any stage—prescribing, preparation, administration, or monitoring—and that safety must be maintained throughout the entire process.

Current evidence demonstrates that standardized concentration practices, electronic prescribing systems, barcode technologies, clinical decision support systems, and smart infusion pumps are effective in enhancing medication safety. Specifically, standardized concentrations have been shown to reduce calculation and preparation errors, while electronic systems prevent errors during the prescribing phase.

Nurses play a central role in maintaining medication safety in the NICU. They assume active responsibility for processes involving order verification, dose calculation, preparation, administration, monitoring, documentation, and error reporting. Therefore, it is essential for them to keep their pharmacological knowledge up to date, effectively utilize technological systems, and integrate evidence-based practices into clinical care processes.

A multidisciplinary team approach is also of great importance in enhancing safety. The involvement of clinical pharmacists in treatment processes contributes to the early identification of medication-related problems and the reduction of adverse events. Studies indicate that medication safety indicators are more favorable in teams that include clinical pharmacists.

Strengthening the patient safety culture is a fundamental requirement for sustainability. The effective use of error reporting systems, the reporting of near-miss events, and the adoption of non-punitive approaches contribute to the transformation of institutions into learning organizations. It is reported that error rates are lower in institutions with a strong safety culture.

The integration of technological advancements will further advance medication safety practices in the future. It is anticipated that artificial intelligence-driven decision systems, automated dose verification mechanisms, and advanced clinical decision support programs can contribute to the prevention of medication errors, particularly among high-risk patient groups. However, further clinical research is needed to evaluate the effectiveness of these systems.

Recommendations

- Standard protocols and checklists should be used across all processes (Bacon and Hoffman, 2020).

- Double-check procedures should be made mandatory for high-risk medications (Alghamdi et al., 2019).

- Electronic prescribing and clinical decision support systems should be widely implemented.

- Barcode systems and smart pumps should be utilized in all NICUs.

- The integration of clinical pharmacists should be supported.

- Regular pharmacology training programs for nurses should be implemented.

- Simulation-based training should be expanded.

- Error reporting systems should be strengthened, and a culture of reporting should be encouraged.

- Neonate-specific dosage charts and administration guidelines should be regularly updated.

- Multi-center research on medication safety with high methodological quality should be increased.

General Assessment

Medication safety in the NICU is an integral part of quality care and patient safety. Safe medication management is a multidimensional process requiring the integration of knowledge, experience, teamwork, technology utilization, and an organizational safety culture. Reducing medication errors in newborns and improving the quality of care will be possible through the widespread adoption of evidence-based practices, the continuous education of healthcare professionals, and the implementation of system-based safety approaches.

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Artificial Intelligence in Gait Analysis and Movement Assessment: Clinical Applications, Evidence, and Future Directions in Physical Therapy

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ABSTRACT

Walking looks effortless until it is not. Subtle changes in how a person walks often appear long before a diagnosis, a fall, or a stalled rehabilitation plan, and physical therapists have always relied on careful observation and simple timed tests to catch them. Laboratory gait analysis can see far more, yet it remains costly, slow, and out of reach for most clinics. Artificial intelligence (AI) is beginning to narrow that gap. This chapter examines how machine learning and deep learning are used to measure gait and movement through wearable inertial sensors, ordinary video, and depth cameras, and what this means for everyday physical therapy practice. We explain the technical foundations in plain language, review clinical applications in neurological conditions, ageing and fall prevention, orthopaedic recovery, and sport, and appraise the strength of the evidence. The literature shows encouraging agreement between AI-based measures and laboratory reference systems for spatiotemporal parameters, whereas accuracy at distal joints, in out-of-plane motion, and in unfamiliar patient groups is less secure. Evidence that these tools improve patient outcomes, rather than simply measuring accurately, is still limited. We also discuss data quality, bias, interpretability, regulation, and workflow integration, and we offer a practical checklist for clinicians considering adoption. The chapter closes with future directions, including smartphone-based musculoskeletal modelling, continuous home monitoring, and explainable decision support. Throughout, AI is framed as an aid to clinical reasoning and not as a replacement for it.

Keywords – artificial intelligence, gait analysis, movement assessment, machine learning, physical therapy, wearable sensors, markerless motion capture, rehabilitation

INTRODUCTION

Picture a physical therapist in a busy outpatient clinic on a Tuesday afternoon. A 68-year-old woman, three months after a stroke, walks the length of the corridor while the therapist watches her knee, her foot clearance, and the small hesitation at each turn. The therapist notices that something is better than last month, but cannot say by how much. Next week, a colleague will see the same patient and may notice something different. This everyday scene captures both the strength and the weakness of traditional movement assessment: it rests on trained eyes and clinical experience, and it is difficult to measure, store, and compare.

Gait is more than a mechanical task. Walking speed has been proposed as a "sixth vital sign" because it summarises so much about a person's health in

one quick measure (Fritz and Lusardi, 2009), and in a pooled analysis of nine cohorts of older adults it was associated with survival (Studenski et al., 2011). Changes in gait rhythm and variability relate to fall risk (Hausdorff, 2007), and slowed or irregular walking can precede cognitive decline (Verghese et al., 2002). For physical therapists, then, gait and movement quality are at once a window into the patient's condition and a target for treatment.

For decades the richest source of gait information has been the instrumented laboratory, with infrared cameras, reflective markers, and force plates. The data it produces are excellent, but the setting is expensive and time-consuming and requires specialist staff, so most patients never experience it (Baker, 2006). Meanwhile, advances in sensors and in artificial intelligence (AI) have made it possible to estimate many of the same quantities from a few wearable devices or from video recorded on a smartphone. The promise is appealing: objective, repeatable movement data in the ordinary clinic, the patient's home, or the sports field.

Promise, however, is not proof. AI-based tools differ widely in how they were built, in the people on whom they were tested, and in what they actually measure. Some have been compared carefully against laboratory systems, others have not. Very few have been tested to see whether using them leads to better outcomes for patients. This chapter therefore has two aims. The first is to explain, without unnecessary jargon, how AI is currently applied to gait analysis and movement assessment. The second is to weigh the evidence honestly, so that clinicians, students, and researchers can judge where these tools are ready for use and where caution is still wise. The chapter is a narrative review, not a systematic one, and because the field moves quickly, readers should check for newer studies before making purchasing or clinical decisions.

The chapter proceeds in seven steps. We first revisit what conventional gait assessment can and cannot do, then introduce the technologies and learning methods behind AI-based assessment. Next we describe clinical applications across several populations, review the evidence, and examine the main challenges. A practical section follows for clinicians who are thinking about adoption, and the chapter ends with future directions and concluding remarks.

FOUNDATIONS OF GAIT AND MOVEMENT ASSESSMENT

Why gait deserves clinical attention

Normal walking is a repeated cycle in which the body is supported, propelled, and swung forward with remarkably little wasted effort (Perry and

Burnfield, 2010). Because the cycle draws on muscle strength, joint mobility, balance, sensation, and motor control at the same time, a problem in almost any of these systems can leave a mark on the way a person walks. This is why gait is useful as a general-purpose clinical signal. A reduced step length in one patient may point to weakness or pain, while an irregular rhythm in another may hint at a problem with motor planning or attention.

Clinicians have long tried to condense the many curves produced by a gait laboratory into a single, interpretable number. The Gait Deviation Index (Schwartz and Rozumalski, 2008) and the Gait Profile Score (Baker et al., 2009) are two widely known examples, and their strengths and limits have been discussed in detail (Cimolin and Galli, 2014). Such summary indices matter for AI because they show the direction in which the field is moving: from raw signals to clinically meaningful measures that can be tracked over time.

Conventional assessment and where it falls short

In most clinics, gait assessment still starts with observation, supported by simple tests. The Timed Up and Go test (Podsiadlo and Richardson, 1991) and short walk tests are quick and inexpensive, and reference values for comfortable and maximum walking speed are available for adults of different ages (Bohannon, 1997). These tests are valuable precisely because they are easy to perform. Their limitation is that they compress a complex movement into a single time or speed. Two patients can finish a ten-metre walk in the same time and yet have very different movement problems.

At the other end of the spectrum sits three-dimensional, marker-based motion capture combined with force plates. The conventional gait models that underpin this approach were developed in the late twentieth century (Kadaba et al., 1990; Davis et al., 1991), and they remain a reference standard. Yet the approach has practical drawbacks. Markers must be placed by an experienced operator, and small placement differences can alter the results. The patient walks in an artificial setting, often for a short time, which may not reflect how they move at home. Studies of Parkinson's disease, for example, have shown that walking in the laboratory and walking in daily life can differ appreciably (Del Din et al., 2016).

Systematic reviews have also reminded us that availability and evidence are not the same thing. Two reviews of instrumented gait analysis found the clearest support in cerebral palsy, where the information can influence surgical decisions and is linked to better outcomes, while evidence for many other conditions remained thin (Wren et al., 2011; Wren et al., 2020). This gap between what technology can measure and what has been shown to help patients is a theme we will return to throughout the chapter.

HOW ARTIFICIAL INTELLIGENCE ENTERS THE PICTURE

From hand-written rules to learning from data

Classical biomechanics relies largely on rules written by experts. A well-known example is the use of marker trajectories to detect the moments of heel strike and toe-off during walking (Zeni et al., 2008). Rules like these work well when the conditions are as expected, but they can fail when a patient walks with an unusual pattern, such as dragging a foot or using a walking aid.

Machine learning takes a different route. Instead of being told what to look for, an algorithm is shown many labelled examples and gradually learns the relationship between the input data and the answer of interest (Halilaj et al., 2018). In supervised learning, the answer may be a category, such as whether a recording comes from a person with Parkinson's disease or from a healthy control, or it may be a continuous value, such as stride length. Deep learning, a branch of machine learning that uses many-layered neural networks, can learn useful features directly from raw signals or images without a human specifying them in advance (LeCun et al., 2015). Reviews of automatic gait-pattern recognition show that a wide range of methods have been applied to motor disorders, with varying levels of reported accuracy (Figueiredo et al., 2018).

A concrete example helps. Hannink and colleagues (2017) trained a deep convolutional neural network to estimate stride length from inertial sensors worn on the feet of geriatric patients, and the network was more precise than a conventional approach based on signal processing. The point is not that the network "understands" walking, but that it can pick up regularities in the signal that are hard to capture with hand-written equations.

Learning-based methods also bring their own pitfalls. Halilaj and colleagues (2018) pointed out that small datasets, repeated recordings from the same person appearing in both training and testing sets, and inadequate validation can all produce results that look excellent on paper and collapse in practice. Clinicians who read studies of AI tools should therefore ask a simple question: was the model tested on people it had never seen?

Sensing technologies

Three families of sensing technology dominate the current literature. Wearable inertial measurement units (IMUs) combine accelerometers and gyroscopes, and they can be strapped to the lower back, the shank, or the foot. Reviews of wearable gait analysis document how these sensors have moved from research prototypes to practical systems (Tao et al., 2012; Muro-de-la-Herran et al., 2014; Chen et al., 2016). Trunk-mounted accelerometers can estimate spatiotemporal parameters with simple models (Zijlstra and Hof,

2003), foot-mounted sensors allow stride-by-stride estimates in older patients (Rampp et al., 2015), and commercial IMU systems have shown acceptable validity and test-retest reliability for several spatiotemporal measures (Kluge et al., 2017).

The second family is markerless video analysis. Pose-estimation algorithms such as OpenPose and DeepLabCut locate body keypoints, such as the hips, knees, and ankles, in ordinary images without the need for reflective markers (Cao et al., 2021; Mathis et al., 2018). The evolution of vision-based motion analysis towards markerless systems has been summarised by Colyer and colleagues (2018). In practical terms, a single camera pointed at a patient's side can already yield step time, step length, and sagittal-plane joint angles. Stenum and colleagues (2021) found good agreement for temporal parameters and step length when two-dimensional pose estimation was compared with a marker-based system, although joint angles at the ankle were harder to estimate than those at the hip and knee. Washabaugh and colleagues (2022) compared several open-source pose-estimation methods and showed that accuracy varied between methods and between joints. A broader review of markerless methods concluded that important limitations remain, particularly for movement outside the sagittal plane and for the foot and ankle (Wade et al., 2022).

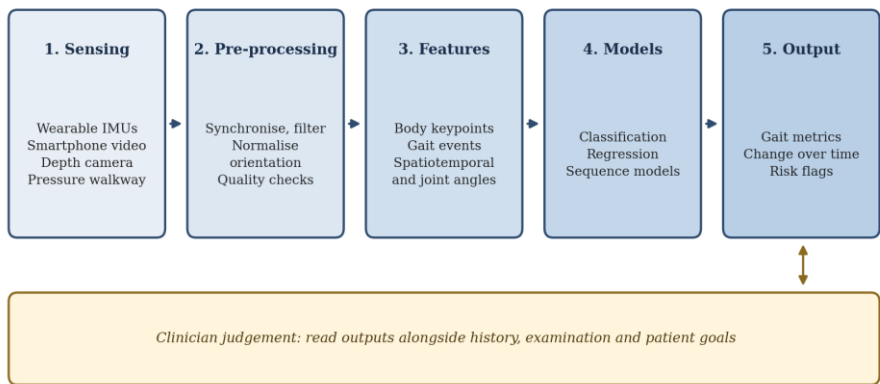
Video has been combined with deep learning to estimate clinically relevant quantities in specific patient groups. Kidziński and colleagues (2020) used keypoints extracted from single-camera videos of children with cerebral palsy to estimate gait parameters and to follow changes over time, a task that traditionally needed a laboratory. In stroke, Lonini and colleagues (2022) tested video-based pose estimation during routine clinical assessments in a proof-of-concept study, illustrating how analysis could be built into ordinary appointments.

The third family consists of depth cameras and pressure-sensing devices. Early work with the Microsoft Kinect showed that depth sensors could measure spatiotemporal and some kinematic variables with reasonable agreement (Mentiplay et al., 2015), and newer devices have been evaluated against gold-standard systems for gait analysis (Albert et al., 2020). Pressure-sensitive walkways and insoles continue to be useful for timing and loading measures.

Beyond measuring joint positions, the next step is to estimate the forces and loads that produce them. OpenSim, an open-source platform for musculoskeletal modelling (Seth et al., 2018), together with full-body muscle-driven models of gait (Rajagopal et al., 2016), has made such simulations accessible. OpenCap, introduced by Uhlich and colleagues (2023), connects

smartphone videos to these models so that joint kinematics and musculoskeletal dynamics can be estimated without a laboratory. This is an important development because it points towards a future in which the question is no longer only "how does the patient move?" but also "how are the tissues loaded when they move that way?"

Figure 1: A typical AI-supported gait assessment pipeline



Source: Prepared by the authors.

Each sensing option involves trade-offs. Table 1 sets out the main strengths and limitations of the technologies discussed above, in a form intended to support practical decisions.

Table 1: Sensing options for AI-supported gait and movement assessment

Technology	Typical setting	Main strengths	Main limitations
Marker-based laboratory capture	Specialist gait laboratory	Reference standard; full 3D kinematics and kinetics with force plates	Costly; needs space, time, and trained staff; artificial walking environment
Wearable IMUs	Clinic, home, field	Portable; suited to long recordings and free-living monitoring	Sensor placement and drift; limited direct view of posture; adherence
Markerless RGB video	Clinic, telehealth	Low cost; uses existing cameras or smartphones; no body attachments	Sensitive to camera angle, lighting, clothing, and occlusion; weaker at the ankle and out-of-plane motion
Depth cameras	Clinic	Direct depth information; simple setup	Limited range and field of view; accuracy varies by device

Technology	Typical setting	Main strengths	Main limitations
Pressure walkways and insoles	Clinic, shoe-based use	Accurate timing and loading information	No direct joint kinematics; walkway length restricts walking patterns

Source: Prepared by the authors, drawing on Chen et al. (2016), Colyer et al. (2018), Wade et al. (2022), and Kluge et al. (2017).

CLINICAL APPLICATIONS

Neurological conditions

Neurological disorders are where gait analysis has most to offer, because walking problems are common, varied, and strongly linked to quality of life. In Parkinson's disease, gait impairments include reduced step length, slower speed, and increased variability, and they respond to treatment in complex ways (Mirelman et al., 2019). Wearable sensors allow clinicians to follow these features outside the clinic, which matters because performance in a short supervised test can overestimate or underestimate everyday walking (Del Din et al., 2016). AI methods are used to classify gait patterns, to detect episodes of impaired walking, and to estimate disease-related change from continuous recordings.

In stroke rehabilitation, the therapist's main questions usually concern asymmetry, foot clearance, and walking speed, and whether these are changing in response to treatment. Video-based pose estimation could make such measurements part of routine appointments, as the proof-of-concept study by Lonini and colleagues (2022) suggests. In cerebral palsy, the combination of established laboratory practice and emerging video-based estimation (Kidziński et al., 2020; Wren et al., 2020) makes the condition an important test case for how far AI can extend access to detailed movement analysis in children.

Ageing, falls, and cognition

Falls are a major concern in geriatric rehabilitation, and sensors are an attractive way to identify risk early. A review of fall-risk assessment with inertial sensors found that most studies used sensors on the lower back or the feet, that many were retrospective, and that prospective evidence remained limited (Howcroft et al., 2013). That observation has not lost its relevance. Algorithms can often separate people who have fallen from those who have not in retrospective datasets, but a tool becomes clinically useful only when it predicts future falls in new patients and when acting on its predictions reduces harm.

Gait speed, variability, and rhythm are also being studied as markers of cognitive health. Gait abnormalities have been shown to predict the later onset of some forms of dementia (Verghese et al., 2002), and variability measures link walking to attention and executive function (Hausdorff, 2007). AI-based analysis of long recordings may eventually help therapists notice such changes sooner, although this use is still largely at the research stage.

Orthopaedic and post-surgical rehabilitation

After joint replacement, ligament reconstruction, or fracture, patients often keep favouring the unaffected side long after the pain has settled. Movement asymmetry is easy for a patient to hide and hard for a clinician to quantify by eye. Wearable sensors and smartphone-based systems can record how a patient walks, climbs stairs, or rises from a chair over the weeks of recovery, and open-source approaches to remote gait analysis for post-surgery patient monitoring have been demonstrated (Gurchiek et al., 2019). More broadly, mobile health technology has been proposed as a way to obtain daily activity and outcome data from wearable sensors during neurological and orthopaedic rehabilitation (Dobkin and Dorsch, 2011).

Sport and return to activity

In sport, the questions shift from "is this person walking safely?" to "is this athlete ready to cut, jump, and sprint?" Inertial sensors have been used in the field, outside the laboratory, to evaluate sport performance, which supports their role in screening movement quality and monitoring load (Camomilla et al., 2018). Smartphone-based systems that estimate joint kinematics and loading (Uhlrich et al., 2023) offer a further route to individualised return-to-sport testing. In this area, AI is most useful when it makes screening faster and more consistent, leaving decisions about progression to the clinician.

Remote monitoring and telerehabilitation

Remote care has grown quickly, and gait and movement assessment is a natural fit. A patient can record a short video of a prescribed exercise or a walk in the hallway, and an algorithm can extract measures that are then reviewed by the therapist. The same data can be used to give the patient feedback between visits. These applications depend heavily on the quality of the recording: camera position, lighting, clothing, and available space all affect accuracy (Wade et al., 2022). Clear instructions and simple quality checks are therefore as important as the algorithm itself.

Table 2 summarises the applications discussed above together with our qualitative appraisal of how mature the supporting evidence is. This appraisal is a judgement of the authors, based on the studies cited in this chapter, and it should be updated as new work appears.

Table 2: Clinical applications of AI-based gait and movement assessment

Population	Typical AI task	Example measures	Evidence maturity (authors' appraisal)
Parkinson's disease	Pattern classification; detection of impaired walking in free-living data	Step length, speed, variability, rhythm	Moderate for measurement; early for treatment decisions
Stroke	Video-based pose estimation; asymmetry estimation	Walking speed, symmetry, joint angles	Early; proof-of-concept studies
Cerebral palsy	Video-to-kinematics estimation; summary indices	Cadence, knee angle, gait indices	Strong for laboratory analysis; emerging for AI video
Older adults and falls	Fall-risk prediction from inertial data	Gait speed, variability, trunk acceleration	Moderate retrospectively; limited prospective evidence
Post-surgical recovery	Remote monitoring; asymmetry tracking	Stride parameters, symmetry over time	Early
Sport and return to activity	Field-based movement screening; load estimation	Joint kinematics, loading, jump and cutting mechanics	Early to moderate

Source: Prepared by the authors, based on the studies cited in this chapter.

REVIEWING THE EVIDENCE

How accurate are AI-based measures?

When AI-based measures are compared with laboratory systems, a consistent pattern emerges. Temporal parameters, such as step time, cadence, and gait events, are usually estimated well. Spatial parameters, such as step length, are often acceptable, especially in the walking direction. Joint angles in the sagittal plane at the hip and knee are generally more accurate than angles at the ankle, and movement in the frontal and transverse planes is hardest to capture, particularly with a single camera (Stenum et al., 2021; Washabaugh et al., 2022; Wade et al., 2022). Studies of wearable systems report acceptable validity and reliability for common spatiotemporal measures in many settings (Kluge et al., 2017; Chen et al., 2016), and smartphone-based musculoskeletal modelling is a promising development (Uhlrich et al., 2023).

Two cautions apply. First, accuracy figures from one study cannot be assumed to transfer to another population, camera setup, or walking environment. A model trained on healthy young adults may perform much worse on a person who uses a walking aid or who has a markedly abnormal

gait. Second, agreement with a reference system is only one aspect of validity. A measure also needs to be repeatable and sensitive enough to detect changes that matter to the patient. Clinicians should therefore compare the size of the change they hope to observe with the typical measurement error of the tool.

Do these tools improve patient outcomes?

This is the question that matters most to patients and also the one with the weakest answer. The evidence for instrumented gait analysis has mostly been judged by whether it changes clinical decisions and whether outcomes improve, and the strongest findings come from cerebral palsy rather than from the conditions where AI-based tools are now being promoted (Wren et al., 2011; Wren et al., 2020). Randomised trials that test whether AI-derived gait feedback leads to better walking, fewer falls, or faster recovery remain scarce. Broader commentary on AI in medicine has made a similar point, stressing the need for prospective, real-world validation before technologies are widely adopted (Topol, 2019).

Improving the quality of reporting is a step in the right direction. Guidelines such as TRIPOD, which sets out items to be reported in studies of prediction models (Collins et al., 2015), help readers judge whether a model was developed and tested appropriately. We encourage authors and reviewers in the movement sciences to use such guidance and to describe the participants, devices, and validation procedures in enough detail for results to be reproduced.

CHALLENGES AND LIMITATIONS

Data and generalisability. Many published models are built on small samples collected in a single centre under controlled conditions. Without diverse training data, performance can drop sharply on new patients, new devices, or new environments (Halilaj et al., 2018). Open datasets and open-source tools, such as those in the OpenSim community, are helping, but representation of older adults, children, people with severe impairment, and people from different ethnic and cultural backgrounds is still uneven.

Bias. An algorithm trained on unrepresentative data may serve some patients less well than others. Obermeyer and colleagues (2019) showed in another area of healthcare that a widely used algorithm underestimated the needs of Black patients because it used healthcare cost as a proxy for health need. Although that example did not concern gait, the lesson carries over: choices about what a model is trained to predict, and for whom, have real consequences for fairness. For markerless systems, differences in body shape, skin tone, clothing, and use of mobility aids deserve explicit testing.

Interpretability and trust. Therapists are understandably reluctant to rely on a number they cannot explain to themselves or to the patient. Rudin (2019) argued that in high-stakes settings, interpretable models should be preferred to opaque ones whenever possible, rather than explaining black-box models after the fact. For gait analysis, this suggests favouring outputs that map onto familiar clinical concepts, such as cadence, step symmetry, or joint range, and showing the underlying video or signal so the therapist can check that the output makes sense.

Privacy, consent, and regulation. Video of a patient's body is sensitive personal data. Clinics need clear consent processes, secure storage, and a decision about whether images are kept or only the derived measurements. Software that supports clinical decisions may also fall under medical-device regulation, depending on the jurisdiction and the intended use, so clinics should confirm the regulatory status of any product they use.

Workflow and access. A tool that adds fifteen minutes to a thirty-minute appointment will not be used, however accurate it is. Successful tools tend to fit existing routines, produce short, readable reports, and require little technical knowledge. Cost and digital access also matter: if AI-supported assessment is available only in well-resourced centres, it may widen existing inequalities instead of narrowing them.

PRACTICAL GUIDANCE FOR CLINICIANS

For therapists considering AI-based gait or movement tools, the following questions can serve as a starting point. They are not a formal protocol, but they reflect the issues repeatedly raised in the literature discussed in this chapter.

- Start with the clinical question. Decide what you need to know, such as walking speed, asymmetry, or fall risk, and choose a tool that has been tested for that purpose.
- Check who was in the validation study. Does the population resemble your patients in age, diagnosis, and level of impairment?
- Look for evidence of testing on new participants and, where possible, in settings similar to yours.
- Standardise your setup. Fix camera position, lighting, clothing instructions, and sensor placement so that repeated measurements are comparable.
- Compare the tool with something you trust in your own clinic for a few patients before relying on it.
- Know the measurement error. Interpret a change only when it is clearly larger than the tool's typical variation.

- Keep the clinician in the loop. Treat outputs as one source of information alongside history, physical examination, and the patient's own goals.
- Protect privacy. Obtain informed consent, decide what data are stored, and follow local data protection rules.
- Document what the tool was used for and how it influenced decisions, so that its value can be judged over time.

FUTURE DIRECTIONS

Several developments seem likely to shape the next decade. The first is the move towards smartphone-based musculoskeletal analysis. Work such as OpenCap (Uhlrich et al., 2023) suggests that estimates of joint dynamics, and not only joint angles, may become available outside the laboratory, which would allow therapists to consider loading as well as movement. For this to be useful in clinics, such systems will need independent validation in patient groups rather than in healthy volunteers alone.

The second is continuous monitoring. Wearable sensors already allow gait to be recorded over days and weeks, and this can capture variability and real-world function that short clinic tests miss (Del Din et al., 2016; Dobkin and Dorsch, 2011). The challenge will be to turn this stream of data into a small number of reliable, clinically meaningful signals, rather than overwhelming therapists with dashboards.

The third is better models and better data. Larger, more diverse, openly shared datasets, together with careful validation practices (Halilaj et al., 2018), should improve generalisation. Methods that allow models to learn from data held at different sites without moving the raw data, such as federated learning, may help address privacy concerns while widening the training pool.

The fourth is explainability and decision support. If AI tools are to earn clinical trust, their outputs must be understandable and linked to treatment options (Rudin, 2019). A system that merely flags an abnormal pattern is less helpful than one that shows what is unusual, how it has changed since the last visit, and which interventions have been associated with improvement.

Finally, and perhaps most importantly, the field needs well-designed clinical trials. Studies should test whether AI-supported assessment changes decisions, improves outcomes, and is cost-effective, and they should report results using accepted standards (Collins et al., 2015; Topol, 2019). Education will matter as well. Physical therapy curricula that include basic data literacy will prepare future clinicians to question and use these tools sensibly.

CONCLUSION

AI is changing how gait and movement can be measured. Wearable sensors, smartphone video, and depth cameras, combined with machine learning, can already supply objective information that was once confined to specialised laboratories. The strongest evidence supports the measurement of temporal and spatial gait parameters, with more uncertainty for distal joints, out-of-plane movement, and populations that differ from those used to train the models. Evidence that using these tools improves patient outcomes is, so far, limited.

For physical therapists, this combination of promise and uncertainty suggests a measured approach. Tools can be adopted where they have been validated for the intended purpose and population, where they fit into clinical routines, and where privacy and fairness have been considered. They should support, not replace, the clinical reasoning that has always been at the heart of physical therapy. The woman in our opening example deserves both: a therapist who knows how to read a stride, and a tool that can tell them, objectively, whether this week's stride is better than last week's.

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Neuropathic Pain in Para-Athletes: A Physiotherapy Perspective

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ABSTRACT

Neuropathic pain arises from a lesion or disease of the somatosensory nervous system and is a common problem in para-athletes. More than half of people with spinal cord injury and about two thirds of people with limb amputation live with pain of this kind. Yet para sport research has only recently addressed the issue. In one study of 47 athletes with spinal cord injury, two thirds of the participants reported moderate neuropathic pain. This chapter brings together current knowledge on neuropathic pain in para-athletes from a physiotherapy perspective and offers a framework for clinical practice. It covers the definition and classification of neuropathic pain, how it differs across impairment types, its relationship with sport, and its assessment and physiotherapy management; the problems that medication poses for athletes and the return-to-sport process are also discussed. The available data suggest that elite para-athletes report more neuropathic pain than recreational athletes, that they find it hard to describe, and that it is often mistaken for overuse injury. Screening tools such as the DN4, together with a careful sensory examination, help separate neuropathic from musculoskeletal pain. TENS, adjusting the exercise dose, mirror therapy and pain education stand out as options that may reduce the need for medication and the anti-doping risk that comes with it. Monitoring training load alongside pain also gives return-to-sport decisions a firmer footing. However, most of the evidence comes from non-athlete patients, and longitudinal and randomised controlled studies covering different impairment groups are needed.

Keywords – Para athlete, neuropathic pain, spinal cord injury, phantom limb pain, physiotherapy, TENS

INTRODUCTION

The Paralympic movement has grown rapidly over the past thirty years, and the number of people with disabilities taking part in high-performance sport has risen markedly. Research on the health of para-athletes has grown alongside it, but attention has focused mainly on sports injuries, classification and performance physiology. Pain, and neuropathic pain in particular, has stayed on the margins of most of this work.

The International Olympic Committee consensus statement on pain management in elite athletes notes that neuropathic pain is common in Paralympic athletes with spinal cord injury (Hainline et al., 2017). In able-bodied athletes, pain usually signals tissue damage and treatment is planned accordingly. The picture is different in para-athletes. The source of pain is not only the mechanical load of training; the neurological or structural impairment that makes the athlete eligible for para sport can itself cause

pain. When this distinction is missed, neuropathic pain may be handled as an overuse injury and treated wrongly (Todd et al., 2024).

Physiotherapists are among the health professionals who see para-athletes most often during training and competition. Recognising neuropathic pain, telling it apart from musculoskeletal pain and managing it without drugs are therefore core skills for a physiotherapist working in para sport. This chapter brings together what is currently known about neuropathic pain in para-athletes from a physiotherapy point of view and points out the questions that remain open.

DEFINITION, MECHANISMS AND CLASSIFICATION OF NEUROPATHIC PAIN

The International Association for the Study of Pain (IASP) defines neuropathic pain as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (Jensen et al., 2011). This definition separates neuropathic pain from nociceptive pain caused by tissue damage. The later concept of nociplastic pain describes pain that arises from altered nociception and can be explained neither by tissue damage nor by a nerve lesion (Kosek et al., 2016). In para-athletes these mechanisms often coexist. A paraplegic wheelchair basketball player may have nociceptive shoulder pain and, at the same time, neuropathic pain below the level of injury.

No single mechanism lies behind neuropathic pain. Ectopic discharges in damaged peripheral fibres, central sensitisation in the dorsal horn, weakened descending inhibition and reorganisation at the thalamocortical level all play a part (Colloca et al., 2017). Patients may describe spontaneous pain that burns, tingles, shoots like an electric shock or stabs, and evoked pain such as allodynia and hyperalgesia may accompany it. These complaints usually appear in an area of sensory loss. Feeling pain in a part of the body that has lost sensation is one of the reasons athletes find it hard to put their experience into words.

Pain after spinal cord injury is assessed with the International Spinal Cord Injury Pain (ISCIP) Classification. This system first divides pain into four groups, namely nociceptive, neuropathic, other and unknown, and then subdivides neuropathic pain into at-level, below-level and other neuropathic pain (Bryce et al., 2012). Below-level pain is felt at least three dermatomes below the level of injury and is linked to central mechanisms, whereas at-level pain is attributed to root or cord damage at that level. Knowing which subgroup a pain belongs to is useful in the clinic; for instance, it guides electrode placement when TENS is to be used.

NEUROPATHIC PAIN BY IMPAIRMENT TYPE

Spinal Cord Injury

Spinal cord injury is the best-documented example of neuropathic pain in para sport. A meta-analysis of 17 studies and 2529 patients calculated a point prevalence of 53% for neuropathic pain, with 19% for at-level and 27% for below-level pain. The same analysis found neuropathic pain to be more common in patients with tetraplegia, in older patients and one year after injury (Burke et al., 2017). A more recent meta-analysis based on the ISCIP Classification reported a pooled prevalence of 58% (Hunt et al., 2021). Heterogeneity was high in both studies, so these figures should be read as approximate.

Data from athletes, however, are scarce. In a study of 47 athletes with spinal cord injury, 66% of the participants reported moderate neuropathic pain that interfered mildly to moderately with daily activities and sleep. The athletes said they had difficulty noticing the pain, describing it and pointing to where it was (Todd et al., 2024). Another study comparing Paralympic and recreational athletes found that Paralympic athletes reported both more neuropathic pain and higher positive affect and well-being (Todd et al., 2023). This seemingly contradictory result suggests that heavy training may increase pain, while sport itself may make it easier to live with.

Amputation

Pain after amputation should be considered under three headings: phantom limb pain, residual limb pain and non-painful phantom sensations. Phantom limb pain, felt in the missing limb, is regarded as a form of neuropathic pain. A meta-analysis of 39 studies found a prevalence of 64% and identified persistent pre-amputation pain, proximal amputation, lower limb amputation, residual limb pain and phantom sensations as risk factors (Limakatso et al., 2020).

About athletes with amputation, however, we know almost nothing. A study comparing amputee football players with amputees who did not play sport found that football did not change the frequency or intensity of phantom limb pain, although the players had less frequent and milder low back pain (Jóźwik et al., 2024). In a case report of a transfemoral amputee track athlete, phantom knee pain that worsened during running was managed by retraining the running pattern. The authors noted in the same report that no published data exist on how often phantom limb pain occurs in athletes with amputation (Santer et al., 2021). How the prosthesis, socket fit or high-load movements such as sprinting and jumping affect phantom and residual limb pain remains unanswered.

Other Impairment Groups

Spina bifida, cerebral palsy, multiple sclerosis and peripheral nerve injuries such as brachial plexus lesions can also cause neuropathic pain. Yet no study examining neuropathic pain in para-athletes from these groups was found while this chapter was being prepared. In athletes with visual or intellectual impairment, neuropathic pain is not a natural consequence of the impairment; it becomes relevant only when there is nerve damage due to a coexisting condition or injury. In short, almost all of the knowledge in this field rests on spinal cord injury, and part of it on amputation.

THE RELATIONSHIP BETWEEN SPORT, EXERCISE AND NEUROPATHIC PAIN

Much of what we know about the effect of exercise on neuropathic pain comes from animal experiments. In spinal cord injury models, exercise has been shown to reduce hypersensitivity to mechanical, thermal and cold stimuli, although the effect depends on when exercise starts and how long it continues (Palandi et al., 2020). Another meta-analysis reported that exercise reduced mechanical allodynia and thermal hyperalgesia, and that the effect was more marked when voluntary, continuous exercise was started in the subacute phase (Toloui et al., 2023).

Human studies are fewer and less consistent. In a study of wheelchair users with spinal cord injury, athletes reported less chronic pain than people who exercised and people who did not exercise at all (Kosmidou et al., 2017). This study, however, did not distinguish between pain types.

The only comparative study in athletes does not fit this picture. Paralympic athletes reported more neuropathic pain than recreational athletes, and pain rose as weekly time spent in moderate-intensity exercise increased. No significant relationship was found between the frequency of heavy-intensity exercise and pain (Todd et al., 2023). The authors suggested that frequent moderate- to high-intensity exercise may intensify neuropathic pain in people with spinal cord injury.

There may be more than one explanation for the gap between experimental studies and this finding. The pain-relieving effect of exercise may be dose-dependent, and the training load of elite sport may reach a level at which the effect reverses. Nociceptive input from overloaded regions such as the shoulder may also feed central sensitisation and worsen neuropathic pain. On the other hand, the study was cross-sectional; it cannot rule out that people with more pain were drawn to competitive sport, or that Paralympic athletes simply reported their pain in more detail. Answering this question will require longitudinal studies that track training load and pain together.

ASSESSMENT AND DIFFERENTIAL DIAGNOSIS

When assessing pain in a para-athlete, the first question is whether the pain is nociceptive, neuropathic or mixed. Answering it calls for a detailed history, a pain map, a sensory examination and standard screening tools used together. Because athletes find it hard to describe neuropathic pain spontaneously, a structured interview that asks about symptoms one by one is especially useful (Todd et al., 2024).

Screening Tools

The DN4 (Douleur Neuropathique en 4 Questions) consists of seven interview items and three examination items and can be completed in a few minutes (Bouhassira et al., 2005). Its Turkish version has been shown to be valid and reliable; in the same study, the sensitivity of the DN4 was 95% compared with 70.2% for the LANSS (Ünal-Çevik et al., 2010). For athletes with spinal cord injury, the International Spinal Cord Injury Pain Basic Data Set allows the type, intensity and daily impact of pain to be recorded in a standard way (Widerström-Noga et al., 2014). None of these tools has been validated separately in athletes, so their results should be interpreted together with examination findings.

Differential Diagnosis

Shoulder pain is common in wheelchair athletes, and low back and residual limb pain are common in athletes with amputation. These pains are mostly nociceptive but may coexist with neuropathic pain. Features that can help in differential diagnosis are summarised in Table 1.

Table 1: Features Helpful in Distinguishing Neuropathic from Nociceptive (Musculoskeletal) Pain

Feature	Suggests neuropathic pain	Suggests nociceptive pain
Description	Burning, tingling, electric shock-like; pain with numbness	Aching, throbbing; deep and localised pain
Location	Dermatomal, diffuse below the level of injury or in the missing limb	Over a loaded joint, tendon or muscle
Relation to mechanical load	Weak or inconsistent	Increases reproducibly with a specific movement or load
Sensory examination	Allodynia or hyperalgesia in an area of sensory loss	Sensation usually normal; tenderness on palpation
Change with rest	May increase at night and at rest	Usually eases with rest

Source: Prepared by the author.

In athletes with an injury at or above T6, it should be kept in mind that painful stimuli below the level of injury can trigger autonomic dysreflexia. When these athletes complain of pain, they should also be asked about headache, sweating and a rise in blood pressure.

PHYSIOTHERAPY MANAGEMENT

No study has directly tested physiotherapy interventions for neuropathic pain in para-athletes. The recommendations below adapt evidence from non-athlete patients with spinal cord injury or amputation to the athletic setting and should be read with this limitation in mind.

Exercise and Training Load

Exercise is one of the cornerstones of neuropathic pain management. In para-athletes, the problem is rarely too little exercise; it is usually the dose. Exercise reduces pain in experimental models (Palandi et al., 2020). In elite athletes, by contrast, a high weekly training volume has been associated with more pain (Todd et al., 2023). Pain therefore needs to be monitored regularly alongside training load. In practice, pain intensity and its effect on sleep can be recorded weekly together with perceived exertion and training volume. Adjusting volume in weeks when pain clearly rises and protecting overloaded structures such as the shoulder address both the nociceptive and the neuropathic component of pain.

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is the most widely studied electrotherapy method for neuropathic pain after spinal cord injury. A study in which 33 patients were randomised reported that low-frequency TENS may reduce neuropathic pain and complement drug treatment (Çelik et al., 2013). In a cross-over study comparing visual illusion with TENS, two weeks of TENS significantly reduced the highest and lowest pain levels and eased the negative effect of pain on mood, relationships with others and sleep (Özkul et al., 2015). On the other hand, a Cochrane review covering various types of neuropathic pain concluded that, because the quality of the evidence was very low, it could not be said with confidence whether TENS is more effective than sham stimulation (Gibson et al., 2017).

TENS offers para athletes some practical advantages. The device is portable and can be used at training camps and competitions. As it is not a drug, it raises no anti-doping concerns, and it has none of the side effects, such as sedation or poor concentration, that could affect performance. Electrodes should be placed primarily over areas with preserved sensation; if stimulation is applied over an area of sensory loss, the skin should be checked before and after every session. The optimal parameters of TENS in

athletes, whether it should be applied before or after training, and its long-term effects have not yet been studied.

Mirror Therapy and Visual Illusion

Mirror therapy targets cortical reorganisation in phantom limb pain. In a randomised, sham-controlled study of people with lower limb amputation, phantom limb pain decreased after four weeks in patients who received mirror therapy (Chan et al., 2007). In spinal cord injury, visual illusion has been tried; it has been reported to improve qualities of pain such as heat, sharpness and unpleasantness and to lessen the negative effect of pain on the ability to move (Özkul et al., 2015). Mirror therapy can be given to athletes with amputation as a home programme during periods when phantom limb pain flares. This recommendation, however, has not yet been tested in athletes.

Pain Education and Psychosocial Support

Athletes find it difficult to recognise and describe neuropathic pain (Todd et al., 2024). This makes education part of the treatment. Knowing that neuropathic pain does not mean tissue damage, and that not every rise in pain calls for stopping training, can reduce avoidance behaviour. That Paralympic athletes report higher well-being despite more pain suggests that sport itself may be a way of coping (Todd et al., 2023). For athletes who catastrophise markedly about their pain, working together with a sport psychologist is advisable.

PHARMACOLOGICAL TREATMENT AND ANTI-DOPING CONSIDERATIONS

Drug treatment of neuropathic pain is the physician's responsibility. Still, the physiotherapist is expected to know how these drugs may affect the athlete, to notice side effects early and to refer the athlete to the physician when needed. Current recommendations place gabapentinoids, serotonin-noradrenaline reuptake inhibitors and tricyclic antidepressants first line and tramadol second line (Finnerup et al., 2015). Common side effects of these drugs include dizziness, sedation and reduced attention. In para sports that demand balance, reaction time and fine motor control, these effects can both impair performance and raise the risk of injury.

There is also an anti-doping side for the athlete. Since 1 January 2024, the World Anti-Doping Agency (WADA) has prohibited tramadol in competition. The decision was driven by the widespread use of tramadol in sport and its potential to enhance performance (World Anti-Doping Agency [WADA], 2024). A para-athlete using tramadol for neuropathic pain now has to apply for a therapeutic use exemption (TUE) or discuss switching to another treatment with the physician. Because the Prohibited List is updated

every year, the athlete's medications should be rechecked each season before the competition calendar begins.

These drug-related restrictions make non-pharmacological methods all the more valuable for para-athletes. By reducing the need for medication, TENS, adjusting the exercise dose, mirror therapy and pain education can lower both the risk of side effects and the anti-doping risk.

RETURN TO SPORT AND LOAD MANAGEMENT

For most para-athletes, neuropathic pain is a lasting condition. The "pain-free return to sport" criterion used for able-bodied athletes therefore makes little sense in this group. The aim is not to eliminate pain completely but to enable the athlete to train and compete safely and sustainably while living with it. Mistaking neuropathic pain for an acute injury can lead to unnecessary breaks in training and a delayed return to sport (Todd et al., 2024).

Although evidence is limited, the following approach can be used in the clinic. At the start of the season, the location, character and usual intensity of the athlete's known neuropathic pain are recorded with the DN4 and a pain map. When a new pain appears during the season, it is compared with this record. Pain that appears in a different area, or that rises reproducibly with a particular load, should first be treated as a nociceptive injury. Pain that increases in a known area and with a known character, on the other hand, is most likely a flare of neuropathic pain.

During flares, it is more appropriate to reduce volume and intensity for a while than to stop training altogether, while monitoring pain intensity, sleep and perceived exertion together. Before competitions, the possibility that travel, temperature changes and disrupted sleep may worsen pain should be taken into account, and portable methods such as TENS as well as an anti-doping check of the medication list should be planned in advance. Sharing the athlete's pain profile among the coach, the physician and the physiotherapist also helps to prevent pain from being misinterpreted. This approach is an untested proposal and should be adapted to each athlete's impairment type, sport and pain history.

CONCLUSION

Neuropathic pain is common in para-athletes, especially those with spinal cord injury or amputation, yet it is often overlooked. Athlete-specific knowledge consists of only a few cross-sectional studies, and nearly all management recommendations are carried over from non-athlete patients. The physiotherapist has a large share in addressing this problem: separating neuropathic from musculoskeletal pain, monitoring training load alongside

pain and using non-pharmacological methods such as TENS, mirror therapy and pain education are largely within the physiotherapist's remit.

Many questions remain open. We do not know how often neuropathic pain occurs in athletes with spina bifida, cerebral palsy, multiple sclerosis or peripheral nerve lesions. The frequency of phantom and residual limb pain in athletes with amputation, and how prostheses and sport-specific loads affect these pains, are also unclear. The dose-response relationship between training load and neuropathic pain should be examined in longitudinal studies, the validity of screening tools such as the DN4 should be tested in athletes, and the effects of TENS, mirror therapy and exercise dosing should be evaluated in randomised controlled trials. National data on this topic among para-athletes in Türkiye are also needed.

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Celiac Disease: Etiopathogenesis, Clinical Features, Current Diagnostic Strategies, and Therapeutic Approaches

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ABSTRACT

Celiac disease (CeD) is a chronic, systemic, immune-mediated enteropathy triggered by the ingestion of gluten-containing proteins in genetically susceptible individuals. It is characterized by intestinal mucosal inflammation, increased intraepithelial lymphocytes, crypt hyperplasia, and varying degrees of villous atrophy. Although traditionally regarded as a gastrointestinal disorder, celiac disease is now recognized as a multisystem condition with heterogeneous clinical manifestations involving hematological, neurological, dermatological, hepatobiliary, endocrine, reproductive, and skeletal systems. The global prevalence of celiac disease is approximately 1%, although substantial geographical and methodological variations have been reported. Diagnosis is primarily based on disease-specific serological testing and, when indicated, histopathological examination of duodenal biopsy specimens obtained while the patient is consuming a gluten-containing diet. Measurement of immunoglobulin A antibodies against tissue transglutaminase (tTG-IgA), together with total serum IgA, represents the preferred initial diagnostic strategy.

Recent advances in diagnostic algorithms have introduced biopsy-sparing approaches for carefully selected adults with strongly positive serological findings. The updated ESSCD and BSG guidelines support a no-biopsy diagnostic pathway in appropriately selected patients with tTG-IgA concentrations at least ten times the upper limit of normal, provided that the relevant confirmatory requirements are fulfilled.

A strict lifelong gluten-free diet remains the cornerstone of treatment. Comprehensive management additionally requires nutritional assessment, correction of micronutrient deficiencies, specialist dietary counseling, structured clinical and serological follow-up, and evaluation of mucosal recovery when clinically indicated. Refractory celiac disease represents a rare but potentially serious complication requiring specialized diagnostic assessment and individualized management.

Novel therapeutic strategies, including gluten-degrading enzymes, tissue transglutaminase inhibitors, intestinal barrier modulators, and antigen-specific immunotherapies, are currently under investigation. Nevertheless, no pharmacological intervention has been established as a replacement for a lifelong gluten-free diet in routine clinical practice.

Keywords: Celiac disease; gluten, tissue transglutaminase; HLA-DQ2; HLA-DQ8; villous atrophy; gluten-free diet; refractory celiac disease.

1. INTRODUCTION AND DEFINITION

Celiac disease is a chronic, immune-mediated enteropathy precipitated by dietary gluten exposure in genetically predisposed individuals. Its pathogenesis involves complex interactions between genetic susceptibility, environmental factors, intestinal epithelial barrier function, and innate and adaptive immune responses [1–3].

Gluten comprises a heterogeneous group of storage proteins, including gliadins and glutenins in wheat, hordeins in barley, and secalins in rye. These proteins are particularly rich in proline and glutamine residues, rendering them relatively resistant to complete degradation by human gastrointestinal proteases.

Historically, celiac disease was predominantly considered a pediatric malabsorption syndrome characterized by chronic diarrhea, abdominal distension, weight loss, and growth failure. However, advances in serological testing, endoscopic assessment, and epidemiological research have demonstrated that the disease may develop or become clinically apparent at any age.

Furthermore, the clinical spectrum extends considerably beyond classical gastrointestinal manifestations. Patients may present with iron deficiency anemia, osteoporosis, infertility, neurological abnormalities, dermatitis herpetiformis, unexplained elevations in liver aminotransferases, or persistent fatigue, even in the absence of overt gastrointestinal symptoms.

Delayed diagnosis and inadequate treatment may result in persistent intestinal inflammation, nutritional deficiencies, metabolic bone disease, reproductive complications, and, in a small proportion of patients, intestinal malignancies.

Celiac disease must be distinguished from wheat allergy and non-celiac gluten/wheat sensitivity. Whereas celiac disease is associated with a characteristic adaptive immune response and disease-specific autoantibodies, wheat allergy involves allergic immunological mechanisms. Non-celiac gluten/wheat sensitivity is characterized by symptoms associated with wheat or gluten ingestion without the defining serological and histopathological features of celiac disease.

2. EPIDEMIOLOGY

Celiac disease is among the most prevalent chronic immune-mediated gastrointestinal disorders worldwide.

A comprehensive systematic review and meta-analysis reported a global seroprevalence of approximately 1.4% and a biopsy-confirmed prevalence of approximately 0.7% [6]. Nevertheless, prevalence estimates vary substantially according to geographical region, population characteristics, screening strategies, diagnostic criteria, and genetic background.

The disease is diagnosed more frequently in females than males and may manifest during childhood, adulthood, or advanced age.

Epidemiological investigations conducted in Türkiye have also demonstrated that celiac disease represents an important public health concern. Diagnostic delays remain particularly relevant among individuals presenting with mild gastrointestinal complaints or predominantly extraintestinal manifestations.

2.1. Populations at increased risk

The prevalence of celiac disease is higher in several clinical populations, including:

- First-degree relatives of individuals with celiac disease.
- Patients with type 1 diabetes mellitus.
- Individuals with autoimmune thyroid disorders.
- Patients with selective IgA deficiency.
- Individuals with Down syndrome, Turner syndrome, or Williams syndrome.
- Patients with otherwise unexplained iron deficiency anemia or osteoporosis.
- Individuals presenting with chronic diarrhea, unexplained weight loss, or clinical evidence of malabsorption.

The prevalence among first-degree relatives may reach approximately 5–10%. Consequently, screening should be considered in appropriate individuals, even in the absence of gastrointestinal symptoms.

3. ETIOLOGY AND PATHOGENESIS

The pathogenesis of celiac disease involves the interaction of genetic predisposition, gluten exposure, intestinal epithelial permeability, and dysregulated immune responses.

3.1. Genetic susceptibility

The vast majority of patients with celiac disease carry HLA-DQ2 or HLA-DQ8 susceptibility haplotypes.

Approximately 90% of affected individuals express HLA-DQ2.5, while a substantial proportion of the remaining patients carry HLA-DQ8 or other disease-associated HLA-DQ2 configurations.

However, approximately 30–40% of the general population carries at least one of these susceptibility haplotypes, whereas only a minority subsequently develop celiac disease.

Therefore, HLA-DQ2/DQ8 positivity is not sufficient to establish the diagnosis. Conversely, the absence of the relevant susceptibility haplotypes has substantial negative predictive value and makes celiac disease highly unlikely.

Non-HLA genetic loci also contribute to disease susceptibility. Variants involving IL2/IL21, CTLA4, and several additional immune regulatory pathways have been implicated in the genetic architecture of celiac disease.

3.2. Immunological effects of gluten

Gluten proteins are incompletely digested within the gastrointestinal tract. The resulting proteolysis-resistant gliadin peptides may cross the intestinal epithelial barrier and initiate an immune response in genetically susceptible individuals.

Tissue transglutaminase 2 (TG2) catalyzes the deamidation of specific glutamine residues within gluten peptides, thereby increasing their binding affinity for HLA-DQ2 and HLA-DQ8 molecules.

Following antigen presentation, deamidated gluten peptides activate gluten-specific CD4⁺ T lymphocytes, resulting in a proinflammatory immune response.

This process is associated with increased production of interferon-gamma, interleukin-15, and other inflammatory mediators.

Interleukin-15 plays a particularly important role in promoting the cytotoxic activity of intraepithelial lymphocytes, thereby contributing to epithelial injury.

The resulting immunopathological cascade includes:

1. Increased intraepithelial lymphocyte infiltration.
2. Crypt hyperplasia.
3. Progressive distortion of villous architecture.
4. Reduction in the functional intestinal absorptive surface.
5. Development of malabsorption and systemic complications.

3.3. Intestinal microbiota and environmental factors

Alterations in intestinal microbiota composition, early-life infections, antibiotic exposure, and other environmental influences have been investigated as potential contributors to the development of celiac disease.

However, the causal relationships between these factors and disease initiation remain incompletely understood.

Current evidence does not establish that introducing gluten at a particular time during infancy reliably prevents the subsequent development of celiac disease.

4. CLINICAL MANIFESTATIONS

Celiac disease exhibits considerable clinical heterogeneity. Its presentation varies according to age, duration of gluten exposure, severity of intestinal injury, nutritional status, and the presence of associated autoimmune disorders.

4.1. Gastrointestinal manifestations

Classical celiac disease is predominantly characterized by manifestations of intestinal malabsorption.

Common gastrointestinal symptoms include chronic diarrhea, steatorrhea, abdominal bloating, excessive flatulence, abdominal pain, weight loss, nausea, dyspepsia, and, in selected patients, constipation.

In children, impaired growth and delayed physical development may be prominent.

Importantly, adults may present with symptoms resembling irritable bowel syndrome without overt evidence of malabsorption.

4.2. Extraintestinal manifestations

Celiac disease may affect multiple organ systems.

Table 1. Extraintestinal manifestations of celiac disease

Organ system	Clinical manifestations
Hematological	Iron deficiency anemia, folate deficiency, vitamin B12 deficiency
Skeletal	Osteopenia, osteoporosis, osteomalacia
Dermatological	Dermatitis herpetiformis
Neurological	Peripheral neuropathy, gluten-related ataxia
Hepatobiliary	Unexplained elevation of aminotransferases
Reproductive	Infertility and adverse pregnancy outcomes
Oral	Recurrent aphthous stomatitis, dental enamel defects
Psychological	Depressive symptoms and anxiety
General	Persistent fatigue and weakness

Extraintestinal manifestations may precede the development of recognizable gastrointestinal symptoms by several years.

4.3. Dermatitis herpetiformis

Dermatitis herpetiformis represents the characteristic cutaneous manifestation of celiac disease.

It typically presents with intensely pruritic, symmetrical papulovesicular lesions involving extensor surfaces, particularly the elbows, knees, buttocks, and back.

Diagnosis is established by direct immunofluorescence examination of a perilesional skin biopsy demonstrating granular IgA deposits within the dermal papillae.

A lifelong gluten-free diet constitutes the fundamental treatment. Dapsone may be administered in selected patients to achieve more rapid symptomatic control.

5. DIAGNOSIS OF CELIAC DISEASE

The diagnosis of celiac disease requires an integrated assessment of clinical findings, disease-specific serology, duodenal histopathology, and, in selected circumstances, genetic testing.

An essential principle is that diagnostic investigations should be performed while the patient is consuming an adequate amount of gluten.

Initiation of a gluten-free diet before completion of the diagnostic evaluation may reduce circulating antibody concentrations and promote intestinal mucosal recovery, potentially resulting in false-negative serological or histopathological findings [1–5].

5.1. Serological diagnosis

Measurement of anti-tissue transglutaminase IgA (tTG-IgA), together with total serum IgA, is recommended as the initial diagnostic approach.

Table 2. Serological and genetic investigations used in the diagnosis of celiac disease

Investigation	Principal clinical application
tTG-IgA	First-line serological screening and diagnostic evaluation
Total serum IgA	Identification of IgA deficiency
Endomysial antibody IgA (EMA-IgA)	Confirmation in selected patients and assessment of diagnostically uncertain cases

Deamidated gliadin peptide IgG (DGP-IgG) Alternative serological investigation in patients with IgA deficiency

tTG-IgG Diagnostic assessment in patients with IgA deficiency

HLA-DQ2/DQ8 genotyping Exclusion of celiac disease in selected diagnostically challenging cases

The tTG-IgA assay demonstrates high diagnostic sensitivity and specificity in patients consuming gluten who do not have IgA deficiency. However, test sensitivity may be reduced in individuals with mild enteropathy, limited gluten exposure, immunosuppression, or selective IgA deficiency.

In patients with confirmed IgA deficiency, IgG-based serological assays should be employed.

Although EMA-IgA demonstrates excellent specificity, its routine use as a confirmatory investigation in every patient is limited by operator dependence, laboratory requirements, and availability.

The updated ESSCD guidelines emphasize the importance of using validated, high-performance anti-TG2 assays [2].

5.2. Endoscopic evaluation

Upper gastrointestinal endoscopy may reveal several macroscopic abnormalities suggestive of celiac disease, including:

- 1- Reduction or loss of duodenal folds.
- 2- A mosaic or micronodular mucosal appearance.
- 3- Scalloping of the duodenal folds.
- 4- Increased visibility of the submucosal vascular pattern.
- 5- Mucosal nodularity.

Nevertheless, normal endoscopic findings do not exclude celiac disease.

In particular, mild or patchily distributed intestinal involvement may occur despite an apparently normal duodenal mucosa.

Therefore, when histological confirmation is indicated, adequate duodenal biopsy specimens should be obtained regardless of the macroscopic endoscopic appearance.

5.3. Duodenal biopsy protocol

The updated ESsCD diagnostic guidelines recommend obtaining at least four biopsy specimens from the second portion of the duodenum. Additional duodenal bulb biopsies should be obtained according to the clinical context, particularly when patchy disease or bulb-restricted involvement is suspected [2].

Specimens obtained from the duodenal bulb and distal duodenum should preferably be submitted in separate containers to facilitate accurate histopathological interpretation.

Correct specimen orientation is essential for reliable assessment of villous architecture and the villus-to-crypt ratio.

The principal histopathological parameters include:

1. Intraepithelial lymphocyte density.
2. Villus-to-crypt ratio.
3. Crypt hyperplasia.
4. Degree of villous atrophy.
5. Inflammatory infiltration of the lamina propria.

5.4. Marsh–Oberhuber histopathological classification

The Marsh–Oberhuber classification provides a standardized framework for describing the spectrum of intestinal mucosal abnormalities associated with celiac disease.

Table 3. Marsh–Oberhuber classification of intestinal mucosal injury

Marsh stage	Histopathological characteristics
Marsh 0	Normal intestinal mucosal architecture
Marsh 1	Increased intraepithelial lymphocytes with preserved villous architecture
Marsh 2	Increased intraepithelial lymphocytes accompanied by crypt hyperplasia
Marsh 3a	Partial villous atrophy
Marsh 3b	Subtotal villous atrophy
Marsh 3c	Total villous atrophy

An intraepithelial lymphocyte count exceeding approximately 25 lymphocytes per 100 enterocytes is generally considered abnormal.

However, isolated intraepithelial lymphocytosis is not pathognomonic for celiac disease.

Similar histological abnormalities may occur in association with *Helicobacter pylori* infection, medication-related intestinal injury, infectious enteritis, and other inflammatory disorders.

Accordingly, histopathological findings should always be interpreted in conjunction with the clinical presentation and serological results.

5.5. No-biopsy diagnosis in adults: 2025–2026 guideline updates

One of the most important developments in contemporary celiac disease diagnostics is the introduction of a biopsy-sparing diagnostic pathway for carefully selected adults.

According to the updated ESsCD recommendations, a no-biopsy approach may be considered in eligible adult patients with tTG-IgA concentrations at least ten times the upper limit of normal ($\geq 10 \times \text{ULN}$).

The essential considerations include:

- An initial tTG-IgA concentration of at least $10 \times \text{ULN}$.

- Confirmation of the initial serological result using an independent second blood sample.
- Continued gluten consumption until the diagnostic evaluation has been completed.
- Specialist assessment and appropriate clinical interpretation.
- Shared decision-making between the clinician and patient.
- Absence of clinical features requiring endoscopic investigation for alternative pathology.

The 2026 BSG guidelines also conditionally support a no-biopsy diagnostic strategy in appropriately selected symptomatic adults.

Nevertheless, the introduction of this pathway does not eliminate the role of duodenal histology. Endoscopic biopsy remains important when clinical and serological findings are discordant, when alarm symptoms are present, or when alternative gastrointestinal pathology is suspected [2,4].

5.6. Diagnosis in children

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines permit a no-biopsy diagnostic pathway in children when tTG-IgA concentrations are at least $10 \times$ ULN and EMA-IgA positivity is confirmed in a second blood sample, provided that the relevant diagnostic conditions are fulfilled.

The presence of symptoms is not mandatory for this approach.

Furthermore, demonstration of HLA-DQ2/DQ8 positivity is not routinely required.

In children with tTG-IgA concentrations below $10 \times$ ULN, histological confirmation through duodenal biopsy is generally recommended [5].

5.7. HLA-DQ2 and HLA-DQ8 genotyping

HLA genotyping is not recommended as a routine first-line diagnostic investigation.

Its principal clinical value lies in the evaluation of diagnostically uncertain cases, including:

- Discordance between serological and histopathological findings.
- Initiation of a gluten-free diet before diagnostic testing.
- Suspected potential celiac disease.
- Seronegative villous atrophy.
- Reassessment of a previously established but inadequately documented diagnosis.

The absence of disease-associated HLA-DQ2 and HLA-DQ8 configurations makes celiac disease highly unlikely. However, a positive result does not independently establish the diagnosis.

5.8. Seronegative celiac disease

Seronegative celiac disease is characterized by compatible intestinal mucosal abnormalities, particularly villous atrophy, despite negative disease-specific serological testing.

Before establishing this diagnosis, clinicians should assess the adequacy of gluten exposure, exclude IgA deficiency, and systematically investigate alternative causes of enteropathy.

The diagnosis requires integration of compatible histopathology, genetic susceptibility, exclusion of competing etiologies, and objective improvement following institution of a gluten-free diet.

5.9. Differential diagnosis

Villous atrophy should not automatically be attributed to celiac disease, particularly when disease-specific antibodies are negative.

Table 4. Differential diagnosis of villous atrophy and celiac-like enteropathy

Disease or condition	Relevant diagnostic considerations
1-Giardiasis	Stool parasitological examination and appropriate antigen testing
2-Common variable immunodeficiency	Hypogammaglobulinemia and reduced intestinal plasma cells
3-Autoimmune enteropathy	Severe enteropathy and characteristic histological abnormalities
4-Olmesartan-associated enteropathy	Medication history and improvement following drug withdrawal
5-Tropical sprue	Relevant geographical and epidemiological exposure
6-Crohn's disease	Focal inflammation and involvement of other intestinal segments
7-Whipple's disease	Periodic acid–Schiff-positive macrophages and molecular testing
7-Immunodeficiency-associated enteropathies	Clinical and immunological assessment
8-Intestinal lymphoma	Atypical cellular infiltration and immunophenotypic analysis

A comprehensive medication history is particularly important in patients presenting with seronegative villous atrophy.

5.10. Patients who have initiated a gluten-free diet before diagnosis

Patients who eliminate gluten before undergoing diagnostic investigations may develop normalization of disease-specific antibody concentrations and partial or complete histological recovery.

In such circumstances, previously obtained diagnostic records should first be reviewed. HLA-DQ2/DQ8 testing may be useful when the diagnosis remains uncertain.

A supervised gluten challenge may be considered in selected genetically susceptible individuals when definitive diagnosis is clinically necessary.

The 2026 BSG guidelines describe gluten reintroduction at approximately 3–6 g/day for at least six weeks as one potential diagnostic strategy in appropriately selected adults.

The duration and amount of gluten exposure should be individualized according to clinical circumstances, patient tolerance, and specialist assessment [4].

6. DIAGNOSTIC ALGORITHM

Clinical suspicion of celiac disease

Gastrointestinal symptoms, extraintestinal manifestations, or membership in a high-risk population tTG-IgA and total serum IgA testing while consuming gluten Positive serology

Assess tTG-IgA concentration $\geq 10 \times \text{ULN}$: Consider the validated no-biopsy pathway in eligible adults

Other cases: Upper gastrointestinal endoscopy and duodenal biopsies

Negative serology

Assess total IgA and adequacy of gluten exposure

IgA deficiency: Perform IgG-based testing

Persistent high clinical suspicion: Consider duodenal biopsy and differential diagnosis

Integrated interpretation of clinical, serological, and histopathological findings

If discordant, consider HLA genotyping, histopathological reassessment, and investigation of alternative enteropathies

Confirmed diagnosis → Lifelong gluten-free diet and structured follow-up

7. MANAGEMENT OF CELIAC DISEASE

7.1. Gluten-free diet

A strict lifelong gluten-free diet (GFD) remains the cornerstone of celiac disease management.

Elimination of dietary gluten facilitates resolution of intestinal inflammation, reduction in disease-specific antibody concentrations, improvement in nutritional status, and progressive intestinal mucosal recovery.

A gluten-free diet requires the exclusion of wheat, barley, rye, and gluten-containing products derived from these cereals.

Table 5. Dietary recommendations for patients with celiac disease

Foods to avoid Naturally gluten-free alternatives

Wheat, bulgur, semolina Rice

Barley Corn

Rye Buckwheat

Triticale Quinoa

Conventional gluten-containing pasta Certified gluten-free pasta

Standard wheat bread Appropriate gluten-free bread

Gluten-containing flour products Potatoes and legumes

Oats require particular consideration.

Pure, uncontaminated oats are generally tolerated by most patients with celiac disease. However, cross-contact with wheat, barley, or rye during cultivation, transportation, processing, or packaging may introduce clinically relevant quantities of gluten.

Therefore, only appropriately labeled gluten-free oats should be recommended.

A small proportion of patients may also develop intolerance to oat proteins themselves.

7.2. Gluten exposure and cross-contamination

The internationally recognized regulatory threshold for foods labeled gluten-free is generally less than 20 mg of gluten per kilogram of product (20 parts per million).

Importantly, this concentration threshold should not be confused with the total quantity of gluten consumed per day.

Total daily gluten exposure should be minimized. Approximately 10 mg/day is frequently cited as a cautious exposure threshold, although individual sensitivity may vary.

Cross-contamination represents an important source of unintended gluten ingestion, particularly in restaurants, institutional catering facilities, and domestic food preparation.

Potential sources include shared toasters, contaminated preparation surfaces, communal frying oils, and utensils previously used for gluten-containing foods.

7.3. Nutritional assessment and correction of deficiencies

All newly diagnosed patients should undergo a comprehensive baseline nutritional assessment.

Iron, folate, vitamin B12, vitamin D, calcium, and other micronutrient deficiencies should be investigated according to clinical presentation and individual risk factors.

Table 6. Suggested baseline laboratory assessment

Investigation	Clinical purpose
Complete blood count	Detection of anemia and other hematological abnormalities
Ferritin and iron studies	Assessment of iron deficiency
Vitamin B12 and folate	Identification of micronutrient deficiencies
25-hydroxyvitamin D	Evaluation of vitamin D status

Calcium, phosphate, and alkaline phosphatase Assessment of mineral and bone metabolism

AST and ALT Evaluation of associated liver abnormalities

Serum albumin Assessment of nutritional and protein status

Thyroid-stimulating hormone Evaluation for associated autoimmune thyroid disease when indicated

Identified deficiencies should be corrected through appropriate nutritional or pharmacological supplementation, followed by reassessment of treatment response.

Importantly, a gluten-free diet is not necessarily nutritionally balanced.

Commercially processed gluten-free foods may contain substantial quantities of refined carbohydrates and fats while providing relatively limited amounts of dietary fiber.

Consequently, specialist dietary counseling should address not only gluten avoidance but also nutritional adequacy, dietary diversity, and long-term cardiometabolic health.

7.4. Preservation of bone health

Reduced bone mineral density in celiac disease may result from calcium and vitamin D malabsorption, secondary hyperparathyroidism, chronic inflammation, and other contributing factors.

Dual-energy X-ray absorptiometry (DXA) should be considered particularly in patients with advanced age, postmenopausal status, previous fragility fractures, prolonged malabsorption, or additional osteoporosis risk factors.

Regular physical activity, adequate calcium and vitamin D intake, and smoking cessation should be encouraged.

When osteoporosis is identified, treatment should be individualized in accordance with established osteoporosis management guidelines.

7.5. Vaccination and prevention of infections

Functional hyposplenism may occur in a proportion of patients with celiac disease and can increase susceptibility to certain infections, particularly those caused by encapsulated bacteria.

Vaccination history should therefore be reviewed, and pneumococcal, influenza, and other indicated immunizations should be considered according to age, individual risk factors, and national vaccination recommendations.

Patients with documented hyposplenism may require additional preventive measures.

8. ASSESSMENT OF TREATMENT RESPONSE AND LONG-TERM FOLLOW-UP

Successful treatment of celiac disease should not be defined solely by the resolution of gastrointestinal symptoms. A comprehensive assessment should incorporate clinical improvement, normalization of nutritional parameters, serological response, and histological recovery when indicated.

Gastrointestinal symptoms frequently improve within several weeks after initiation of a gluten-free diet. However, complete intestinal mucosal recovery may require several months or even years, particularly in adults.

8.1. Clinical and serological monitoring

A progressive decline in tTG-IgA concentrations is generally expected following implementation of a strict gluten-free diet.

Nevertheless, normalization of disease-specific antibody concentrations does not invariably indicate complete histological recovery.

Similarly, negative serological findings cannot reliably exclude ongoing low-level gluten exposure.

Table 7. Suggested follow-up schedule for patients with celiac disease

Follow-up interval	Recommended assessment
At diagnosis	Clinical assessment, serology, nutritional evaluation, and identification of baseline deficiencies

3–6 months Dietary adherence, symptoms, weight changes, and reassessment of nutritional deficiencies

6–12 months tTG-IgA, clinical response, and relevant laboratory investigations

12–24 months Serological response, complications, and histological assessment in selected patients

Long-term follow-up Risk-based clinical monitoring, nutritional reassessment, and evaluation for complications

The frequency and intensity of follow-up should be individualized according to disease severity, treatment response, nutritional status, and the presence of complications.

The updated BSG recommendations emphasize structured follow-up during the first two years after diagnosis, followed by a risk-stratified long-term monitoring strategy [4].

8.2. Is follow-up endoscopy necessary?

The role of routine follow-up duodenal biopsy in patients with celiac disease remains an important area of clinical discussion.

Contemporary recommendations favor an individualized approach rather than universal repeat biopsy at a predetermined interval.

Follow-up histological assessment should be considered particularly in patients with:

- Persistent or recurrent symptoms despite treatment.
- Inadequate serological response.
- Severe villous atrophy at diagnosis.
- Persistent unexplained nutritional deficiencies.
- Suspected refractory celiac disease.
- Clinical circumstances in which documentation of mucosal recovery would influence subsequent management.

Duodenal histopathology remains the reference method for directly evaluating intestinal mucosal recovery.

8.3. Measurement of gluten immunogenic peptides

The detection of gluten immunogenic peptides (GIPs) in urine or stool has emerged as a potential objective method for assessing recent gluten exposure.

These assays may identify gluten ingestion that is not recognized through dietary history or conventional serological testing.

However, a negative GIP result does not establish sustained dietary adherence or confirm intestinal mucosal recovery.

Accordingly, GIP testing should be regarded as a complementary investigation in selected patients rather than a replacement for clinical assessment, dietary counseling, or serological monitoring [3].

9. NON-RESPONSIVE AND REFRACTORY CELIAC DISEASE

9.1. Non-responsive celiac disease

Non-responsive celiac disease refers to persistent or recurrent symptoms, or failure to achieve the expected clinical and laboratory improvement, despite implementation of a gluten-free diet.

The initial evaluation should focus on confirming the original diagnosis and identifying ongoing gluten exposure.

Unintentional gluten ingestion remains one of the most frequent causes of an inadequate treatment response.

Table 8. Differential diagnosis of persistent symptoms despite a gluten-free diet

Potential cause	Suggested diagnostic approach
Unintentional gluten exposure	Comprehensive dietary assessment by an experienced dietitian
Lactose intolerance	Clinical assessment and appropriate dietary elimination

Irritable bowel syndrome Symptom-based evaluation after exclusion of alarm features

Microscopic colitis Colonoscopy with colonic biopsies

Small intestinal bacterial overgrowth Appropriate breath testing or other investigations in selected patients

Exocrine pancreatic insufficiency Fecal elastase measurement and clinical assessment

Bile acid diarrhea Appropriate diagnostic investigations or a selected therapeutic trial

Refractory celiac disease Repeat duodenal biopsies and immunophenotypic assessment

Premature classification of patients as having refractory celiac disease should be avoided until alternative explanations have been systematically investigated.

9.2. Refractory celiac disease

Refractory celiac disease (RCD) is characterized by persistent or recurrent malabsorptive symptoms and villous atrophy despite adherence to a strict gluten-free diet, generally for at least 12 months, in a patient with a previously confirmed diagnosis of celiac disease.

The diagnosis requires exclusion of ongoing gluten ingestion, alternative causes of enteropathy, and intestinal malignancy.

RCD is classified into two major subtypes according to the immunophenotypic characteristics of intraepithelial lymphocytes.

Table 9. Comparison of refractory celiac disease subtypes

Characteristic	Type 1 RCD	Type 2 RCD
Intraepithelial lymphocytes	Predominantly	normal phenotype
Aberrant immunophenotype		
Prognosis	Relatively favorable	Less favorable
Risk of intestinal lymphoma	Lower	Substantially increased
Principal management	Strict GFD, nutritional support, and corticosteroids in selected patients	
	Individualized treatment in specialized centers	
Follow-up	Clinical and histological monitoring	Intensive intestinal and hematological surveillance

Type 2 RCD is associated with a markedly increased risk of enteropathy-associated T-cell lymphoma (EATL).

Patients with suspected RCD should therefore be referred to experienced centers with access to specialist gastroenterology, gastrointestinal pathology, and hematology services.

9.3. Treatment of refractory celiac disease

In type 1 RCD, strict gluten avoidance and comprehensive nutritional support remain essential.

Open-capsule budesonide may be considered as first-line pharmacological therapy in appropriate patients.

Steroid-sparing immunomodulatory agents, including azathioprine, may be considered in selected cases requiring prolonged treatment.

Management of type 2 RCD is substantially more challenging.

Corticosteroids, cladribine, and other immunomodulatory approaches have been investigated and may be employed in specialist centers according to individual clinical circumstances.

The 2026 BSG guidelines identify flow-cytometric immunophenotyping of intraepithelial lymphocytes as an important reference approach in the assessment of suspected type 2 RCD.

Small bowel imaging and, where indicated, device-assisted enteroscopy should also be considered to investigate complications and exclude associated malignancy [4].

10. COMPLICATIONS OF CELIAC DISEASE

Untreated or persistently active celiac disease may lead to a variety of intestinal and extraintestinal complications.

10.1. Malnutrition and micronutrient deficiencies

Reduction in the functional intestinal absorptive surface may impair the absorption of iron, folate, calcium, and fat-soluble vitamins.

Iron deficiency anemia is particularly important because it may represent the initial manifestation of celiac disease in adults.

Persistent iron deficiency despite a gluten-free diet should prompt reassessment of dietary adherence, intestinal recovery, and other potential sources of gastrointestinal blood loss.

10.2. Metabolic bone disease

Osteopenia and osteoporosis are important long-term complications of celiac disease.

Although bone mineral density may improve following initiation of a gluten-free diet, complete reversal of skeletal abnormalities is not guaranteed, particularly among adults diagnosed after prolonged periods of untreated disease.

10.3. Risk of malignancy

Enteropathy-associated T-cell lymphoma is among the most clinically significant malignancies associated with celiac disease.

An increased risk of small bowel adenocarcinoma has also been reported.

Nevertheless, the absolute incidence of these complications remains low, and routine lymphoma screening is not recommended for every patient with celiac disease.

Unexplained weight loss, persistent abdominal pain, gastrointestinal bleeding, fever, night sweats, or severe malabsorption despite dietary treatment should prompt further investigation for potential malignancy.

10.4. Reproductive health and pregnancy

Untreated celiac disease may be associated with infertility and certain adverse pregnancy outcomes.

In women planning pregnancy, optimal disease control should be established, nutritional deficiencies should be corrected, and adherence to a strict gluten-free diet should be reinforced.

Adequate folate and iron status are particularly important during preconception assessment and pregnancy.

11. EMERGING AND INVESTIGATIONAL THERAPEUTIC STRATEGIES

Despite the established efficacy of a gluten-free diet, a substantial proportion of patients experience persistent symptoms, unintended gluten exposure, or reduced quality of life.

These limitations have stimulated considerable interest in pharmacological treatments intended either to complement or potentially modify the current dietary management strategy.

11.1. Gluten-degrading enzymes

Enzyme-based therapeutic approaches aim to degrade ingested gluten into smaller, less immunogenic peptides before these reach the intestinal mucosa.

Enzyme combinations such as latiglutenase (ALV003) have been evaluated in clinical trials.

However, the available evidence has not demonstrated sufficient efficacy to permit unrestricted gluten consumption or replacement of a strict gluten-free diet.

11.2. Therapies targeting intestinal barrier function

Larazotide acetate is an investigational agent designed to modulate intestinal epithelial permeability.

Clinical studies have primarily evaluated its potential effects on symptom control and gluten-induced intestinal barrier dysfunction.

Nevertheless, current evidence does not support its use as a substitute for dietary gluten elimination in routine clinical practice.

11.3. Tissue transglutaminase inhibitors

Tissue transglutaminase 2 represents an attractive therapeutic target because of its central role in the immunopathogenesis of celiac disease.

TG2 inhibitors, including ZED1227, are designed to reduce gluten peptide deamidation and thereby attenuate downstream immune activation.

A randomized phase 2 clinical trial demonstrated promising results in reducing gluten-induced intestinal mucosal injury [15].

However, additional studies are required to establish long-term efficacy, safety, and the appropriate clinical indications for these agents.

11.4. Immunological tolerance-inducing strategies

Therapeutic approaches targeting gluten-specific T-cell responses or promoting antigen-specific immune tolerance are also under investigation.

These include peptide-based immunotherapies and other antigen-directed strategies.

The principal objective is to suppress the pathological immune response to gluten without inducing generalized immunosuppression.

11.5. Microbiota-directed interventions

Growing interest in the potential contribution of intestinal dysbiosis to celiac disease has stimulated research into probiotics and other microbiota-modulating interventions.

Nevertheless, current clinical evidence is insufficient to demonstrate that probiotics reliably induce villous recovery or represent an effective alternative to a gluten-free diet.

Table 10. Investigational pharmacological approaches for celiac disease

Therapeutic approach	Proposed mechanism	Clinical status
Latiglutenase	Enzymatic degradation of gluten	Investigational
Larazotide acetate	Modulation of intestinal barrier permeability	Evaluated in clinical trials
ZED1227	Inhibition of tissue transglutaminase 2	Clinical development
Gluten-specific immunotherapy	Induction of antigen-specific immune tolerance	Investigational
Microbiota-directed interventions	Modulation of intestinal microbial composition	Insufficient evidence for routine use
Targeted immunomodulatory agents	Suppression of pathological immune responses	Under investigation, particularly in refractory disease

As of October 2026, a strict lifelong gluten-free diet remains the established standard of care for celiac disease.

12. SPECIAL CLINICAL CONSIDERATIONS

12.1. Celiac disease and liver involvement

Mild-to-moderate elevations in serum aminotransferase concentrations may occur in patients with active celiac disease.

In some individuals, these abnormalities resolve following initiation of a strict gluten-free diet.

Nevertheless, alternative causes of liver enzyme elevation should be systematically evaluated, including viral hepatitis, metabolic dysfunction-associated steatotic liver disease, drug-induced liver injury, and autoimmune liver disorders.

Associations between celiac disease and autoimmune liver conditions, particularly autoimmune hepatitis and primary biliary cholangitis, have also been reported.

12.2. Celiac disease and type 1 diabetes mellitus

Type 1 diabetes mellitus and celiac disease share genetic susceptibility and immunological mechanisms, contributing to their increased coexistence.

Accordingly, celiac disease screening is clinically relevant in patients with type 1 diabetes, even when gastrointestinal symptoms are absent.

Following initiation of a gluten-free diet, changes in dietary carbohydrate composition may necessitate reassessment of glycemic control and diabetes management.

12.3. Celiac disease and exocrine pancreatic insufficiency

In active celiac disease, duodenal mucosal injury and altered enteroendocrine signaling may impair pancreatic exocrine secretion.

Exocrine pancreatic insufficiency should therefore be considered in patients with persistent steatorrhea, weight loss, or malabsorptive symptoms despite adherence to a gluten-free diet.

Fecal elastase measurement may provide useful diagnostic information. However, watery stools may produce falsely reduced fecal elastase concentrations as a consequence of sample dilution.

In patients with confirmed exocrine pancreatic insufficiency, appropriately dosed pancreatic enzyme replacement therapy may be indicated.

12.4. Celiac disease and irritable bowel syndrome

Persistent abdominal pain, bloating, and altered bowel habits despite a gluten-free diet may indicate coexisting irritable bowel syndrome.

However, ongoing gluten exposure and persistent active enteropathy should first be excluded.

In selected patients, a short-term low-FODMAP diet under specialist dietitian supervision may improve symptom control.

Importantly, this intervention should be considered an adjunctive strategy rather than a replacement for the gluten-free diet.

13. COMPARISON OF CONTEMPORARY INTERNATIONAL GUIDELINES

Table 11. Principal recommendations of the ACG, ESsCD, and BSG guidelines

Clinical issue	ACG 2023	ESsCD 2025/2026	BSG 2026
Initial serological assessment	tTG-IgA	Anti-TG2 IgA and total IgA	tTG-IgA with assessment for IgA deficiency
No-biopsy diagnosis in adults	Histological confirmation remains the principal approach, with limited alternatives in selected patients	Conditionally accepted in appropriately selected symptomatic adults	Conditionally accepted in appropriately selected symptomatic adults
Serological threshold for a no-biopsy pathway	Not the standard adult diagnostic approach	≥10 × ULN	≥10 × ULN
HLA genotyping	Selected clinical circumstances	Selected clinical circumstances	Primarily useful for diagnostic exclusion
Standard treatment	Lifelong gluten-free diet	Lifelong gluten-free diet	Lifelong gluten-free diet
Follow-up	Clinical, serological, and histological assessment when indicated	Individualized multidisciplinary monitoring	Structured initial follow-up followed by risk-based monitoring
Refractory disease	Systematic diagnostic reassessment	Specialist-center management	Specialist-center management and immunophenotyping

Adapted from the principal recommendations of the relevant international guidelines [1–5].

14. KEY RECOMMENDATIONS FOR CLINICAL PRACTICE

The principal implications of contemporary evidence for the diagnosis and management of celiac disease can be summarized as follows:

1. Celiac disease is a systemic immune-mediated disorder and should not be regarded exclusively as a gastrointestinal condition.
2. Diagnostic investigations should be performed while the patient is consuming a gluten-containing diet.
3. Measurement of tTG-IgA together with total serum IgA represents the preferred initial serological approach.
4. IgG-based serological investigations should be employed in patients with IgA deficiency.
5. Normal macroscopic findings during upper gastrointestinal endoscopy do not exclude celiac disease.
6. A no-biopsy diagnostic pathway may be considered in carefully selected adults when the relevant serological and confirmatory criteria are fulfilled.
7. HLA-DQ2/DQ8 positivity alone is insufficient to establish the diagnosis.
8. A strict lifelong gluten-free diet remains the cornerstone of treatment.
9. Normalization of disease-specific antibodies does not invariably indicate complete intestinal mucosal recovery.
10. In patients with persistent symptoms despite dietary treatment, the original diagnosis should be reassessed and inadvertent gluten exposure should be investigated.
11. Patients with suspected refractory celiac disease should be referred to experienced specialist centers.
12. The ultimate therapeutic objective extends beyond symptom control and encompasses nutritional restoration, mucosal recovery, prevention of complications, and improvement in long-term quality of life.

15. CONCLUSION

Celiac disease is a chronic, systemic, immune-mediated disorder arising from the interaction between genetic susceptibility and dietary gluten exposure. Its defining pathological feature is immune-mediated injury of the small intestinal mucosa, although clinical manifestations may involve multiple organ systems.

Given the heterogeneous clinical spectrum and frequent occurrence of extraintestinal manifestations, early recognition is important not only in gastroenterology practice but also across numerous medical specialties.

Disease-specific serological testing, particularly measurement of tTG-IgA and total serum IgA, remains central to the initial diagnostic evaluation. Duodenal histopathology continues to provide essential diagnostic information, particularly in patients with discordant clinical and serological findings.

Nevertheless, the updated ESsCD and BSG guidelines represent an important evolution in diagnostic practice by supporting a no-biopsy pathway for carefully selected adults with strongly positive serological findings.

A lifelong gluten-free diet remains the established standard of treatment. Comprehensive management additionally requires specialist nutritional counseling, correction of micronutrient deficiencies, structured long-term follow-up, and histological reassessment when clinically indicated.

Emerging therapeutic strategies, including gluten-degrading enzymes, tissue transglutaminase inhibitors, and antigen-specific immunomodulatory approaches, may expand future treatment options. However, these interventions have not replaced dietary gluten elimination in routine clinical practice.

Ultimately, optimal management of celiac disease requires a multidisciplinary, individualized, and longitudinal model of care aimed at achieving sustained disease control, minimizing complications, and improving patients' long-term health outcomes.

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