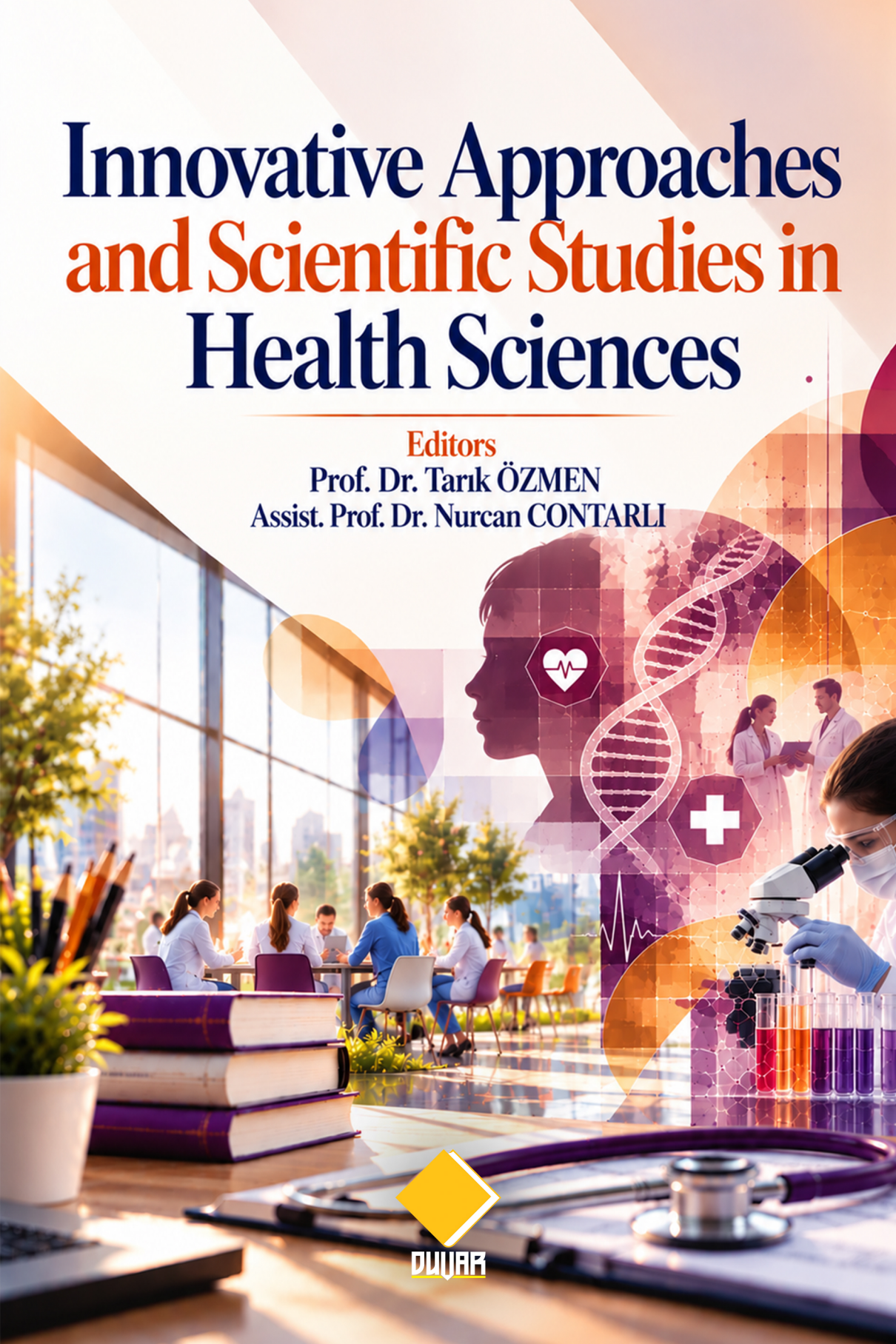
Innovative Approaches and Scientific Studies in Health Sciences

Editors
Prof. Dr. Tarık ÖZMEN
Assist. Prof. Dr. Nurcan CONTARLI



DUVAR

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Chapter 1

The Role of Urbanization in Climate Change and Zoonotic Outbreaks: One Health Education

Burcu KÜÇÜK BİÇER[1], Rüştü TAŞTAN[2]

Abstract

Urbanization reshapes the effects of climate change on zoonotic infections through land use, infrastructure, animal movements, and social inequalities. This chapter examines the effects of climate change and urbanization on zoonotic risks from the perspective of One Health education. It discusses content for teaching the relationships among human, animal, and environmental health, opportunities for interprofessional learning, and approaches to assessment. The competencies expected of health professionals and related occupational groups are considered across a continuum from recognizing environmental hazards to undertaking joint risk assessments. Recent research highlights the importance of contact patterns at urban fringes, in fragmented habitats, and in settlements with inadequate infrastructure. However, current evidence does not support generalizations that urbanization affects all pathogens in the same direction or that every increase in biodiversity reduces transmission. The interactions between climatic and urban processes are discussed through West Nile virus infection, leptospirosis, brucellosis, and tick-borne zoonoses. Studies published in 2025 and 2026 demonstrate the need to account for environmental heterogeneity at the neighborhood level and for surveillance bias. The implementation framework proposed for Türkiye brings together municipal infrastructure investments and human and animal health services around joint risk assessment. The international definition of One Health is considered alongside its conceptualization as a system of thought, with particular attention to interprofessional [3] education, climate literacy, environmental justice, and measurable accountability. Reducing zoonotic risk

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requires intervention in the spatial and social conditions that generate risk, alongside responses after disease has emerged. Educational programs should develop participants' knowledge and their ability to assess exposure, interpret findings across professions, and justify appropriate preventive measures.

Keywords: One Health education, urbanization, climate change, zoonoses, environmental justice, surveillance.

Introduction

The distribution of zoonotic infections in cities cannot be explained solely by the presence of infected animals or vectors. Residential location, stormwater drainage, waste collection, food supply, and access to health services can cause the same biological hazard to produce different outcomes in different communities. Climate change alters the temperature, precipitation, and seasonality components of these relationships, while urbanization determines the conditions under which people encounter other organisms. The explanatory value of One Health for urban settings lies in its capacity to consider these connections within a shared assessment [1-4].

The historical health gains associated with urbanization should not be overlooked. Improved access to safe water, sanitation, and diagnostic services can facilitate the control of many infections. However, settlements where construction outpaces infrastructure development, housing in streambeds, inadequately regulated livestock production at urban fringes, and unmanaged waste accumulation create other exposures. The coexistence of these conditions within the same municipality limits the explanatory value of citywide averages. Disease risk assessment should examine how settlements develop and who receives public services, as well as population density [3,5,6].

This chapter aims to discuss how zoonotic risks associated with climate change and urbanization can be addressed in One Health education. It identifies topics that require different professional groups to learn together and examines how urban health problems can be used in case studies, fieldwork, and joint assessment activities. The educational approach proposed for Türkiye connects scientific knowledge with the recognition of local exposures and joint decision-making across institutions. The discussion focuses on the transmission of zoonotic pathogens from animals to humans and the resulting disease burden in human populations. Human-to-animal transmission, animal welfare, and environmental antimicrobial resistance are addressed insofar as they inform this focus. The proposed municipal practices and indicators reflect an interpretation of the literature in the Turkish context and may inform local policy development. Local publications on One Health education, climate literacy, and

One Health literacy provide the educational foundation for this chapter [7-13]. The activities presented here are proposals for teaching these topics, they should not be interpreted as the results of an educational program with demonstrated effectiveness.

Conceptual Foundations of One Health Thinking

The definition developed by the One Health High-Level Expert Panel describes an integrated approach to sustaining and improving the health of humans, animals, and ecosystems. It recognizes the interdependence of human health, domestic and wild animals, plants, and the wider environment, and envisages collaboration across sectors and communities [1]. In cities, this approach requires clinical presentations to be linked with environmental and animal health indicators. For example, a human case in a particular area may prompt the joint examination of vector sampling, animal health records, and infrastructure problems in that area.

In a 2025 commentary, Taştan reiterates a definition that he attributes to 2021, emphasizing the intellectual character of One Health. It describes a system of thought grounded in human experience and accumulated scientific knowledge, with the potential to address the complex health problems of the Anthropocene through a transdisciplinary approach. Risk reduction and threat prevention are linked to collaboration across disciplines and professions [7]. The expression “system of thought” emphasizes the need to examine connections among diseases together with the conditions that give rise to them.

The international definition and this conceptual perspective address different needs. The former specifies a shared purpose and scope of activity, whereas the latter draws attention to how problems are conceptualized. Urban health requires both. Simply inviting institutions to the same meeting does not ensure that a drainage problem will enter a zoonotic risk assessment. Similarly, agreement on a holistic perspective does not specify which laboratory should receive specimens or which department should fund the work. Translating a conceptual framework into service delivery requires clearly defined responsibilities and decision-making processes. One Health education requires similar clarity. A student's statement that human, animal, and environmental health are related does not demonstrate the ability to assess those relationships in a specific case. Learners should be expected to identify the information required, recognize the limits of their own profession, and explain when input from another specialty is needed. Educational content should therefore combine shared concepts with practical activities that show how different professions

approach the same problem. Existing chapters on education and literacy provide local reference points for discussing these needs [10-12].

Local sources for this discussion in Türkiye include the 2022 book edited by Taştan, Ak, Peker, and Küçük Biçer, and the 2023 volume Güncel Tek Sağlık, edited by Taştan, Ak, Küçük Biçer, and Arslanbaş [8,9]. Their chapters on education and literacy offer a local foundation for discussing the interprofessional learning needed in cities [10-12]. Taştan and Küçük Biçer's 2025 chapter on urban flooding, vectors, and zoonoses is directly relevant to the subject of this volume [13]. Reading this local scholarship alongside recent international research supports conceptual continuity.

Relationships Between Urbanization and Zoonotic Risk

Administrative city boundaries do not coincide with the ecological boundaries within which human and animal populations interact. Cities obtain food, water, and labor from a wider region, while animals and vectors do not move according to administrative boundaries. Assessments of zoonotic risk should therefore encompass surrounding production areas, wetlands, forest edges, and transport connections, as well as central neighborhoods. If the place where a person diagnosed in a city acquired the infection is unknown, treating the residential address as the source of infection may produce misleading conclusions. Exposure histories and spatial records must be assessed together.

Changes in land use may lead to declines in some species and the relative dominance of species that tolerate human disturbance. Gibb and colleagues showed that the species richness and abundance of hosts of known zoonotic pathogens differ in human-modified ecosystems [14]. Host abundance, however, is not equivalent to the incidence of human infection. Pathogen shedding by infected animals, human contact with contaminated environments, and the biological conditions required for infection must also be assessed. Measuring the intermediate steps between habitat change and human cases helps identify appropriate intervention targets [4].

The assertion that urban-adapted animals carry more pathogens also requires careful examination. Albery and colleagues found that a substantial proportion of the difference in known pathogen richness was attributable to research and discovery effort [15]. More pathogens would be expected to be detected in species that are sampled more frequently. This finding demonstrates the need to distinguish research intensity from biological characteristics. A comparable problem in local surveillance arises when heavily sampled neighborhoods appear to be at high risk, while areas without sampling are assumed to be safe.

Simkin and colleagues' 2025 study assessed zoonotic host richness globally in areas where natural habitats and human settlements meet or intermix. The study supports considering potential host distributions alongside social vulnerability [5]. For Türkiye, this approach indicates that urban fringes should be understood as more than a temporary planning issue. Housing, warehousing, livestock production, and recreational land uses at the fringe can be examined together. Nevertheless, global maps of potential distributions do not demonstrate local transmission. Species presence, infection status, and human contact require confirmation through separate field data.

How Climate Changes Transmission Processes

The effects of climate change on infections cannot be reduced to a single linear relationship in which risk rises with temperature. Heat may affect vector development, lifespan, and pathogen replication within the vector in different directions. Extreme temperatures can limit survival in some organisms, while making a previously unsuitable season favorable elsewhere. The timing of precipitation, preceding drought, and the capacity of infrastructure to remove water are as important as the amount of rainfall. The IPCC assessment demonstrates the need to consider climate impacts in conjunction with exposure and vulnerability [2].

The urban heat island adds a local dimension to this assessment. Temperatures recorded at an airport weather station may not represent a shaded park, a narrow street, and a densely built industrial area equally well. Urban risk models should link local temperature and humidity measurements with land cover. Regional climate projections can support long-term preparedness, whereas day-to-day field decisions need to be tested against local observations. Distinguishing these scales can help prevent the use of maps that appear to have high spatial resolution but lack biological validation.

Modeling by Carlson and colleagues predicts that climate-driven shifts in species distributions may create new opportunities for viral sharing among mammals [16]. This result does not directly predict the number of future human pandemics. The interspecific encounters and viral sharing considered in the model represent only certain steps in the pathway toward sustained transmission in humans. Similar models developed for Türkiye should separately examine data gaps, the accuracy of species distribution records, and the likelihood of human contact. Scenario results should be presented with their associated probabilities and uncertainties.

Mora and colleagues documented the range of human pathogenic diseases for which examples of aggravation by climatic hazards have been reported [17].

The percentages in that study cannot be used as the proportion of cases attributable to climate change in a particular city. Identifying at least one example of an interaction for a disease and estimating how much of its burden is caused by anthropogenic climate change are different questions. Estimating attributable burden requires joint modeling of counterfactual climate conditions, other determinants, and local surveillance data. Accordingly, this chapter does not use percentages from global evidence syntheses to explain local increases in disease. This distinction provides an assessment exercise for climate literacy education. Participants could be given a surveillance report, a climate projection, and an observational study concerning the same disease, and asked to discuss which question each source addresses. Examples should be used to examine why covariation between two variables does not, by itself, establish causality. By the end of the activity, participants should be able to preserve the geographical scope, time frame, and uncertainty of a finding when communicating it [2,16,17].

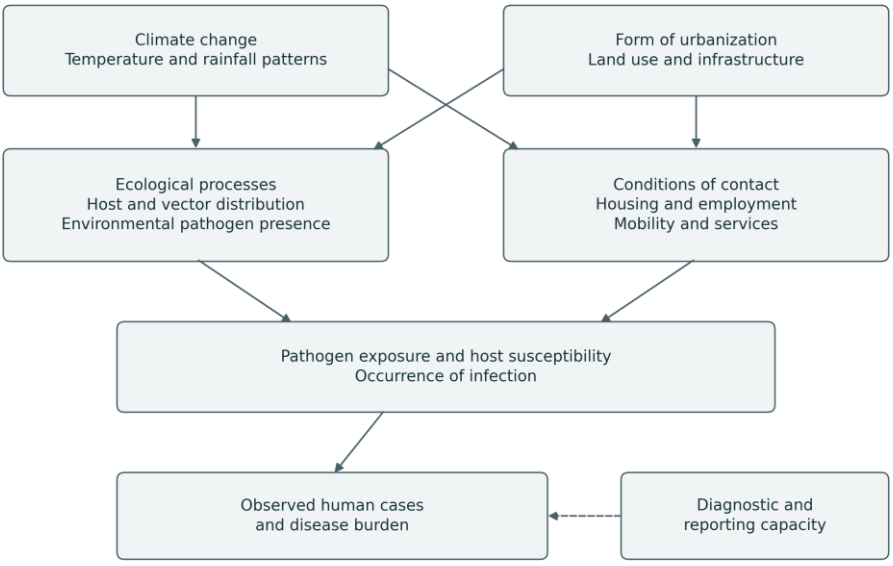


Figure 1. Conceptual relationships among climate, urbanization, and zoonotic infections [1-4,14,16].

Recent Evidence

Some findings do not support the view that urbanization invariably increases infections. In Mahon and colleagues' 2024 meta-analysis, urbanization was associated, on average, with reductions in disease-related outcomes across data from different host-parasite systems. The effects of other drivers of global

change varied in direction, and context-dependent effects were common [18]. This result should not be interpreted as evidence that new construction protects against zoonoses. Rather, the study raises questions about how urbanization is measured and which biological outcomes are combined.

Gibb and colleagues' study, published in September 2026, linked outbreak records for different infections to social and environmental determinants. Mosaic landscapes in which people and livestock live alongside forests and fragmented ecosystems featured prominently, while the effects of determinants differed across disease groups [19]. The difference between this study and the meta-analysis should not be regarded as a direct contradiction. One examines disease outcomes across a wide range of hosts, the other examines reported emergence and outbreak patterns in humans. A change in the phenomenon being measured can yield different results for the same environmental variable.

Taken together, these studies demonstrate the need to disaggregate urbanization into its components. Population density, expansion of built-up areas, and access to sanitation are not the same variable. The first may increase certain contacts, while the third may reduce a different transmission pathway. Combining them in a single urbanization score may conceal effects operating in opposite directions. Analyses that distinguish different risk processes within cities may be more informative than a single urban-rural comparison.

Eby and colleagues' long-term study of Hendra virus demonstrated how the conditions for cross-species transmission develop by tracing connections among land-use change, food resources, and bat behavior [20]. It also showed that urban and agricultural areas do not share identical risk patterns. The transferable lesson for Türkiye concerns sustained observation of environmental change, animal behavior, and exposure, rather than a particular pathogen or host. Preserving environmental records from before an outbreak, instead of collecting samples only afterward, is therefore valuable for local research.

Table 1. Selected recent studies and limits to interpretation

Study	Contribution	Limit to interpretation
Mahon et al. 2024 [18]	Meta-analysis of global change drivers across different host-parasite systems.	The average association with urbanization cannot be generalized to every human zoonosis.
Simkin et al. 2025 [5]	Potential zoonotic host richness at the wildland-urban interface.	Host distribution is not evidence of realized human transmission.
Patzina-Mehling et al. 2026 [21]	Local West Nile virus patterns at sites in Berlin.	Local observational findings do not establish universally applicable design effects.
Li et al. 2026 [22]	Associations of urban expansion and peri-urban fringes with human brucellosis.	Association does not establish an independent causal effect of urbanization.
Wei et al. 2026 [23]	Reported viral diversity in urban-adapted mammals.	Pathogen detection does not establish the direction of transmission to humans.
Gibb et al. 2026 [19]	Analysis of human outbreak records alongside social and environmental determinants.	Reporting bias and differences among diseases must be retained in interpretation.

Urban Flooding and Leptospirosis

Leptospirosis provides a clear example for examining the connection between urban infrastructure and infection of animal origin. Contact with water or soil contaminated by the urine of infected animals is important for transmission. CDC and WHO guidance highlights exposures following heavy rainfall and flooding [24,25]. Flooding alone, however, does not establish that an outbreak will occur. Outcomes depend on local reservoirs, environmental pathogen presence, the nature of water contact, and diagnostic capacity. Attributing every febrile illness after flooding to the same cause can also lead to diagnostic error.

Blasdell and colleagues' study along an urbanization gradient contributes to understanding the relationships between rodents and zoonotic hazards in their habitat context [26]. Reis and colleagues' research in areas of urban poverty showed that social differences could remain associated with infection even after environmental conditions were taken into account [6]. Read together, these forms of evidence demonstrate the limitations of focusing exclusively on animal counts or individual behavior. Research should investigate how exposure occurs at home, at work, and in shared spaces.

Mwachui and colleagues' systematic review demonstrates the diversity of environmental and behavioral determinants [27]. The same measure should not be expected to perform equally well in every city. Local investigations could jointly map open sewage connections, waste accumulation, and recurrent flooding locations, then overlay the sites of human and animal sampling. This would allow investigators to examine whether an apparently high-risk area has frequent exposures or has attracted attention because it has been investigated more intensively.

The priority before flooding is to reduce exposure. Drainage maintenance, secure waste containment, and appropriate protective equipment for workers in high-risk tasks are proposed components of a local program. After flooding, sampling and clinical assessment should follow current national guidance. Taştan and Küçük Biçer's chapter linking urban flooding with One Health education is relevant to connecting education and environmental management [13]. Educational content should be planned alongside municipal maintenance schedules and health service preparedness. Leptospirosis can be used in an interprofessional case study developed for this purpose. Participants could receive information progressively about post-flood presentations with febrile illness, flooded locations, and animal contact. Each professional group could first undertake its own assessment and then contribute to a joint investigation plan. The closing discussion should address missing information, which question each specimen would answer, and who could implement the recommended preventive measures. This activity relates to the local publication addressing urban flooding and education [13].

West Nile Virus and Ecological Differences Within Cities

West Nile virus requires the joint assessment of circulation between birds and mosquitoes and infections in humans and horses. Human cases do not represent the entirety of environmental transmission in this system. The joint surveillance approach of ECDC and EFSA brings human, bird, and equid data into the same epidemiological assessment [28]. For cities, the implication is that human and animal records should be examined using shared temporal and spatial references. Investigators should ask whether increases in one data source are supported by others, while retaining distinctions in the sensitivity of each source.

Patzina-Mehling and colleagues' 2026 study in Berlin demonstrated differences in land cover, host communities, and local viral amplification across nearby urban sites. Infection patterns observed over two transmission seasons were not explained by mosquito abundance alone [21]. This finding does not

support assigning all urban green spaces or water management interventions to a single risk category. The effects of landscape design should be investigated alongside local species composition and maintenance conditions. An observational study should not be expected to establish universally applicable design rules.

Güner and colleagues' 2025 Istanbul cohort is particularly relevant to Türkiye. Using surveillance records from 2010-2024, the study identified major outbreak periods in 2019 and 2024 and seasonality in summer and early autumn [29]. It contributes to understanding the urban disease burden but does not, on its own, determine what proportion is attributable to climate change, construction, or changes in diagnostic access. These questions require additional research linking cases with environmental indicators. Local case data cannot substitute for the other information required for causal attribution. In education, this example could become a data interpretation exercise in which human cases are considered alongside vector and animal findings. Participants should be asked to identify potential risk areas and explain which conclusions the available data do not support. Assessment could therefore examine the ability to reach an appropriate conclusion and to interpret findings within the limits of the evidence [21,28,29].

The joint European report, initially released on the EFSA website on 15 October 2026 and covering data submitted up to 7 October, describes the geographical expansion of West Nile virus activity [28]. This expansion was not equated with an increase in disease severity. The distinction matters for municipal management. Identifying newly affected areas may require broader risk communication and preparedness, whereas statements about clinical severity require their own supporting data. Comparisons between international data and Türkiye should also assess the compatibility of reporting periods, case definitions, and sampling intensity.

Urban Fringes and Changing Host Relationships

Brucellosis demonstrates why discussions of urbanization cannot be confined to mosquitoes and wildlife. Urban demand for animal products connects cities with surrounding livestock production through production and distribution networks. Li and colleagues' August 2026 study examined the association between urbanization and human brucellosis in China, including transmission patterns at expanding urban fringes [22]. Its observational design does not establish that urban growth is independently causal. Nevertheless, it suggests that peri-urban areas should be assessed through production and contact relationships that shift over time, rather than treated as fixed zones.

For Türkiye, the corresponding research question is where urban expansion displaces animal production and whether regulatory oversight follows this movement. Animal records, product sales networks, and workers' access to services could be assessed together in areas newly incorporated into municipal boundaries. Inspection focused solely on the final point of sale may overlook exposures during production and transport. Where data on informal production are unavailable, assumptions should not be converted into quantitative conclusions. Fieldwork should first characterize the production chain and employment relationships.

Wei and colleagues' 2026 study synthesized reported viral diversity and zoonotic potential in selected urban-adapted mammal species [23]. Such research can inform sampling priorities. Detecting a virus in an animal does not establish that the animal is the source of human infection in a particular city. The possibility of human-to-animal transmission should also be considered. Transmission direction cannot be established without molecular evidence, contact histories, and temporal information. Preserving these distinctions in risk communication helps prevent every wild animal encountered in a city from being perceived as a threat.

Gelmi-Candusso and colleagues' 2026 multicity study examined relationships among urban density, habitat connectivity, climate, and wildlife disease [30]. Its specific outcome was sarcoptic mange occurrence in coyotes, rather than the number of zoonotic outbreaks in humans. Animal health warrants monitoring in its own right within One Health. However, translating animal disease occurrence directly into a prediction of human outbreaks may exceed the evidence. Urban health programs should monitor animal welfare indicators alongside human health outcomes and interpret the meaning of each separately.

Conceptual and Practical Distinctions in Vector Borne Infections

Tick-borne zoonoses such as Crimean-Congo hemorrhagic fever require urban-rural distinctions to be considered together with mobility. WHO Regional Office for Europe guidance identifies climate change and the movement of ticks and animal hosts as important factors in geographical spread [31]. An urban resident may acquire infection during rural work, a visit, or animal contact elsewhere. A city case map based on residential addresses should therefore not be interpreted as a map of local vector transmission. The place and timing of exposure and occupational activities should be recorded.

Assessing tick-related risk around cities requires examination of land use and host presence. Grazing areas, animal holding sites, and routes with frequent

human passage can be assessed separately. Risk categories should not be assigned solely from the appearance of vegetation without appropriate field sampling. Vector presence and pathogen carriage are also different indicators. Recording them separately enables local programs to make the rationale for intervention clearer.

Vector-borne infections and zoonoses are not synonymous. WHO describes the urban dengue cycle as circulation between humans and *Aedes aegypti* [32]. Urban dengue should therefore not be placed in the same epidemiological category as urban zoonoses that require an animal reservoir for maintenance. Nevertheless, dengue offers a useful comparison for urban planning because of its connections with water storage and settlement conditions. Presenting examples with this distinction prevents the breadth of One Health from obscuring biological classification. The comparison can be used in education to map transmission cycles. Participants could identify the pathogen, vector, human host, and animal reservoir, where applicable, separately. Their diagrams should inform discussion of which preventive measure can target each step of transmission. The aim is to prevent different infections from being treated as epidemiologically equivalent merely because they have similar symptoms or share vectors.

For rabies, the connection between animal health services and management of human exposure is more direct. WHO's current fact sheet addresses dog vaccination, access to post-exposure prophylaxis, and surveillance together, and states that culling free-roaming dogs is ineffective for rabies control [33]. Proposed urban programs should assess vaccination coverage and continuity before considering the number of doses administered. Without an estimate of the animal population denominator, vaccination counts do not demonstrate adequate protection. Bite reports, animal follow-up records, and time to presentation for health care can be examined together.

Biodiversity and Decision Challenges in Climate Adaptation

It cannot be assumed that increasing biodiversity reduces disease risk everywhere. Species competence for a pathogen, abundance, and interspecific relationships can alter outcomes. Gibb and colleagues' findings on host communities, Mahon and colleagues' synthesis across different systems, and the Berlin field study provide information at different scales [14,18,21]. This variation is not a reason to abandon ecological interventions. The local mechanism that a design is expected to change should be specified, and its outcomes measured. Recording an increase in species richness alone is insufficient to demonstrate a human health benefit.

Public health assessment should be incorporated from the outset when designing rain gardens, permeable surfaces, or water-retaining green infrastructure. Water retention time, maintenance responsibilities, and surrounding land uses can be specified in project documentation. Field monitoring should determine whether the intervention achieves its intended flood-reduction function and whether it creates new opportunities for vector breeding. Success in one city does not guarantee the same result in another with different maintenance capacity. Design and operating conditions need to be assessed together.

The social effects of climate adaptation investments should also be monitored. Environmental justice assessment should examine who can benefit from neighborhood improvements. If low-income households are displaced, the intended beneficiaries may lose access to the improved environment. This possibility should be investigated using housing costs, displacement, and service access indicators rather than assumed to be an observed outcome of a particular project. Assessing health benefits within neighborhood boundaries alone may be insufficient. The subsequent circumstances of the population living there before the intervention could also be followed.

Optimizing a single criterion in local decision-making may create other problems. Focusing solely on rapid water removal may affect downstream settlements, removing habitat solely to reduce animal contact may generate new movement patterns. The proposed assessment therefore examines whether risk is displaced elsewhere, as well as the expected benefit. Such analysis should occur before environmental and health departments are asked to comment on a completed project. Alternative designs can be compared in terms of maintenance costs and measurable health indicators.

Social Inequalities and Environmental Justice

The same rainfall event can generate different exposures under different housing and working conditions. Reis and colleagues' findings demonstrate the importance of social conditions in leptospirosis assessment [6]. Global research on the wildland-urban interface also supports considering potential host diversity alongside health service access and housing conditions [5]. The implication for Türkiye is that risk scores should not rely exclusively on environmental indicators. The ability to avoid flooding, obtain protection at work, and receive timely care should be examined separately.

Occupational exposures may be obscured in analyses based on neighborhood populations. Sewage and waste workers, slaughterhouse workers, veterinary personnel, and disaster response teams may encounter animals or contaminated

environments during different tasks [25]. Occupational health assessment should record the tasks actually performed and the equipment used, as well as the type of employment. The recording structure proposed in this chapter makes task and exposure information available for joint analysis without unnecessarily disseminating workers' personal information across institutions. Health monitoring should be kept distinct from employers' disciplinary procedures.

Discussions of migration and population mobility should avoid portraying infection risk as an inherent characteristic of particular communities. Local assessments should measure housing, employment, and service access conditions. A higher number of reported cases in a community may reflect greater exposure or more intensive screening in that group. Migration status should not be treated as a sufficient explanation, it should be examined alongside comparable exposure data. The language of risk communication should facilitate care-seeking and avoid stigma that could discourage information sharing.

Participation mechanisms should move beyond viewing the public solely as recipients of education. Residents can report where flooding occurs, where waste accumulates, and when services are disrupted. These reports should be paired with field verification. Complaint counts alone should not be treated as indicators of disease or animal density because opportunities to report may differ. Explaining which reports led to which decisions enables the practical consequences of participation to be assessed. This can establish a transparent connection between technical assessment and local experience.

Designing Integrated Surveillance in Cities

One Health surveillance aims to support joint decisions, beyond simply bringing different institutions' records together. The Joint Plan of Action and its national implementation guide address the institutional arrangements for multisectoral work [34,35]. The proposed first step at the city level is to identify the priority decision question. For example, if the objective is to assess post-flood leptospirosis risk, the sampling, environmental, and clinical presentation data needed for that decision can be specified, rather than attempting to collect all available data on every zoonosis. Aligning the scope of data collection with its purpose improves feasibility.

The spatial and temporal units used in human health, animal health, and environmental records should be compatible. Directly comparing weekly human cases with annual animal records may conceal some changes. Likewise, using different neighborhood boundaries may create spurious spatial matches. Institutions could establish a shared data dictionary, with separate fields for case

date, specimen collection date, probable exposure location, and laboratory result. Verification status and missing information should also be retained. Retrospective corrections should preserve the audit trail of earlier records.

Sampling design determines how results can be interpreted. Collecting mosquitoes only on streets that generate complaints does not constitute a city-representative survey. Targeted sampling may nevertheless be useful for rapid investigation of a problem. These purposes should be distinguished explicitly. In the proposed surveillance arrangement, fixed monitoring sites would reveal change over time, while event-based investigations would examine new signals. Recording the reason for sampling helps prevent inappropriate pooling of these data in subsequent analyses. Negative findings should also be retained together with measures of sampling effort.

Laboratory findings can represent different levels of evidence. Seropositivity may indicate past exposure, while molecular detection does not invariably demonstrate a viable pathogen or transmission to humans. The question addressed by host, vector, and human specimens should be specified in advance. Local programs should report positive findings with the method, specimen type, and clinical context. Results from different methods should not be pooled into a single positivity rate. Repeat samples from the same person or multiple records from the same animal should be linked to avoid inflated counts.

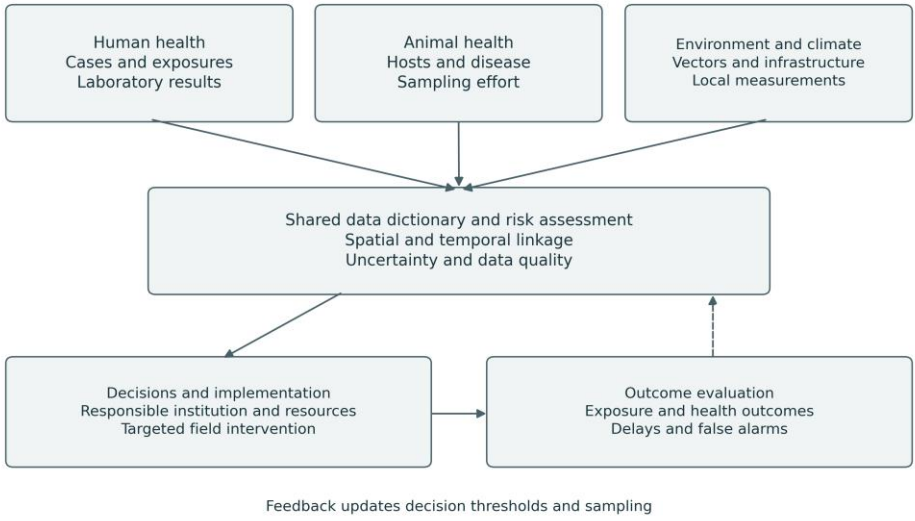


Figure 2. Proposed data, decision-making, and feedback arrangements for urban One Health surveillance [28,34,35].

Early Warning and Decision Making

Early warning concerns the translation of environmental changes into intervention decisions. Temperature, rainfall, vector findings, and clinical presentations can provide useful signals, but no numerical threshold for an indicator should be assumed to apply to every city. Thresholds derived from historical data should be evaluated prospectively. Warning lead time, missed events, and false alarms should be assessed together. A model that explains past outbreaks alone should not be regarded as a system ready for future operational use.

Temporal validation is important in model development. Randomly allocating observations from neighboring areas in the same period to training and test sets may overstate performance. The proposed research design would use a subsequent season or a different city for independent validation. Calibration should be examined alongside predictive accuracy: the observed frequency of events in areas classified as high risk should be consistent with the predicted probabilities. Data gaps and changes in surveillance intensity can be reported alongside model outputs. Cartographic detail should not be confused with measurement precision.

The cost of a false alarm extends beyond the resources spent. Repeated warnings may reduce the responsiveness of field teams and the public to subsequent alerts. A low threshold may nevertheless be appropriate for events with potentially severe consequences. The response should therefore be proportionate to the alert level. A low-level signal might trigger data verification, whereas a corroborated signal from several sources might require targeted field investigation. These stages should be developed according to local capacity and disease characteristics, rather than presented as validated national thresholds. Decision rationales should be recorded for subsequent review.

Using automated analysis for decision support does not transfer responsibility to an algorithm. Experts should assess data quality, model validity, and the feasibility of proposed interventions. Users should be able to see the date represented by a map and the data included in its most recent update. At a minimum, each alert should be linked to a responsible unit, a decision date, and a follow-up result. The system's value can then be assessed through its contribution to timely and appropriate decisions, rather than the number of notifications generated. Actions that could not be implemented despite an alert, and the reasons for this, should also be recorded.

Risk Communication and Scientific Uncertainty

Public communication of a zoonotic hazard should explain the meaning of the finding in its opening sentence. Detection of a pathogen in a mosquito specimen is different from confirmation of a human case. The statement should specify the

specimen type, date, and scope of the finding. Declaring a definitive source while a local investigation remains underway may undermine trust if subsequent findings change. A communication plan can therefore distinguish what is known, what remains under investigation, and which actions are recommended. Acknowledging uncertainty does not preclude providing practical prevention advice.

Numerical data should be accompanied by their denominators. For example, an increase in positive specimens during a period of increased sampling does not necessarily mean that the positivity rate has risen. Public statements about human cases should distinguish confirmed records from those still under investigation and specify the comparison period. This is particularly important for seasonal diseases. Comparing a complete year's total with partial data from an ongoing year may be misleading. Local reports should display dates and data cutoffs consistently. The reasons for retrospective corrections should also be explained.

Risk communication should account for different groups' ability to follow recommendations. A sewage worker advised to avoid water contact should also be told how the work can continue safely and who will provide protective equipment. Conditions that prevent compliance should not be interpreted as individual behavioral failings. Similarly, recommendations to reduce household water storage require assessment of the continuity of water services. Behavioral advice should be accompanied by relevant service arrangements so that communication does not become a list of obligations people cannot meet.

Institutions could establish a shared process for verifying information to prevent conflicting public statements. This does not require reducing every institution's specialist perspective to a single text. Agreement is needed on the verification status of human cases, animal findings, and environmental investigations. The spokesperson, the institution supplying each item of information, and the timing of the next update can be specified. Accessibility should also be assessed. Providing a plain-language explanation alongside the technical report supports public access to information while preserving scientific detail.

Scale and Causal Interpretation in Research

The choice of observational unit can affect the results of urbanization research. An association at district level may not hold in the same way at neighborhood or individual level. The study area should therefore be justified in relation to the research question rather than data availability alone. People may become infected elsewhere while working during the day, visiting on weekends, or having contact with animals. Analyses using residential addresses should state this limitation explicitly. Where feasible, mobility information can be

collected using a privacy-preserving approach limited to the necessary level of detail.

Developing a causal model requires consideration of each variable's position in the process. If land-use change increases animal contact and contact affects infection, adjusting for contact may statistically remove part of the total effect. Conversely, access to health services may affect both case detection and the observed association with settlement characteristics. Adding numerous variables without specifying the effect of interest does not ensure a more accurate result. Diagramming the hypothesized relationships in the research protocol can help distinguish confounders from mediators. Figure 1 provides a conceptual framework for this distinction.

Temporal ordering must also be preserved. Animal movements that change after an outbreak cannot be used as indicators of pre-outbreak exposure. Reduced vector counts after an intervention do not imply that baseline risk was low. Linking the dates of environmental observations with intervention dates can reduce such confusion. Analyses of lagged effects should use biologically plausible intervals and avoid testing many lags while reporting only significant findings. A prespecified analysis plan supports reproducibility and evaluation in other cities.

Displaying areas without data as low risk is particularly problematic. These areas can be shown in a separate category indicating insufficient data. High predicted risk accompanied by high uncertainty may suggest a need for additional sampling. Low predicted risk with high uncertainty likewise requires cautious interpretation. Decision-makers should receive information on both predictions and data adequacy, rather than a single colored map. This presentation can help direct research resources toward the least understood areas and prevent unmeasured locations from being assumed safe.

Local Governance and a Service Model for Türkiye

The starting point for a model applicable in Türkiye is to connect existing institutional responsibilities with joint risk assessment. The national implementation guide considers governance, institutional development, and evidence-informed action together [35]. In the proposed urban model, human health and veterinary services would work regularly with environmental, water, and planning departments. Universities could contribute to methodological development and evaluation. Establishing a new committee should not, by itself, be considered a measure of success. What matters is which decisions it can make, what information it can share, and which resources it can use.

During the first year, priorities should be selected without attempting to address every biological hazard in the city simultaneously. Prioritization could consider local disease presence, potential consequences, preventable exposures, and the capacity to generate data. The rationale for selection should be explained and reviewed periodically. A question concerning recurrent flooding, for example, could be addressed through drainage and rodent management, whereas a West Nile virus question might require a different arrangement centered on vector and host monitoring. A One Health program should not be expected to apply the same intervention package to every disease.

Budget arrangements for joint work must be explicit. A decision to share data may remain unimplementable if field team transport, specimen transport conditions, and laboratory costs have not been specified. Routine monitoring and event investigations could be costed separately in the program budget. The costs of joint work should be visible alongside each institution's own service expenditure. If one institution continually covers another's responsibilities, the program may become dependent on personal relationships. Written workflows support continuity during staff turnover and help identify the point at which a service disruption occurs.

Health assessment of urban planning decisions can also be incorporated into this structure. Flooding, waste services, livestock activities, and ecological connectivity in new development areas should be examined during project planning. The proposal does not imply an identical assessment burden for every project. Assessment can be proportionate to project scale and potential exposure pathways. Field investigation may be requested where preliminary assessment leaves a risk unresolved. Discussing changes early, before they become difficult and costly to implement, is consistent with preventive public health. These assessments are proposed practices rather than new obligations replacing existing legislation.

The extension of the Joint Plan of Action's implementation period to 2029, announced in 2026, is a recent development supporting continuity of the international framework [36]. It does not automatically redefine local institutional responsibilities. The model proposed for Türkiye must be specified within national arrangements and local mandates. The international framework provides a shared direction, while implementation details depend on local administrative conditions. Comparable municipal indicators could enable evaluation of different approaches. Such comparisons should account for differences in population, ecological conditions, and surveillance capacity.

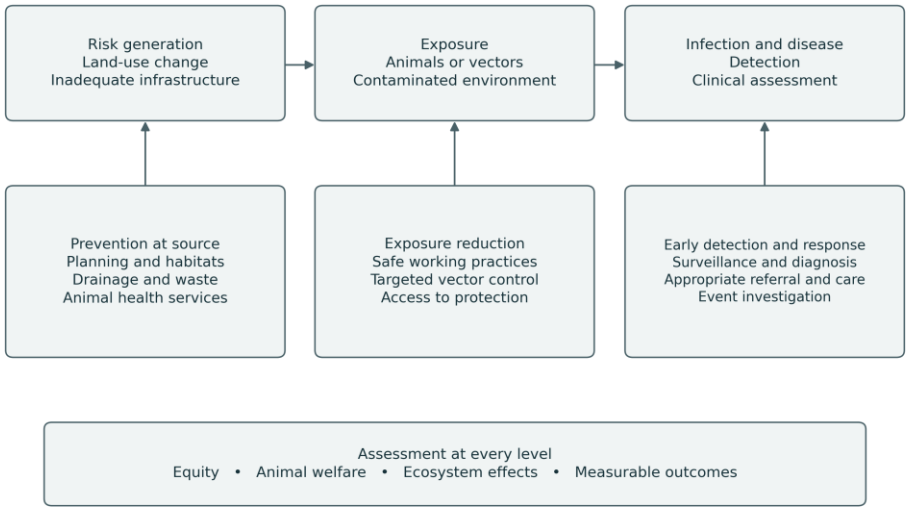


Figure 3. Areas for prevention from the generation of zoonotic risk to the clinical response [2,34,35,37].

Planning and Evaluating One Health Education

Local sources on One Health education include Taştan and Küçük Biçer's chapter on the development of a holistic paradigm in the health professions, Küçük Biçer and Taştan's chapter on education and climate literacy, and Küçük Biçer, Kaşkatepe, and Taştan's chapter on One Health literacy [10-12]. These publications demonstrate the place of this educational agenda within local scholarship. Building on these topics, the educational design proposed here focuses on shared practical competencies for urban decision-making. A book's coverage of a subject does not, by itself, establish the effectiveness of a particular teaching method. Program development should begin by identifying the target group's responsibilities and the problems it encounters. Medical students, veterinarians, municipal employees, and environmental health specialists will not require the same level of detail. Nevertheless, explaining how exposure occurs, interpreting different data sources together, and recognizing situations requiring collaboration can be treated as shared learning domains. Content selection should begin with what participants are expected to be able to do after the program, before deciding what information they should recall.

Interprofessional learning requires more than enrolling participants from different professions in the same class. In the proposed flood scenario, a health

professional would assess potential clinical signals, a veterinarian would examine animal-related information, an environmental engineer would assess water and waste systems, and a planning specialist would examine settlement decisions. Participants would be asked to develop a joint investigation plan in addition to presenting their own perspectives. The plan should make its data requirements, responsibilities, and uncertainties explicit. Collaboration can then be assessed through an observable task rather than an abstract question about attitudes. Learning outcomes should state clearly what participants are expected to do. In a case study, participants could identify plausible exposure pathways, connect human and animal health findings with environmental data, and justify the need for further investigation. Shared tasks could assess their ability to define the responsibilities of different professions and contribute to a feasible investigation plan. These outcomes should also guide the selection of assessment instruments used at the end of the program.

Climate literacy should include the ability to distinguish a weather event from a long-term climate trend. Demonstrating the relationship of a particular flood or disease cluster to anthropogenic climate change requires specific methods [2,17]. Teaching could examine why a single hot summer is not sufficient causal evidence and why the existence of a trend does not explain every event in the same way. Participants should be expected to distinguish types of evidence. A model projection, a surveillance finding, and a causal attribution study do not answer the same question. This distinction improves the accuracy of both academic writing and public communication. Teaching methods should provide opportunities to apply these skills. In small-group work, different professional information concerning the same event could initially be provided to separate groups, the subsequent joint assessment could reveal how participants integrate it. During fieldwork, participants could record an environmental problem, explain its potential health effects, and identify the institutions that should contribute to assessment. Each activity should end with discussion of the evidence supporting the decisions made and the alternative explanations that remain possible. The search for a correct answer would thus be combined with the ability to justify decisions and recognize uncertainty.

Program evaluation should extend beyond satisfaction surveys and knowledge tests. Tasks could include obtaining an appropriate exposure history from a sample record, identifying missing data, and notifying the relevant institution. For a municipal team, the central post-training question is whether workflows have changed. Indicators could include implementation of joint investigation plans, specimen transport errors, and reporting delays. These outcomes may also be affected by staffing and resource changes unrelated to

education. The contribution of the educational program should therefore be evaluated using a comparative design where feasible.

Assessment instruments should align with learning outcomes. Knowledge questions can demonstrate understanding of basic concepts, while case analyses and observation forms can assess the application of knowledge. In collaborative tasks, consideration of other professions' perspectives, recognition of missing information, and justification of recommendations should be defined as observable criteria. Assessment immediately after training may provide insufficient information about retention or service change. Reassessment of the same skills after an appropriate interval can therefore be planned. Attributing a change in disease burden to education additionally requires examination of concurrent changes in infrastructure, staffing, and services.

Prevention Investments and Program Evaluation

Preparedness for zoonotic outbreaks requires environmental investments that reduce exposure, alongside hospital and laboratory capacity. Bernstein and colleagues compared the costs of actions for the primary prevention of zoonotic pandemics with potential losses [37]. Cost ratios from this global assessment cannot be treated as the economic outcome of a specific municipal project in Türkiye. Local decisions require separate estimates of project costs, the target population, expected effects, and alternative uses of resources. Concealing uncertainty in an economic analysis does not strengthen confidence in the benefits of prevention, making uncertainty explicit reveals the assumptions to which a decision is sensitive.

The evaluation framework should monitor process, exposure, and health outcomes together. The number of pesticide applications is a process indicator, whereas a reduction in targeted breeding sites is a more proximal environmental outcome. Changes in human cases are affected by multiple determinants. Recording these levels together helps explain why an intervention may not have produced the expected result. A decline in case counts should not be treated as success if diagnostic services have also declined. Conversely, detecting more cases during the early years as surveillance improves does not establish program failure. Denominators and changes in service utilization should be monitored.

Feasible comparisons can be established to evaluate intervention effects. One option is to follow areas with improved drainage and comparable areas before and after intervention. The selection of comparison areas, other changes over time, and spillover effects on neighboring areas should be considered in the analysis. Causal interpretation depends on whether the necessary assumptions are met. Not every before-and-after difference can be attributed to

the project. An evaluation plan established at the outset can prevent selective reporting of favorable indicators and the use of ambiguous success criteria.

Antimicrobial resistance can be included as a related environmental health issue. The UNEP report addresses the role of the environment in the development and spread of resistance [38]. However, not every resistant infection is zoonotic, and detecting a resistance gene in the environment does not, by itself, identify the source of a human infection. If urban sampling is planned for wastewater or animal production systems, the question it is intended to answer should be specified. Addressing several problems within one program may facilitate resource use, but combining distinct outcomes into a single success score may reduce interpretability.

Research Priorities and Conclusion

Understanding the relationships among climate change, urbanization, and zoonotic diseases in Türkiye requires sustained research across different seasons and settlement characteristics. Positivity surveys in a particular area provide valuable information on pathogen presence or past exposure. Alone, however, these findings do not explain the conditions under which infection occurs, how it changes over time, or which groups face greater risk. Research should link human and animal health findings with environmental changes and living conditions. The health effects of urbanization should be examined through land use, production relationships, infrastructure, and access to services, as well as population growth [2,3].

Multicenter longitudinal studies could jointly cover urban centers, peri-urban areas, and surrounding agricultural production zones. Data collected at defined intervals using consistent methods would facilitate interpretation of regional differences. The question addressed by each indicator must nevertheless be specified in advance. An increase in vector abundance is not equivalent to an increase in the proportion of infected vectors. Detection of a pathogen in an animal likewise does not establish that the animal is the source of human infection. Understanding zoonotic spillover requires consideration of the successive steps from pathogen presence in the reservoir to human susceptibility [4,23]. Sampling and analysis should be tailored to the step addressed by the research question.

Long-term observations are particularly important where climatic variables and land use operate together. Eby and colleagues' Hendra virus research demonstrates the explanatory value of monitoring environmental changes alongside animal feeding and roosting behavior [20]. The lesson for studies in Türkiye is not to transfer a particular host or disease model directly. The central

need is to observe local ecological relationships over a sufficiently long period. Preserving the temporal sequence of rainfall, temperature, animal movement, and human exposure permits more reliable assessment of pre-outbreak conditions. Periods and locations in which the expected relationship is absent should also be recorded, examining only positive specimens or areas with outbreaks provides an incomplete account of the process.

The research agenda should not assume that urbanization affects every infection in the same direction. Mahon and colleagues' meta-analysis found that urbanization was associated, on average, with reduced disease-related outcomes across the host-parasite systems examined, illustrating the limits of generalization [18]. Gibb and colleagues' 2026 research highlights mosaic landscapes where humans, animals, and fragmented ecosystems coexist, and determinants that differ by disease [19]. These studies answer different questions. For Türkiye, the appropriate approach is to investigate which component of urbanization generates risk, for which pathogen, and under which conditions. Combining population density, urban expansion, and improved sanitation within a single variable may obscure distinct effects. Educational research should also form part of this agenda. Studies could examine One Health learning needs across professional groups in Türkiye, existing educational content, and experience with collaborative practice. The conditions under which case-based learning, fieldwork, and interprofessional activities can be implemented could be investigated. Outcomes should include knowledge gains, skill retention, and application in everyday work. Local publications on education and literacy can inform the development of research questions [10-13].

Data generated in Türkiye should contribute more fully to this research agenda. Güner and colleagues' examination of West Nile virus infections in Istanbul over 2010-2024 illustrates the contribution of local surveillance records to longitudinal investigation [29]. Such records help characterize seasonal patterns and clinical features. Subject to appropriate data availability and permissions, a next step could link human cases with probable exposure locations, vector findings, and environmental conditions. However, residential address and place of infection acquisition must be distinguished. A person diagnosed in a city may have been exposed elsewhere during work or travel.

How social conditions are measured is also consequential. In Reis and colleagues' leptospirosis study, the association of socioeconomic differences with infection persisted after accounting for environmental characteristics, demonstrating that risk cannot be explained through pathogen and host characteristics alone [6]. Studies in Türkiye could assess housing

characteristics, access to safe water, continuity of waste services, working conditions, and access to health facilities. Such information helps explain why residents of the same neighborhood experience different levels of exposure. The feasibility of prevention advice also depends on these conditions. For example, a worker advised to avoid floodwater contact should be asked how the work can continue and whether the necessary protective equipment is accessible.

For research findings to inform services, institutions need shared working arrangements. Linking records collected for different purposes by human health services, veterinary services, environmental management, and local authorities depends on compatible definitions. Case date, sampling date, probable exposure location, and laboratory result should be held in separate fields, with missing and unverified information visible. The Quadripartite's national implementation guide similarly addresses governance, institutional capacity, and information sharing together [35]. Shared data dictionaries and regular joint assessment could support local implementation of this framework in Türkiye.

Program evaluation should anticipate that stronger surveillance may identify more cases. An increase in reported cases may reflect greater transmission, improved diagnostic access, or increased reporting sensitivity. Gibb and colleagues' finding that health service access strongly shapes the observed geography of outbreaks supports the importance of this distinction [19]. Case counts should therefore be interpreted alongside testing volume, sampling locations, and changes in service utilization. Areas without data should not be assumed to have low risk. Displaying these areas separately may help direct research and service resources toward the greatest information gaps.

Intervention evaluation should also be a research priority. Before implementation, programs can specify which outcome a drainage improvement, waste management intervention, or animal health program is expected to change. Activities delivered, changes in environmental exposure, and human health outcomes should be monitored separately. Where feasible, following intervention areas and comparable areas over time may provide more informative results. International cost ratios should not be transferred directly to local projects in economic evaluations. Bernstein and colleagues' analysis of primary prevention demonstrates that preventive investments can be examined economically [37]. Decisions in Türkiye require separate estimates of local costs, expected benefits, and the uncertainty surrounding those expectations.

Data sharing and ethical protection should not be treated as technical details to resolve after research is completed. WHO's ethical guidance on public health surveillance calls for attention to the relationships among privacy, equity, and public benefit [39]. Detailed case maps may permit identification of individuals,

particularly in small communities, even after names have been removed. The level of detail required for internal institutional assessment should therefore be determined separately from that appropriate for public reporting.

An education-oriented One Health approach expects participants to apply their own professional expertise to the joint assessment of a health problem. Examples involving climate change and urbanization provide concrete settings for developing this capability. Educational programs should specify who will assess which information together and which decisions participants should be able to justify. Program success should be examined through the ability to transfer learning to a new case and to contribute to work involving different professional groups. This approach makes the contribution of One Health education to services an empirical question that can be investigated.

Abbreviations

Abbreviation	Full term
CDC	Centers for Disease Control and Prevention
WHO	World Health Organization
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Authority
IPCC	Intergovernmental Panel on Climate Change
UNEP	United Nations Environment Programme

Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this chapter, the authors used ChatGPT (OpenAI; accessed on 27 October 2026) to assist with academic language editing, and terminology consistency. These activities supported manuscript preparation. The authors retain full responsibility for the scientific accuracy, interpretation, originality, references, and final content of the chapter.

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Chapter 2

Exosomes Derived from Mesenchymal Stem Cells: Expanded Biological Insights, Therapeutic Mechanisms, and Translational Perspectives

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Abstract

The regenerative and immunomodulatory functions and their wide range of applicability in tissue repair have been widely studied in mesenchymal stem cells. A growing body of evidence suggests that the therapeutic activity of mesenchymal stem cells is largely dependent on paracrine, but not direct cellular, delivery. One of the most important mediators of these paracrine effects has been the exosomes, a specialized form of extracellular vesicles released by mesenchymal stem cells. These vesicles are nanoscale vesicles, which carry a complex molecular cargo, including proteins, lipids and nucleic acids, which modulate immune regulation, angiogenesis, apoptosis, and tissue remodeling. This review includes an in-depth and extended debate on biogenesis, molecular composition, biological roles, and therapeutic capacity of exosomes produced by mesenchymal stem cells, issues, production concerns, and future outlooks on clinical translation.

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Introduction

The mesenchymal stem cells (MSCs) refer to multipotent stromal cells originally discovered in the bone marrow microenvironment and then found in a wide variety of other adult and perinatal tissues, such as adipose tissue, umbilical cord, placenta, dental pulp, and synovial membrane [1–3]. The extensive tissue distribution of MSCs gives credence to the idea that MSCs are playing a critical role in tissue integrity and injury response. The characteristics that define MSCs include self-renewal, plastic adherence in culture and the differentiation into osteogenic, chondrogenic and adipogenic lineage [2,3].

In addition to the differentiation, MSCs have strong immunomodulatory characteristics and are actively engaged in an interaction with innate and adaptive immune cells to control the inflammatory reactions [4]. These properties have promoted comprehensive research on the use of MSCs as therapeutic agents of the inflammatory, autoimmune and degenerative diseases, with hundreds of clinical trials registered around the world.

First, MSC-based therapies were supposed to act by homing and engrafting within injury sites. Nevertheless, in vivo experiments have repeatedly shown low persistence of MSC after transplantation although therapeutic benefit is long-term [5]. Such paradox resulted in a paradigm shift to paracrine mechanisms as the leading forces of MSC-based tissue repair [6].

Exosomes have become major biological effectors among the secreted paracrine mediators. These cellular vesicles secure and transfer intricate molecular burden to target cells, allowing strict control of cell reactions [7-9]. Exosomes prepared by MSCs are currently seen as being a promising cell-free approach to conventional stem cell therapy.

Biogenesis and characterization of exosomes

Exosomes are endosomally generated nanosized extracellular vesicles with a size range of 30-150nm [7,8]. They are formed by the invagination of plasma membrane to create early endosomes which are developed to late endosomes. Endosomal membrane inwards budding forms intraluminal vesicles in multivesicular bodies discharged as exosomes in the event of a merger with the plasma membrane [8].

ESCRT-dependent and ESCRT-independent pathways either regulate the biogenesis of exosomes. ESCRT apparatus promotes cargo sorting and membrane remodeling and lipid raft-related processes that contain ceramide and tetra-spanin proteins, e.g., CD9, CD63 and CD81, also play an important role [9]. The pathways affect the exosome heterogeneity, cargo choice and biological activity.

To achieve the reproducibility of the experimental results and clinical translation, comprehensive characterization of exosomes is required. Vesicle morphology is verified by transmission electron microscopy and cryo-electron microscopy, whereas nanoparticle tracking analysis offers the quantitative data of size distribution and concentration [10]. Detection of canonical exosomal markers like CD63, CD81, TSG101 and Alix are part of molecular profiling. It is advisable that various forms of analysis be used together in order to have the correct identification of the vesicles by international guidelines [10].

Molecular Composition of MSC-Derived Exosomes

The exosomes that are produced by MSCs are dynamic, biologically active, and reflect the physiological condition and tissue source of the parent cells [10]. Proteomic studies have revealed signaling, cytoskeletal, adhesion, and enzyme molecules that participate in repairing the tissues, angiogenesis, and immune regulation [11,12].

Lipids in the MSC-derived exosomes are significantly different to the lipids in the cell membrane. These vesicles contain high concentration of cholesterol, sphingomyelin and ceramide, which make these membranes stiffer and less vulnerable to breakdown [9]. The lipid components are also involved in membrane fusion and intracellular trafficking which facilitates effective delivery of cargo to the recipient cells [13].

Exosomal microRNAs execute an inflammatory response, angiogenesis, apoptosis, and fibrotic reaction by acting on several signaling pathways simultaneously [14].

Other components that are of most significance functionally include exosomal nucleic acids. Exosomes produced by MSCs deliver messenger RNAs and a wide variety of non-coding RNAs, especially microRNAs that modify gene expression, at the post-transcriptional level [5,15].

Biological MSC-Derived Exosomes Functions.

The exosomes produced by MSCs act as intercellular communicators which deliver bioactive cargo to target cells by fusion across the membranes, endocytosis, or receptor-mediated endocytosis [9]. Exosomal contents once internalized control intracellular signaling pathways and gene expression patterns.

These mechanisms allow MSC-derived exosomes to control tissue-repair through regulation of immune responses, owing to the beneficial effects on endothelial cell activity, shields parenchymal cells against damage, and regulating fibroblast activity [11,12]. They have a strong context-dependency on

their biological effects and depend on both the exosome composition and the recipient tissue microenvironment.

Therapeutic Applications of MSC-Derived Exosomes

Exosomes produced by MSC have been shown to have therapeutic efficacy in numerous models of preclinical diseases. Exosome treatment in cardiovascular diseases minimizes the size of infarctions, stimulates angiogenesis and promotes the function of the heart after cardiac injury [11].

MSC-derived exosomes in the context of neurological conditions stimulate neuroprotection, inhibit neuroinflammation, and neuroplasticity. They have the capacity to transport therapeutic cargo across the blood-brain barrier to neural tissues, facilitating stroke and traumatic brain injury model recovery [13-16].

Other therapeutic uses are kidney damage, liver fibrosis, lung illness, osteoarthritis and chronic wound healing [12]. Preliminary clinical studies show that the safety profiles are promising, but large randomized studies are yet to be conducted [17,18]

Immunomodulatory effects

Exosomes of MSC have strong immunoregulatory properties when they interact with innate immune cells, including macrophages and dendritic cells [19]. They encourage macrophage differentiation towards the anti-inflammatory M2 phenotype and inhibit dendritic cells maturation resulting in a decreased pro-inflammatory response [20,21].

Exosomes produced by MSCs prevent the proliferation of T-cells and the production of effector cytokines and enhance the growth of regulatory T-cells in the adaptive immune system [14,22].

They also inhibit the B-cell differentiation and antibody secretion. All of these effects justify the clinical application of MSC-exosomes in the treatment of autoimmune diseases, inflammatory diseases, and complications associated with transplantation [21,22].

Angiogenesis and Tissue Regeneration

Vascular regeneration requires that MSC-derived exosomes be engaged in angiogenesis. The exosomal cargo contains pro-angiogenic proteins and MicroRNAs which trigger endothelial cell proliferation, migration and capillary formation [11,23].

Besides angiogenesis, MSC-derived exosomes can support tissue regeneration through cell survival, attenuation of oxidative stress, and alteration of remodeling

of the extracellular matrix [24,25]. These effects are proved in models of myocardial infarction, ischemic injury and musculoskeletal disorders [11,26].

Anti-Apoptotic and Anti-Fibrotic Activities

Fibrosis is common with chronic injury and this impairs the functioning of organs. MSC-derived exosomes prevent fibroblast stimulation and differentiation of myofibroblasts, decreasing too much collagen deposition and retaining tissue architecture [27,28].

MSC-secreted exosomes trigger intracellular survival signalings including PI3K/Akt and ERK, which prevents cells against apoptosis under ischemic or inflammatory stress [29]. This anti-apoptotic protects tissue viability and promotes functional recovery.

Advantages of Exosome-Based Therapy Over MSC Therapy

Exosome therapeutics have a number of benefits compared to direct MSC transplantation. Being acellular objects, exosomes exclude the threat of uncontrolled growth, tumorigenicity, and microvascular blockage [30]. They have low immunogenicity which allows them to be used as allogens without immunosuppressing them highly.

Exosomes are more stable compared to living cells and can be stored, sterilized and transported more easily, which is why they enable creating standardized off-the-shelf therapeutic products [19,31]. Additionally, exosomes may be modified to perform targeting in a more specific way, or they can be filled with therapeutic molecules, which allows the use of precision-based regenerative medicine approaches [16, 32].

Manufacturing, Standardization, and Quality Control of MSC-Derived Exosomes

A bottleneck in translations lies in large-scale production of MSC-derived exosomes. Significant variation in exosome yield and composition is determined by the source of MSCs, the variability of donors, culture conditions and passage number [18,19]. The absence of standardized production strategies can greatly affect the therapeutic efficacy due to the variability of batch to batch.

New bioprocessing methods such as three-dimensional bioreactors and other microcarrier-based cultures have demonstrated potential in improving MSC growth and exosome release [33]. Exosome cargo can still be enhanced with preconditioning things like hypoxia or inflammatory stimulation to change therapeutic potency, but these processes should be carefully validated [24].

Well-developed quality control systems are required to guarantee the consistency and safety. The important quality features are the particle size, concentration, purity, cargo composition and the biological activity. Regulatory guidelines focus on approved potency assays and standardized release criteria as a requirement to regulatory approval [10,33].

Clinical Translation, Regulatory Considerations, and Ongoing Trials

Clinical translation of MSC-derived exosomes is progressing, with an increasing number of early-phase trials evaluating safety and feasibility across inflammatory, pulmonary, neurological, and musculoskeletal conditions [17,18]. Initial data suggest favorable safety profiles, supporting further clinical development.

Nevertheless, the control pathways are still complicated because exosomes are unique in terms of their biology. Before approval, regulatory bodies have to be provided with detailed characterization, mechan-of-action research and prolonged safety information [17,19]. International harmonization of regulatory standards will be essential in the process of speeding up the adoption of clinical standards.

The best dosage-based and route administration techniques are also not established. The dosing of exosomes is varied depending on the number of particles, content, or parent cell equivalents, indicating the necessity to introduce homogeneous dosing paradigms [18].

Challenges and Limitations

Nevertheless, even though there are promising opportunities of clinical translation of MSC-derived exosomes, there are several challenges facing the translation in reality. They include lack of standard procedures of isolation and purification, heterogeneity of preps and variability due to donors [18,33].

Regulatory uncertainty also adds to the problem of development because exosomes-based products are in a grey zone between biologics and advanced therapy medicinal products. Regulatory frameworks and potency assays still need to be developed [17,19].

Future Perspectives

The future studies will be aimed at the enhancement of scalable production, cargo engineering, and unique delivery strategies of MSC-derived exosomes [16,34]. With further development of bioengineering, it is anticipated that the creation of exosomes of the next generation will be possible and be more therapeutically precise.

Exosome therapies that are personalized and based on the specifics of the patient could be a new possibility. Ongoing work between researchers, clinicians, and regulatory authorities will be needed to convert these innovations into the standard clinical practice [35].

Conclusion

MSC-derived exosomes is a potent and highly versatile cell-free therapeutic in which several of the advantages of stem cell therapy are harnessed and associated risks are reduced to minimum. Their ability to control immune responses, facilitate angiogenesis and facilitate tissue repair make them promising drugs in a broad spectrum of clinical uses. As ongoing research studies, standardization, and regulatory advancements continue, MSC-derived exosomes have a disruptive role in regenerative medicine.

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Chapter 3

Ultrasound Guidance for Venous Access

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ABSTRACT

Ultrasound has transformed venous access from a procedure based largely on surface landmarks into one guided by the patient's actual vascular anatomy. A complete ultrasound-guided strategy includes preprocedural mapping, real-time needle-tip control, confirmation of guidewire position, device selection suited to the intended therapy, and focused postprocedural assessment. The clearest benefits occur in difficult peripheral intravenous access and central venous catheterization performed with dynamic guidance by trained clinicians. Ultrasound does not compensate for inadequate asepsis, inappropriate catheter choice, advancement without tip visualization, or failure to confirm final catheter position. This chapter presents a practical framework for peripheral and central venous access, integrates current guidance with quantitative clinical evidence, and emphasizes safety checks before puncture, before dilation, and before the catheter is used.

Keywords: ultrasonography; vascular access; difficult intravenous access; peripheral intravenous catheter; central venous catheter; needle-tip visualization; guidewire

LEARNING OBJECTIVES

- Assess a target vein by integrating patency, compressibility, caliber, depth, course, and relationships to arteries, nerves, and pleura.
- Distinguish static ultrasound localization from dynamic guidance and select an imaging plane that permits reliable needle-tip control.
- Select a peripheral or central access device according to therapy, required flow, vessel characteristics, and expected dwell time.
- Apply aseptic, guidewire, catheter-tip, and postprocedural safety checks.
- Recognize when ultrasound findings require pressure measurement, blood gas analysis, intracavitary electrocardiography, radiography, or specialist consultation.

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1. INTRODUCTION

Reliable venous access is essential for the administration of medications, fluids, blood products, and nutritional support throughout the perioperative period. In patients whose peripheral veins are neither visible nor palpable, repeated attempts may delay treatment and cause pain, hematoma, and loss of usable venous sites. During central venous access, reliance on surface landmarks cannot reveal individual variations in vascular anatomy or pre-existing thrombosis. Ultrasonography permits assessment of the target vein and adjacent structures, visualization of needle advancement, and bedside evaluation of selected early complications (Lamperti et al., 2020; Practice Guidelines for Central Venous Access, 2020).

This chapter examines the principles of ultrasound-guided peripheral and central venous access, with particular attention to vein and catheter selection, real-time needle guidance, asepsis, confirmation of catheter position, and management of complications. The clinical benefit of ultrasound depends on appropriate indications, operator competence, and safety checks maintained throughout the procedure (Boulet et al., 2023).

The strongest clinical use of ultrasound is therefore not as a late rescue maneuver after multiple failures, but as one component of an access plan that defines the device, vessel, puncture technique, confirmation method, and rescue strategy before the procedure begins. Contemporary guidance describes three linked roles: precannulation assessment, dynamic guidance during cannulation, and recognition of local complications (Vegas et al., 2025).

2. ULTRASOUND PRINCIPLES

Vein Identification and Preprocedural Assessment

A high-frequency linear transducer generally provides adequate resolution for superficial veins; a lower-frequency transducer may be necessary for deeper femoral targets or challenging anatomy. The intended vein should be examined along its course rather than in a single cross-section. Depth, diameter, trajectory, branching, adjacent arteries and nerves, local infection, and existing catheters should be considered together. A vein usually compresses under gentle transducer pressure, whereas an artery may be recognized by pulsatility and a thicker wall. Nevertheless, hypotension, thrombosis, or excessive transducer pressure can alter these appearances. Compression findings should therefore be interpreted alongside color Doppler when indicated (Lamperti et al., 2020; Boulet et al., 2023).

Echogenic intraluminal material, incomplete compressibility, or altered flow should raise suspicion of thrombosis. A thrombosed segment should be avoided,

and an alternative vein or side assessed. Successful puncture does not, by itself, establish that the selected catheter is appropriate: sufficient intraluminal length for a peripheral catheter and suitability for the intended therapy must be evaluated separately (Bruant & Normand, 2025).

Transverse and Longitudinal Imaging

In transverse, or short-axis, imaging, the vein appears approximately circular. This view facilitates assessment of spatial relationships with adjacent structures, but the hyperechoic point on the screen may represent either the needle tip or part of its shaft; controlled transducer movement is needed to distinguish them. Longitudinal, or long-axis, imaging can display the needle tip as it approaches the vein and its relationship to the posterior wall, provided that the needle remains within the imaging plane. Minor transducer movements can cause the needle to disappear from view. An oblique view combines features of the two approaches. Imaging-plane selection should reflect the anatomy of the target vein and the operator's ability to maintain visualization (Boulet et al., 2023; Lamperti et al., 2020).

With real-time guidance, the transducer is held in one hand and the needle in the other. Before skin puncture, the transducer marker is matched to screen orientation, and imaging depth and focal zone are optimized. If the needle tip is lost, advancement is stopped until the relationship between needle and imaging plane has been re-established. Static ultrasound localization before puncture is useful for mapping anatomy, but it does not provide real-time visualization of needle advancement (Practice Guidelines for Central Venous Access, 2020).

Needle visibility can be improved through small adjustments of the puncture angle and transducer tilt. During transverse imaging, the transducer can be advanced just beyond the needle tip and the tip identified again; this sequence is repeated as the needle advances. Longitudinal imaging requires the needle, target vein, and ultrasound beam to remain aligned. A hyperechoic line on the screen does not, by itself, confirm visualization of the tip. Advancing without confirming tip position may injure the posterior venous wall, an artery, or the pleura (Vegas et al., 2025; Boulet et al., 2023).

Ultrasound-Guided Venous Access Techniques

Ultrasound may be used statically or dynamically. In the static approach, the vein and adjacent structures are mapped and the skin is marked before puncture; the needle is not observed during advancement. With dynamic guidance, puncture is performed under real-time imaging. In central venous catheterization, preprocedural assessment should be followed by dynamic

needle guidance whenever feasible. These methods serve different purposes: puncture after skin marking alone should not be described as real-time ultrasound guidance (Practice Guidelines for Central Venous Access, 2020; Vegas et al., 2025).

In the out-of-plane approach, the needle crosses the ultrasound beam toward a vein imaged in the transverse plane. It appears as a hyperechoic point; the transducer must be moved incrementally to establish whether that point is the tip. In the in-plane approach, the needle advances within a longitudinal imaging plane so that its shaft and tip can be seen together when alignment is maintained. Visibility is lost if the needle deviates from the ultrasound beam. An oblique approach may display adjacent structures while allowing a longer visible needle trajectory. Technique selection should be based on local anatomy and the reliability of continuous tip visualization rather than a presumed universal superiority of one plane (Boulet et al., 2023; Vegas et al., 2025).

Catheter insertion may proceed by direct cannulation or over a guidewire. With a short peripheral catheter, the vein is entered using a needle-over-catheter device and the plastic catheter is advanced. In the Seldinger technique, venous puncture is followed by guidewire passage, dilation when required, and advancement of the catheter over the wire. Modified Seldinger techniques use a wire to facilitate controlled catheter advancement, although individual steps vary with the device. Resistance to guidewire passage should prompt reassessment of needle-tip position rather than forceful advancement. Before dilation for a large-bore central catheter, the guidewire should be confirmed within the vein (Lamperti et al., 2020; Practice Guidelines for Central Venous Access, 2020).

2.4. Equipment and Image Optimization

A high-frequency linear transducer, commonly in the 8–15 MHz range, provides the resolution needed for superficial vessels. Deeper targets may require a lower-frequency linear, microconvex, or curvilinear transducer. Depth should be minimized while retaining the target and relevant deeper hazards; the focal zone is placed at or just below the vessel, and gain is adjusted to preserve the vessel wall and needle. Before puncture, the transducer marker must be matched deliberately to the screen orientation.

Feature	Short-axis / out-of-plane	Long-axis / in-plane	Oblique
Anatomic overview	Excellent comparison of vein and adjacent structures.	Limited view of structures beside the vessel.	Retains part of the transverse overview.
Needle appearance	Echogenic dot; tip and shaft may be confused.	Shaft and tip may be seen together if alignment is maintained.	A longer needle segment may remain visible.
Main failure mode	The shaft is advanced while mistaken for the tip.	The needle leaves the imaging plane and continues unseen.	Probe–needle coordination is more complex.
Required safeguard	Dynamic tip positioning with incremental probe and needle movement.	Stop immediately if the tip disappears; restore alignment.	Confirm tip identity before each advance.

3. DEVICE SELECTION AND SAFETY

3.1. Selecting the Access Device

Device selection begins with the therapy rather than the visibility of a vein. Expected duration, infusion rate, pH and osmolarity, vesicant or irritant properties, number of lumens, need for blood sampling, and future access requirements determine whether a short or long peripheral catheter, midline, peripherally inserted central catheter, or centrally inserted catheter is appropriate. Visualization of a deep vein does not make a short peripheral catheter suitable, and a technically successful peripheral puncture does not justify peripheral administration of a drug requiring central delivery (Johnston et al., 2025; Bruant & Normand, 2025).

The smallest catheter that satisfies the clinical requirement should be placed in the largest appropriate vein. Catheter diameter, vessel caliber, required flow, and the amount of catheter expected to remain intraluminal should be considered together. The 2025 Association of Anaesthetists guideline advises that a catheter should ideally occupy no more than one third of the vessel cross-sectional area; this practical principle must still be interpreted in light of position, hydration, respiration, and probe pressure (Johnston et al., 2025).

3.2. Asepsis and Preparation

Central catheterization requires hand hygiene, cap, mask, sterile gown and gloves, skin antisepsis, a large sterile drape, a sterile transducer cover, and sterile gel. Peripheral access should follow the institutional aseptic standard appropriate to the device and expected dwell. The final scan is repeated after

patient positioning because vessel relationships may change. A procedural pause should confirm the indication, site and side, device, allergies, coagulation concerns, equipment, rescue plan, and responsibility for guidewire accounting (Practice Guidelines for Central Venous Access, 2020; Johnston et al., 2025).

3.3. Guidewire Safety

Before dilation, the guidewire must be demonstrated unequivocally within the target vein at the puncture site and, when feasible, in an additional proximal segment. If venous placement remains uncertain, pressure waveform analysis or blood gas comparison is required before a dilator or large-bore catheter is advanced. Dark, nonpulsatile blood is unreliable in shock and hypoxemia. Resistance during wire passage should lead to reassessment, never forceful advancement (Practice Guidelines for Central Venous Access, 2020; Vegas et al., 2025).

The operator should retain control of the wire, announce and document its removal, and reconcile all components before leaving the field. If a dilator or large-bore catheter has entered an artery, it should not be removed blindly; the device should remain in place while urgent vascular or interventional advice is obtained (Johnston et al., 2025).

Checkpoint	Minimum confirmation	Escalation trigger
Before puncture	Patent target; safe trajectory; artery, nerve, and pleura identified.	Thrombosis, uncertain anatomy, or no safe path.
After venipuncture	Tip visualized in the lumen plus compatible blood return.	Discordant blood features or poor visualization.
Before dilation	Guidewire unequivocally visualized in the intended vein.	Wire not seen, resistance, ectopy, or unexpected course.
Before use	Lumens aspirate and flush; wire accounted for; tip plan completed.	Poor function, pain, swelling, arrhythmia, or uncertain tip.

4. PERIPHERAL VENOUS ACCESS

4.1. Patient and Vein Selection

Ultrasound-guided peripheral cannulation is particularly relevant when veins are neither visible nor palpable, following repeated failed attempts, or in patients with obesity, edema, or previously used venous sites. The expected treatment duration and properties of the infusate remain central to device selection. Visualization of a peripheral vein does not justify administration through a peripheral catheter of medication requiring central delivery. When

access will be needed for a prolonged period, a longer peripheral catheter, midline catheter, or central device should be considered according to the clinical indication (Bruant & Normand, 2025).

Straight forearm veins of adequate caliber that are less affected by joint movement are often suitable targets. The close relationship of the brachial veins to the artery and nerves, variable depth of the basilic vein, and tortuosity of the cephalic vein require assessment before puncture. A single diameter threshold is not appropriate for every patient. Vein diameter, depth beneath the skin, catheter outer diameter, and the intraluminal catheter length that can be achieved should be considered together. Inserting a short catheter into a deep vein may yield initial blood return yet result in early dislodgement or infiltration (Bruant & Normand, 2025).

4.2. Insertion and Confirmation of Function

After application of a tourniquet, the target region is scanned systematically to identify an appropriate straight venous segment. Skin antisepsis is performed, and transducer covering and gel are selected according to institutional aseptic practice for peripheral cannulation. The skin entry point is chosen with regard to venous depth and anticipated needle angle. The tip is observed as it approaches and enters the anterior venous wall; unnecessary advancement is avoided once intraluminal entry is established. The catheter is advanced only when sufficient intravascular length can be achieved. Blood return alone does not prove that the catheter tip remains within the lumen (Bruant & Normand, 2025).

If resistance, pain, or local swelling develops during catheter advancement, infusion should not be forced. Gentle saline flushing may be accompanied by ultrasound assessment of intraluminal flow and any accumulation of fluid around the vein. The catheter is secured and subsequently assessed for infiltration, phlebitis, and loss of function. Evaluation of procedural success should include catheter survival and usability during treatment, rather than first-pass puncture success alone (Bruant & Normand, 2025).

In difficult peripheral access, a predefined limit on consecutive attempts may reduce tissue injury associated with repeated failed punctures. A hematoma at the intended site can also impair subsequent ultrasound-guided access. During time-sensitive care, such as induction of anesthesia, the vascular access plan should be coordinated with airway and hemodynamic management. Visualization of a vein does not necessarily mean that an appropriate device can be inserted; a different vein or catheter should be selected if adequate intraluminal length cannot be achieved (Bruant & Normand, 2025; Johnston et al., 2025).

4.3. Catheter Length and Preservation of Venous Access

A short peripheral catheter can sometimes be directed into a deep vein under ultrasound guidance, but limited intraluminal catheter length increases susceptibility to movement, dislodgement, and extravasation. As target depth increases, a longer peripheral or midline catheter should be considered according to the intended therapy. Selection of an unnecessarily large catheter relative to vein caliber may compromise blood flow and venous health. Catheter outer diameter, required infusion rate, and available vein diameter should therefore be evaluated together; selecting the largest visible vein is not synonymous with selecting the safest access (Johnston et al., 2025; Bruant & Normand, 2025).

4.4. Quantitative Evidence and Catheter Survival

A 2022 Cochrane review of 14 randomized and two quasi-randomized trials involving 2,267 adults found that ultrasound increased first-pass success in difficult access (risk ratio 1.50, 95% confidence interval 1.15–1.95) and overall success (risk ratio 1.40, 95% confidence interval 1.10–1.77). Evidence certainty was low to very low for these outcomes. In patients categorized as having easy access, routine ultrasound did not improve outcomes and reduced first-pass success in the available evidence (Tada et al., 2022). The practical implication is selective early use in DIVA, not indiscriminate use for every straightforward cannulation.

Catheter length becomes increasingly important as vein depth increases. In a prospective single-center study, every catheter with less than 30% of its length within the vein failed, whereas no failure occurred when at least 65% was intraluminal; those exact thresholds should not be treated as universal because of the study design (Pandurangadu et al., 2018). In a randomized comparison of veins 1.2–1.6 cm deep, median survival was 4.04 days for a 6-cm extended-dwell catheter and 1.25 days for a 4.78-cm catheter (Bahl et al., 2019). These findings support choosing a longer device when a deep target would leave a short catheter with little intraluminal purchase.

5. CENTRAL VENOUS ACCESS

5.1. Indications, Site Selection, and Risk Assessment

Central venous access may be indicated for vasopressor administration, inadequate peripheral access, particular infusions, hemodynamic monitoring, or prolonged treatment. The optimal site is not selected on ultrasound appearance alone. Infection, thrombosis, and mechanical risks should be balanced against anatomy, patient positioning, coagulation status, existing devices, and

anticipated duration of therapy. Preprocedural scanning of the right and left internal jugular veins, the infraclavicular axillary/subclavian region, and the femoral veins may identify anatomical variations or segments unsuitable for cannulation (Lamperti et al., 2020; Practice Guidelines for Central Venous Access, 2020).

The internal jugular vein is commonly selected because of its relatively superficial location and accessible sonographic window. Trendelenburg positioning may increase venous caliber but should be assessed in relation to intracranial pressure, respiratory mechanics, and patient tolerance. Excessive head rotation may increase overlap between the internal jugular vein and carotid artery. In axillary/subclavian access, the clavicle and pleura constrain imaging; selecting a visible axillary segment can facilitate needle-tip tracking. Femoral access may be useful in selected urgent situations in which thoracic complications are particularly undesirable, although the risks associated with the inguinal site must be considered (Boulet et al., 2023; Lamperti et al., 2020).

For internal jugular access, demonstration of a patent vein alone is insufficient. The relationship between vein and carotid artery may change with head rotation, transducer pressure, and respiration; the safest path must be reassessed at the intended puncture level. The axillary vein is often deeper, requiring an approach that permits continued visualization of the tip while accounting for the artery, pleura, and rib shadow. In the femoral region, scanning from proximal to distal reveals changes in the relative positions of the artery and vein. An alternative site should be identified before repeated punctures become necessary (Boulet et al., 2023; Vegas et al., 2025).

5.2. Sterile Preparation and Real-Time Catheterization

Central venous catheterization requires hand hygiene, appropriate skin antisepsis, a mask and cap, sterile gown and gloves, and a large sterile drape. The transducer should be enclosed in a sterile cover and used with sterile gel; cover integrity must be maintained throughout the procedure. After adequate analgesia and local anesthesia, the vein, artery, pleura, and other structures at risk are reassessed. A previous scan should not be relied upon after a change in patient position or when anatomy is difficult (Practice Guidelines for Central Venous Access, 2020; Lamperti et al., 2020).

The approach of the needle to the anterior venous wall and its entry into the lumen should be visualized in real time. Unnecessary needle advancement after blood return is avoided to limit posterior wall puncture. A guidewire that does not advance freely should never be forced. Venous location of the wire should be established before a dilator is used, especially for large-bore access, because

inadvertent arterial dilation can lead to serious injury. Following catheter insertion, blood is aspirated and each lumen is flushed. Tip position and possible complications are assessed using methods appropriate to the insertion site and local protocol (Boulet et al., 2023; Practice Guidelines for Central Venous Access, 2020).

Dark, nonpulsatile blood is insufficient on its own to establish venous placement; shock and hypoxemia can make visual assessment misleading. When anatomy is challenging, direct visualization of the wire within the venous lumen can be supplemented, where necessary, by pressure waveform analysis or blood gas assessment. Visualization of the wire within the vein does not establish that the catheter tip has reached an appropriate central position. Tip location should be verified according to the device and intended infusion. Intracavitary electrocardiography, ultrasound, and radiography are used in different circumstances according to institutional expertise (Practice Guidelines for Central Venous Access, 2020; Vegas et al., 2025).

5.3. Site-Specific Puncture Approaches

Anterior, central, and more lateral approaches to the internal jugular vein have been described. With ultrasound guidance, however, the skin entry point is determined primarily by the actual relationship between the vein, carotid artery, and other adjacent structures rather than by fixed surface landmarks. If the vein overlaps the artery substantially, the puncture level or imaging angle should be changed. A straight segment that allows visualization of the tip is preferred, and depth and trajectory should be controlled to avoid injury to deeper vessels or the pleura (Lamperti et al., 2020; Vegas et al., 2025).

For infraclavicular axillary access, the transducer is placed distal to the clavicle to assess the vein, artery, and pleura; an entry point obscured by clavicular shadow should be avoided. Femoral access generally targets the common femoral vein below the inguinal ligament, with careful assessment of its relationship to the artery and of positional changes distally. The proposed needle path and its distance from the artery, pleura, and other vulnerable structures should be reassessed for each attempt. If a safe trajectory cannot be maintained, an alternative site should be selected rather than repeating punctures at the same site (Boulet et al., 2023; Vegas et al., 2025).

5.4. Interpretation of Guidelines and Clinical Evidence

The 2020 ASA guideline and PERSEUS recommendations emphasize preprocedural anatomical assessment and real-time ultrasound guidance for appropriate venous access procedures. The 2025 American Society of Echocardiography update addresses peripheral and central access as a

continuum that includes preprocedural assessment, guidance during puncture, and recognition of complications. Preprocedural scanning identifies the target and adjacent hazards, whereas continuous needle tracking helps control the puncture trajectory. Mere availability of an ultrasound machine does not establish that the procedure was performed with effective ultrasound guidance (Practice Guidelines for Central Venous Access, 2020; Lamperti et al., 2020; Vegas et al., 2025).

Comparative studies of ultrasound-guided internal jugular catheterization report benefits in first-pass success, number of attempts, and mechanical complications, although clinical settings and operator experience vary. A prospective multicenter cohort demonstrated that mechanical complications persist despite widespread use of ultrasound. The evidence therefore supports ultrasound as part of a broader strategy that includes technique, operator proficiency, and individualized risk assessment, rather than as a guarantee against complications (Adrian et al., 2022; Boulet et al., 2023).

In the multicenter observational study by Adrian and colleagues, limited operator experience and an increasing number of skin punctures were associated with mechanical complications. These associations do not establish causation, but they support reassessment of the plan after unsuccessful attempts rather than repetition of an unchanged technique. Observational risk associations should be distinguished from guideline recommendations, and procedural decisions should remain specific to the patient's anatomy and clinical indication (Adrian et al., 2022; Lamperti et al., 2020).

5.5. Site Trade-offs

No insertion site is optimal for every patient. In the 3SITES randomized trial, subclavian access produced fewer bloodstream infection or symptomatic thrombosis events than jugular or femoral access but more mechanical complications, principally pneumothorax. The result supports individualized site selection rather than a categorical hierarchy (Parienti et al., 2015).

Site	Advantages	Principal concerns	Ultrasound emphasis
Internal jugular	Superficial, compressible, broad acoustic window.	Carotid overlap, posterior-wall puncture, neck dressing.	Limit head rotation; scan at the intended puncture level; confirm wire before dilation.
Axillary/subclavian	Comfortable exit site; may reduce late infection/thrombosis.	Pleura, artery, clavicular shadow, pneumothorax.	Prefer a visible extrathoracic axillary segment; include pleura and artery in the safety survey.
Femoral	Rapid, compressible, and free of thoracic complications.	Contamination, thrombosis, mobility, noncompressible bleeding if too proximal.	Identify the inguinal ligament and artery–vein overlap; remain below the ligament.
PICC / upper-arm central	Useful for intermediate or prolonged therapy.	Thrombosis, migration, and central-tip malposition.	Map basilic, brachial, and cephalic veins; match device to vessel and confirm central tip.

6. CONFIRMATION BEFORE USE

6.1. Three Distinct Questions

Confirmation must address three separate questions: is the needle in a vein; is the guidewire in the intended venous system; and is the catheter tip in an acceptable final position? Blood return does not answer all three. Local ultrasound visualization of a wire before dilation confirms its position at the observed segment but cannot prove that the wire or catheter has not entered an unintended central vein.

Final tip confirmation depends on the device, insertion site, clinical urgency, and local expertise. Options include intracavitary electrocardiography, fluoroscopy, radiography, and ultrasound-based protocols that combine vascular views, transthoracic echocardiography, and a rapid right-atrial contrast test. When a test is incomplete or discordant with the clinical picture, another validated method is required (Vegas et al., 2025; Johnston et al., 2025).

6.2. Ultrasound and Radiography

A meta-analysis of 15 studies and 1,553 catheter placements reported ultrasound sensitivity of 0.82 and specificity of 0.98 for malposition, with a mean confirmation-time reduction of 58.3 minutes compared with chest radiography. Risk of bias and clinical heterogeneity were high (Ablordeppey et al., 2017). A positive ultrasound finding is useful, but a negative or technically limited study cannot exclude every malposition.

After cervical or infraclavicular access, lung ultrasound may compare pre- and postprocedural pleural sliding and other pneumothorax signs. Absence of sliding is not specific for pneumothorax. Radiography or computed tomography remains appropriate when sonographic windows are inadequate, tip position is uncertain, symptoms develop, or the consequence of missing a malposition is substantial.

7. SPECIAL CIRCUMSTANCES AND COMPLICATIONS

7.1. Pediatric Patients, Coagulopathy, and Emergencies

In children, small venous caliber, susceptibility of veins to compression, and short skin-to-vein distance increase the importance of precise needle control. Transducer, needle, and catheter dimensions should be matched to age and anatomy. Although anesthesia improves procedural tolerance, visualization of the tip and protection of adjacent structures remain essential. In the presence of coagulopathy, the need for access and bleeding risk should be considered alongside whether the puncture site is compressible; ultrasound guidance does not abolish the risk of hemorrhage (Lamperti et al., 2020).

Hypovolemia can markedly reduce venous caliber during emergency access, and excessive transducer pressure may collapse the target vein. Selection among peripheral, central, and alternative emergency access routes depends on circulatory status, the required infusion rate, and urgency. Early recognition of difficult access should prompt involvement of an experienced operator and an appropriate imaging strategy rather than repeated blind attempts (Bruant & Normand, 2025; Boulet et al., 2023).

7.2. Prevention of Mechanical and Infectious Complications

Arterial puncture, hematoma, arrhythmia, pneumothorax, hemothorax, and guidewire or catheter malposition are important complications of central access. Loss of needle-tip visualization is particularly hazardous near the pleura. Accidental arterial needle puncture must be distinguished from placement of a large-bore catheter within an artery; following dilation, uncontrolled removal of the catheter should be avoided pending assessment by an appropriate specialist team. New dyspnea, hypoxemia, chest pain, or hemodynamic deterioration after the procedure

warrants prompt investigation (Practice Guidelines for Central Venous Access, 2020; Boulet et al., 2023).

Assessment of pleural sliding by lung ultrasound after cervical or infraclavicular access may contribute to evaluation for pneumothorax, but a single image or a negative examination does not exclude all complications. In experienced settings, ultrasound techniques such as visualization of rapid right atrial contrast may contribute to assessment of catheter tip location. Such findings should not be interpreted as a stand-alone test that excludes every malposition or mechanical injury. Additional imaging should not be delayed when clinical suspicion persists (Vegas et al., 2025; Boulet et al., 2023).

Ultrasound does not replace sterile technique. A torn transducer cover, contaminated gel, or breach of the sterile field can increase infection risk. The continued need for each catheter should be reviewed regularly, with removal when it is no longer indicated. Peripheral catheters should be monitored for infiltration and extravasation, and central catheters for infection and thrombosis, alongside routine assessment of function (Bruant & Normand, 2025; Lamperti et al., 2020).

7.3. Training and Quality Assessment

Ultrasound-guided venous access requires accurate interpretation of images as well as technical proficiency in acquiring them. Training should encompass venous anatomy, transducer handling, needle-tip tracking, guidewire confirmation, aseptic practice, and recognition of complications. Simulation, supervised procedures, and structured feedback should precede independent practice. Quality measures include first-pass success, total number of punctures, procedure time, mechanical complications, and functional catheter dwell time. The 2025 Association of Anaesthetists guideline likewise places device selection, training, and catheter maintenance within a comprehensive approach to access safety (Lamperti et al., 2020; Vegas et al., 2025; Johnston et al., 2025).

7.4. Evidence Boundaries

In pediatric peripheral access, evidence varies with case mix. One 2022 systematic review of nine trials found overall success of 78% with ultrasound and 66% with landmark techniques, with the greatest benefit in difficult access (Mitchell et al., 2022). Another review that excluded DIVA-only trials found no clear benefit in general pediatric populations and substantial heterogeneity (Kleidon et al., 2022). Ultrasound should therefore be targeted to difficulty and operator competence rather than generalized without context.

Evidence that ultrasound itself reduces catheter-related bloodstream infection is uncertain. A 2022 meta-analysis of four randomized trials found an imprecise

reduction in infection (risk ratio 0.46, 95% confidence interval 0.16–1.32) and no reduction in catheter colonization (Takeshita et al., 2022). Ultrasound cannot justify any relaxation of insertion or maintenance bundles.

8. TRAINING, DOCUMENTATION, AND QUALITY

Competence is not established by attendance at a lecture or completion of a fixed procedure count. Training should combine ultrasound physics and controls, anatomy, vessel mapping, asepsis, needle-tip tracking in more than one plane, guidewire confirmation, device selection, and complication recognition. Simulation permits deliberate practice of hand–eye coordination and recovery after loss of tip visualization before patient exposure.

A 2023 systematic review of 35 educational studies found that 97.1% used blended teaching with didactic and simulation components, but competency definitions and assessment methods varied substantially (Morrow et al., 2023). Programs should use an objective checklist or rating scale, supervised clinical performance, explicit criteria for independent practice, and continuing outcome review rather than procedure counts alone.

Documentation should identify the vessel and side, device and size, use of real-time guidance, number of attempts and operators, wire confirmation, tip-confirmation method, lung assessment when relevant, immediate complications, and guidewire removal. Service-level metrics should include first-pass success, total punctures, escalation, arterial puncture, pneumothorax, malposition, peripheral infiltration or extravasation, unplanned replacement, dwell time, and completion of intended therapy.

Domain	Observable performance	Evidence of competence
Assessment	Identifies patency, hazards, suitable device, and rescue plan.	Direct observation in simulation and clinical practice.
Image acquisition	Optimizes orientation, depth, focus, and orthogonal views.	Structured image review.
Needle control	Keeps the tip identifiable and stops when visualization is lost.	Task checklist or global rating scale.
Wire and catheter safety	Confirms wire before dilation; avoids force; accounts for wire.	Observed procedure and documentation audit.
Complication response	Recognizes arterial placement, pneumothorax, infiltration, and malposition.	Simulation scenarios and case assessment.
Clinical outcomes	Maintains acceptable success, complication, and dwell metrics.	Longitudinal log and service audit.

9. CONCLUSION

Ultrasonography allows the venous access plan to be tailored to the patient's actual anatomy. It supports more directed cannulation in difficult peripheral access and enables assessment of the target vein, artery, and other adjacent structures during central catheterization. Its clinical value depends on careful preprocedural scanning, reliable visualization of the needle tip and guidewire, selection of a device appropriate to treatment, and meticulous aseptic technique. Training, postprocedural confirmation, and surveillance for complications are integral components of ultrasound-guided venous access.

CLINICAL PEARLS

- Scan the vessel along its course; a favorable single image is not an access plan.
- If the needle tip is not seen, do not advance.
- Blood return confirms vascular entry, not venous identity, guidewire course, or final catheter-tip position.
- Never dilate until the guidewire has been confirmed within the target vein.
- Deep peripheral veins usually require longer catheters to obtain adequate intraluminal purchase.
- Ultrasound reduces risk but does not replace asepsis, maintenance bundles, or escalation pathways.
- A dilator or large-bore catheter inadvertently placed in an artery should remain in place for specialist management.
- Judge success by reliable completion of therapy, not by puncture alone.

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Chapter 4

Art-Based Nursing Approaches

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Preface

The intersection of nursing and the arts represents a dynamic and evolving field that integrates scientific knowledge, clinical expertise, and human creativity. This work aims to examine the multifaceted role of artistic and expressive interventions such as visual arts, music, dance, narrative storytelling, drama, and meditative practices in enhancing the well-being of patients, caregivers, and healthcare professionals. By combining both empirical evidence and theoretical perspectives, this text highlights how creative approaches can complement conventional nursing care, promote holistic healing, and support emotional, cognitive, and social development.

The work particularly emphasizes the potential of art-based interventions to alleviate stress, anxiety, depression, and pain while fostering resilience, mindfulness, and self-expression. Therapeutic modalities that respect cultural contexts, individual experiences, and developmental needs are highlighted, providing a person-centered framework for care. Furthermore, the importance of equipping nursing students and professionals with the knowledge, skills, and reflective capacities necessary to implement these interventions effectively in clinical and educational settings is underscored. This text will serve as both an academic resource and a practical guide, inspiring nurses, educators, and healthcare professionals to adopt creative, evidence-informed approaches in practice, ultimately enhancing the quality of care and supporting the holistic health and well-being of those they serve.

Introduction

The integration of arts and holistic approaches into nursing and healthcare has increasingly gained recognition for its profound impact on patient well-being and therapeutic outcomes (Ağaç & Alkaya, 2025). Throughout history, artistic expression has been closely linked with mental health, providing individuals with

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avenues for self-expression, emotional release, and psychological recovery across diverse cultures and civilizations (Tatarkiewicz, 1974; Lane, 2006). In contemporary therapeutic practice, these connections have been formalized, with art therapy emerging as a powerful intervention for addressing mental health challenges such as depression, anxiety, and emotional distress (Vaartio-Rajalin et al., 2021; Zhang et al., 2024; Brooks et al., 2020). It examines the historical and philosophical foundations of these approaches, highlighting their role in fostering emotional expression, supporting mental health, and promoting overall psychological well-being (Bender et al., 2021; Pandey et al., 2024). The discussion encompasses a wide range of modalities, including visual arts and painting, music and sound therapy, dance and movement therapy, folklore and ritual, masks and puppetry, animal-assisted therapeutic approaches, literature and storytelling, drama and role-playing techniques, mindfulness, mandala art, and meditative practices (Chang & Chen, 2012; Dawn, 2025; Majore-Dusele et al., 2021; Li, 2025).

These diverse interventions offer numerous therapeutic benefits, including improved emotional regulation, increased self-esteem, reduced anxiety and depression, and facilitation of personal growth and self-discovery (Apriyana et al., 2020; Brooks et al., 2020; Li, 2025; Zhang et al., 2024; Lee, 2025). From supporting emotional expression in trauma survivors to promoting psychological well-being among healthcare professionals during periods of high stress, the applications of these creative and holistic methods are both extensive and varied (Oruç et al., 2025; Ağaç & Alkaya, 2025). By examining these interconnected fields, this work aims to demonstrate their potential to enrich nursing practice and provide truly comprehensive, person-centered care.

1. The Artistic Origins of Nursing and the Role of Florence Nightingale

The origins of the nursing profession are rooted in fundamental human emotions such as empathy, compassion, and a genuine concern for others qualities that have shaped caregiving practices since ancient times. Throughout history, these deeply human sentiments have guided the provision of care, transforming nursing from a purely medical task into both a humanitarian and an artistic endeavor.

Florence Nightingale, recognized as the founder of modern nursing, not only established nursing as an independent profession but also laid the groundwork for its artistic and aesthetic dimensions (Karimi, 2015). Her approach extended beyond technical knowledge and scientific methods, integrating the human connection between nurse and patient with carefully organized environmental factors. Nightingale embraced a holistic perspective that considered not only the

physical needs of the patient but also their psychological and environmental requirements. In doing so, she positioned nursing as an art form intertwined with ethical and professional standards.

Nightingale emphasized empathy, shared experience, and the creation of meaningful interactions with patients. This understanding strengthened the aesthetic dimension of nursing, fostering a form of care that transcends words, seeks to enhance the patient's emotional well-being, and cultivates a sense of unity between nurse and patient. She highlighted the importance of building trust-based relationships, demonstrating that such professional communication reflects the artistic and humanistic aspects of nursing (Karimi, 2015).

Her environmental theory, which assigned central importance to factors such as cleanliness, light, ventilation, and quietness, underscored the role of the environment in the healing process. Managing these elements requires attentiveness and aesthetic awareness, thereby attributing an artistic quality to nursing practice. Through her work, Florence Nightingale transformed nursing from a solely scientific and technical practice into one enriched by human touch, empathy, and aesthetic sensitivity. Her legacy ensures the continuity of this artistic and compassionate spirit within contemporary nursing.

2. Holistic and Integrative Approaches in the Art of Nursing Care

Nursing is a discipline grounded in a robust philosophical foundation and seeks to understand the human experience through both its scientific and artistic dimensions. Philosophy plays a pivotal role in the development of nursing and in shaping the domains in which it is practiced (Bender, 2021). The proposed central unifying focus of the nursing discipline is to facilitate humanization, meaning, choice, quality of life, and healing across the spectrum of life and death. In this context, the history of nursing serves as a valuable philosophical tool that can be used to cultivate a critical perspective toward societal transformations (Willis, 2008).

Care, the central concept of nursing, is a universal philosophical element that guides the practice of all health professionals. Although nursing historically evolved from the maternal role, its maturation as a scientific discipline has brought greater clarity to the meaning of care and to nursing's position as a "pure science of caring." Throughout this evolution, nursing philosophy has shifted away from positivist thinking toward an interpretive paradigm that incorporates phenomenology, humanism, and a holistic worldview (Sapountzi-Krepia, 2013).

Holistic nursing and integrative care approaches are grounded in philosophical traditions that conceptualize the individual as a unified whole, encompassing physical, mental, emotional, and spiritual dimensions. This approach views

philosophical traditions such as evolutionary idealism as an appropriate metaphysical foundation for the development of nursing theory (Berg, 2003). The philosophical, ethical, and theoretical underpinnings of holistic nursing define the identity, values, and existential purpose of holistic nurses (Cowling, 2016). This comprehensive perspective is deeply interwoven with interpretations of the concepts of person, health, illness, and nursing (Berg, 2003). Furthermore, the establishment of a holistic understanding of health requires critical examination of systems science and holistic philosophical foundations.

The *art* dimension of holistic nursing practice lies at the heart of this philosophical integration. The art of nursing encompasses human elements such as relationship-building, communication, creativity, presence, and compassion (Cowling, 2016). Nursing care is not merely a practical or ethical activity; it is also a creative act. This creative dimension enables the emergence of something new, unique, and meaningful within the nurse–patient interaction.

3. Definition of Art

In antiquity, art was defined as the capacity to create something in accordance with established rules. However, formulating a single, universal definition of art has proven to be an enduring challenge. Throughout history, various aesthetic theories including Formalism, Voluntarism, Emotionalism, Intellectualism, Intuitionism, and Organicism have attempted to identify the necessary and sufficient characteristics of art. Although each of these theories has claimed to articulate the true nature of art, successive eras and artistic movements have rejected or revised earlier definitions, offering new conceptualizations in their place. This ongoing process reveals that the essence of art remains a subject of persistent debate.

Moreover, the historical evolution of the concept of art, its classification, and its relationship to adjacent notions such as poetry, beauty, creativity, and *mimesis* (imitation) have all significantly influenced attempts to define it (Tatarkiewicz, 1974).

4. Dimensions of Art in the Context of Nursing

Creativity and Tradition

Art exists within a dynamic interplay between creativity and tradition. Similarly, in nursing, creativity enables practitioners to integrate empirical knowledge and clinical experience with traditional caregiving practices to generate patient-specific solutions. As seen in contemporary applications such as artificial intelligence and digital art, motivation, self-awareness, and emotion contribute to advancing patient-centered care within nursing practice (Liu, 2023).

Aesthetic Experience

Art aims to evoke an aesthetic experience in its audience (Carroll, 2010). In the nursing context, the aesthetic experience reflects heightened empathy, sensitivity, and quality of communication during nurse–patient interactions. The arrangement of the care environment, the tone of communication, and the use of creative methods in patient engagement all enhance patients' emotional comfort and overall well-being.

Value Dimension

The relationship of art to moral, ethical, and political domains corresponds to the ethical and value dimension of nursing practice (Carroll, 2010). Nurses make ethical decisions while upholding justice, respect, and human dignity in care principles that constitute fundamental values within the art of nursing. Concepts in art such as virtue, remembrance, and alienation can be understood in parallel with nurses' efforts to comprehend the patient experience and sustain their ethical responsibilities.

Emotion and Human Nature

Art engages with human nature, mood, and emotional relationships (Carroll, 2010). Likewise, in nursing, emotional awareness and the establishment of an empathetic bond with the patient enhance the quality of care. By observing patients' emotional and psychological states, nurses provide appropriate support, which forms an integral component of holistic care.

Narrative and Humor

Art encompasses dimensions such as narrative, ethical life, and humor. In nursing, listening to patients' stories, constructing meaning throughout the care process, and when appropriate using humor to provide relief all serve to strengthen the nurse–patient relationship and enhance the overall care experience (Carroll, 2010).

Three-Dimensional and Virtual Art

Virtual reality and media arts integrate participation, aesthetic experience, and interaction. In nursing education, virtual environments through simulation and interactive case studies enable students to develop empathy, clinical decision-making skills, and competencies in patient interaction. Additionally, the recontextualization of the body and lived experience enhances nurses' capacities for awareness and sensitivity (Carroll, 2010).

Interdisciplinary Approach

Art brings together diverse disciplines (Carroll, 2010). Similarly, in nursing, the integration of fields such as philosophy, psychology, drama, music, and dance strengthens holistic approaches to care. These interdisciplinary practices are

effective in cultivating creativity, empathy, and ethical awareness among nursing students.

5. Nursing as Both a Science and an Art

While nursing draws its knowledge base from scientific principles, it acquires an artistic dimension through the ability to adapt this knowledge to the unique needs of each patient. The expression "the art and science of nursing" represents the integration of the humanities and the natural sciences and forms the foundation of the discipline (Khastar, 2024). Nursing knowledge has developed through the scientific investigation of phenomena, and within the framework of evidence-based practice (EBP), nurses make informed decisions by integrating current research evidence, clinical expertise, and patient values (Güneş, 2017; Khastar, 2024).

The art of nursing is defined as the simultaneous integration of scientific facts, awareness, and the nurse's knowledge and understanding. It encompasses functions such as clinical decision-making and judgment, interpreting the meaning of patient interactions, establishing meaningful relationships, and carrying out nursing interventions with skill and refinement (Khastar, 2024). Unique qualities such as compassion, advocacy, calmness, attentiveness, and empathy form the core of the nursing art, enabling the creative and aesthetic application of both scientific and humanistic principles of care (Kolcaba, 1995).

The balance between evidence-based practice and individualized care reveals the distinctiveness of nursing, enhances the quality of patient care, and creates a meaningful professional experience for nurses. Educational approaches such as the use of visual arts and storytelling help students integrate artistic and scientific perspectives by strengthening skills in observation, communication, narrative sequencing, and empathy. For example, comfort care, which involves comforting actions and the enhancement of overall comfort, is a form of nursing art that requires the creative application of scientific and humanistic principles (Kolcaba, 1995).

6. The Relationship Between Aesthetics and Ethics in Nursing Philosophy

Within nursing philosophy, the relationship between aesthetics and ethics represents a fundamental dimension that profoundly influences care decisions, empathy, and compassion. This relationship demonstrates that in nursing practice, "good actions cannot be separated from good behavior." Nursing aesthetics belongs to the branch of philosophy known as aesthetics and constitutes an integral element of the professional art of nursing. It values

patients' meaningful moments, remains sensitive to diverse circumstances, and appreciates the unique qualities of humanity (Chang, 2012; Kong, 2023).

An aesthetic disposition grounded in Kantian theories of care relationships can be applied to nursing, enabling the nurse to experience the beautiful and the sublime through imagination and free play, via reflective aesthetic judgment. A nurse with such an aesthetic stance can act as a moral agent, contributing to the preservation and enhancement of human dignity within care relationships (Kong, 2023). Ethical nursing requires adherence to a patient-centered approach and fundamental principles. The ultimate aim of philosophy is "goodness," and the foundation of caregiving behavior is "love" (Chang, 2012).

In traditional Western thought, the connection between ethics and aesthetics can be directly applied to nursing practice, underscoring that virtuous actions are inseparable from virtuous behavior. A nurse educated with an aesthetic disposition acts as a moral agent, contributing to the protection and cultivation of human dignity (Kong, 2023).

This intrinsic connection between aesthetics and ethics shapes nurses' care decisions. An aesthetic disposition that incorporates reflective aesthetic judgment enables nurses to act as moral agents in their professional practice (Kong, 2023). The inseparability of virtuous actions from virtuous behavior signifies that ethical considerations are inherently embedded within the aesthetic execution of care. Consequently, nurses make holistic decisions that are not only guided by technical competence but also attuned to the unique needs and human values of their patients (Chang, 2012).

Empathy is a complex, multidimensional construct considered fundamental in nursing practice (Gerace, 2020). Although often conflated with compassion, empathy is distinct. It is experienced as an emotional response involving an attempt to understand and acknowledge an individual's suffering through emotional resonance. Empathy encompasses both a cognitive component perspective-taking and an affective component compassion (Sinclair, 2016).

High levels of empathic disposition are positively correlated with perceptions of individualized care among palliative care nurses (Kayikci, 2025). Empathy is one of the defining attributes of compassion, which constitutes a fundamental aspect of nursing practice and is essential in patient care, influencing both nurse–patient relationships and care outcomes. Compassion extends beyond a mere emotional response, enriching empathy through identifiable features such as the motivation of love, the altruistic role of the responder, actionable interventions, and small, additional acts of kindness (Sinclair, 2016).

The defining characteristics of compassion include empathy, relational understanding, intentionality, presence, and action-oriented care, with the

recognition of suffering serving as a primary precursor. Ethical compassion encompasses altruism and empathy and is influenced by cultural and organizational factors. Patients report that compassion is beneficial and effective, aligns with care actions, and can be conveyed even through the smallest nursing gestures (Sinclair, 2016). High levels of compassion satisfaction positively impact perceptions of individualized care (Kayikci, 2025).

7. The Place of Art in Nursing Theories

The role of art in nursing theories is particularly prominent in Jean Watson's Theory of Human Caring, though it is also addressed indirectly or within a broader context of "artistry" in the work of other theorists. Watson's Theory of Human Caring emphasizes the balance between science and care in nursing and frames the nurse–patient relationship as a moral ideal (Watson, 1988).

Sitzman and Watson (2014) have proposed the use of art as an alternative pathway to understanding nursing theory. Specific art forms such as pointillism, mandalas, and photography have been highlighted as particularly effective for engaging with Watson's theory. These art forms can aid in visualizing and deeply understanding the concepts that form the foundation of the theory. Watson focuses on the philosophical (existential-phenomenological) and spiritual underpinnings of care, positioning caring as the ethical and moral ideal of nursing (Cohen, 1991). She demonstrates her own artistry in her care portrait (Cohen, 1991) and discusses concepts such as the "Advanced-Carative Healing Arts" and "Transpersonal Nursing as an Ontological Artistry" (Watson, 1988).

Martha Rogers' Science of Unitary Human Beings conceptualizes the person and their environment as an inseparable whole. Building on this framework, Smith's Unitary Care Theory incorporates core concepts such as "Inviting Creative Emergence," which requires nurses to create a nurturing space that encourages the emergence of innovative, novel patterns by supporting, educating, and instilling confidence in patients (Kavosi, 2024). This underscores the significance of creativity and an artistic approach within nursing practice.

Madeleine Leininger's Theory of Cultural Care emphasizes the importance of situating care within a cultural context, as care patterns can vary across cultures. Leininger also demonstrates her artistry in her care portrait (Cohen, 1991). Her theory links the concept of comfort with holistic and culturally congruent human care, highlighting it as an indispensable element. This necessitates that nurses adopt culturally sensitive and creative approaches in delivering patient care.

8. The Aesthetic Dimension of Compassion in Nursing

The aesthetic dimension of compassion in nursing is closely linked to the manner in which care is delivered, with the calmness of vocal tone playing a particularly important role. Compassion is the process of recognizing a patient's suffering, witnessing it, and actively striving to alleviate it (Kondaguli, 2023). Nurses can convey compassion more effectively by establishing trust-based relationships with patients through both verbal and nonverbal communication skills (Varghese, 2025).

The calmness of vocal tone constitutes a key component of "relational compassion" as perceived by patients, serving as an expressive dimension of the verbal language nurses use to communicate their emotions. A serene tone of voice is an integral aspect of nurse–patient interactions that helps patients feel acknowledged and valued. Such communication fosters a sense of being cared for, enabling patients to perceive emotional support and feel that their well-being is prioritized. Therefore, the calmness of vocal tone serves as a crucial communicative tool that constitutes the aesthetic dimension of compassion in nursing, signaling that care is being delivered with subtlety and sensitivity.

Facial expressions constitute a critical aspect of body language in healthcare communication. Nurses utilize facial expressions to attune to patients, clarify their needs, and plan care, thereby contributing to humanistic nursing. For instance, a compassionate touch serves as a silent means of demonstrating culturally competent care and fostering nurse–patient relationships, while the eyes and facial expressions represent a significant subtheme of meaning for intensive care nurses (Sandnes, 2022).

In Indonesian nursing, aesthetics is expressed not merely through visual beauty or orderliness but also through compassionate care, the art of communication, pain alleviation, and innovation. Compassionate care encompasses multiple components, including personal, empathetic, and relational qualities, with the knowledge, skills, and attitudes of nursing staff being predominant. *Establishing trust-based* relationships with patients through verbal and nonverbal communication significantly enhances the conveyance of compassion (Varghese, 2025).

Research indicates that facial expressions can convey satisfaction and well-being in nursing care. Furthermore, studies on nursing students' empathy have identified nonverbal expressions of care, including facial expressions, as fundamental behavioral indicators. Patients' facial expressions can also influence nurses' perceptions and subsequent care decisions (Lee, 2024). Even in contexts involving robotic assistance in long-term care facilities, residents' facial

expressions have been observed to become more positive, suggesting improvements in overall quality of life (Kato, 2022).

The sensitivity of touch plays a pivotal role in patient interactions and the delivery of care. Touch constitutes an integral component of human interaction and is indispensable in healthcare, particularly within the nursing profession (Pepito, 2023). Nurses employ physical touch to meet patients' needs and establish meaningful connections. This "expressive touch" or "compassionate touch" contributes to social development, stress and anxiety reduction, and adaptation. Nurses' perceptions of expressive touch encompass its association with comfort, job satisfaction, and its role as a form of compassion and/or communication, as well as its impact on the humanization of patients. Empathic skills play a positive role in anticipating compassionate touch, indicating that empathy and compassion mutually reinforce one another (Öztürk, 2021).

In intensive care nursing, compassionate touch serves as a silent means of demonstrating culturally competent care and establishing or sustaining nurse–patient relationships. Such touch contributes to enhancing the ethical dimensions of patient dignity (Sandnes, 2022). The sensitivity of touch enriches the aesthetic dimension of compassion in nursing by improving the quality of nurse–patient relationships, strengthening communication, and promoting patients' physical and emotional comfort. This allows care to be perceived not merely as procedural but as a humanistic and responsive art form.

The arrangement of a patient's room is a crucial factor in supporting the recovery process and enhancing overall well-being. Aesthetics in nursing practice is not limited to visual beauty or orderliness; it is also understood as an expression of compassionate care, communication, and innovation. In this context, the organization of the patient's room is part of an effort to create a "sympathetic care environment" (Betriana, 2022).

The design of the hospital environment, and particularly the layout of patient rooms, can influence patient satisfaction, clinical outcomes, and recovery. Single-patient rooms contribute to privacy, confidentiality, dignity, and comfort. In newly constructed hospital settings, room features such as natural light, storage, and writing surfaces have been shown to enhance satisfaction for both staff and family members. In pediatric hospitals, the perception of a child's room as a "healing environment" has been associated with significant improvements in family satisfaction (Brown, 2006).

Research on evidence-based healthcare design demonstrates that features such as single-patient rooms, optimal acoustics, nature-based distractions, daylight, and appropriate lighting are critical for patient safety and recovery. Jean Watson's Theory of Human Caring similarly emphasizes the importance of establishing

trust, respect, and emotional connection by creating an environment conducive to healing, while considering cultural diversity (Florentin, 2023). The design and arrangement of patient rooms have the potential to promote recovery and well-being. As part of the aesthetic dimension of compassion in nursing, this reflects an effort to provide an environment that supports patients not only physically but also emotionally and spiritually (Brown, 2006).

9. Therapeutic Mechanisms of Art: A Biopsychosocial Perspective

Stress and Anxiety

The therapeutic effects of art have gained prominence in nursing, particularly due to its potential to reduce stress and anxiety. Art therapy is recognized as an effective intervention that supports the mental well-being of both nurses and patients, enhancing emotional wellness (Ağaç, 2025; Zhang, 2024). Given that nursing is a profession associated with high levels of stress and intense emotional demands, nurses are at elevated risk for mental health challenges. In this context, art therapy has been shown to significantly reduce anxiety, depression, and perceived stress levels among clinical nurses (Zhang, 2024).

Moreover, engagement with art can diminish maladaptive coping strategies while enhancing adaptive coping capacities, thereby strengthening psychological resilience and promoting the development of self-awareness among nurses (Ağaç, 2025).

Art therapy produces similar therapeutic effects in patients. In individuals undergoing hematopoietic stem cell transplantation, engagement in art-making has been shown to alleviate treatment-related symptoms such as numbness and difficulties with concentration. Occupational art therapy programs conducted with older adults have demonstrated significant reductions in depression, anxiety, and stress scores (Megasari, 2024). A pilot study in an acute psychiatric unit revealed that art therapy not only reduces anxiety and stress levels but also enhances overall psychological well-being (Laranjeira, 2019). Additionally, narrative writing and art therapy interventions for parents in neonatal intensive care units have been found to mitigate stress and anxiety associated with the emotional burden of intensive care (Gundo, 2022).

In the general population, art therapy has been shown to influence stress physiology, reducing cortisol levels and alleviating state anxiety. In particular, art therapy serves as a supportive intervention for depression in older women, significantly improving both depressive symptoms and anxiety manifestations (Ciasca, 2018). Collectively, these findings indicate that art therapy is an effective intervention not only for clinical populations but also for individuals experiencing stressful life circumstances more broadly.

From the perspective of nursing practice, art-making represents a readily adaptable and easily implementable intervention within clinical settings. It strengthens the care relationship by supporting positive communication processes between nurses and patients. Studies involving nursing students have confirmed that art-based interventions, such as aromatherapy and music therapy, exert a reducing effect on exam-related anxiety, state anxiety, and stress (Son, 2019). Consequently, art-based applications are considered an essential component of both nursing care and nursing education.

Pain

The therapeutic effects of art have yielded significant findings, particularly in studies aimed at reducing pain perception. Art-based visual stimuli have been shown to increase pain threshold and pain tolerance, and such interventions are considered effective nursing strategies for creating a more calming environment by mitigating anxiety-inducing sights and sounds within hospital settings. Furthermore, art therapy has been found to be beneficial in chronic pain management as part of multidisciplinary approaches that address biological, psychological, and social components of the pain experience. These interventions have been shown to reduce pain intensity and depressive symptoms while simultaneously enhancing overall quality of life. Art therapy also functions as a distraction mechanism, producing beneficial effects on stress levels and mood.

Studies in oncology and pediatric settings particularly emphasize the therapeutic potential of art. Art programs implemented in oncology units have been found to strengthen patients' coping skills for managing pain, improve nurse–patient communication, and positively influence patients' attitudes toward hospitalization. In pediatric oncology, creative art therapy has enhanced the quality of life for children with cancer, alleviating symptoms such as pain, nausea, and anxiety. Art-based interventions have also been reported to reduce levels of anxiety, fear, and pain in children undergoing treatment (Raybin, 2022).

Creative interventions in nursing practice have been shown to reduce hospital length of stay and decrease the need for analgesic medications (Lane, 2006). Consequently, it is recommended that nurses integrate art-based approaches into care processes. Nursing students have also recognized art therapy as a significant tool for establishing therapeutic communication and supporting patients' mental health, highlighting the importance of incorporating art therapy into nursing education programs (Rice, 2017).

Psychological Resilience and Sense of Hope

The therapeutic effects of art play a significant role in fostering psychological resilience and cultivating a sense of hope. Art therapy has emerged as an effective intervention that enables individuals to express their emotions, cope with stress,

and enhance their psychological resilience (Ağaç, 2025; Kashaka, 2025). Creative expression processes have been shown to support emotional healing and strengthen overall psychological well-being (Kashaka, 2025). Furthermore, a study involving mothers of children with disabilities demonstrated that participation in art-based activity groups increased psychological well-being and life satisfaction while simultaneously reducing caregiver burden (Çulhacik, 2020).

The use of metaphors in art-making has been reported to enhance resilience in individuals experiencing chronic stress or trauma (Sheridan, 2024). Both group and individual art activities have also been observed to exert positive effects on adolescents' mental health. Additionally, art therapy facilitates access to authentic emotions, encourages exploration of these feelings, and aids in reconstructing meaning, thereby supporting more effective coping with traumatic experiences (Reed, 2020).

The utilization of art in nursing offers significant benefits for both patients and healthcare professionals. Considering the high stress levels and intense emotional demands inherent in the nursing profession, art therapy is regarded as a promising intervention to support nurses' psychological well-being (Ağaç, 2025). Creative art therapies hold potential as interventions for preventing burnout and enhancing resilience among healthcare professionals (Reed, 2020). Nurses play a critical role in integrating creative art practices into care processes through the strong relational bonds they establish with patients. Research conducted in eldercare settings indicates that art therapy reduces feelings of loneliness and serves as a complementary approach that supports the psychological well-being of older adults (Antonio, 2025).

10. Painting and Visual Arts

Painting and visual arts can play a significant role in the expression and management of pain, trauma, and emotional distress within the field of nursing. These art forms are utilized as non-pharmacological therapeutic interventions, assisting individuals in expressing their inner emotions, alleviating negative affect, and enhancing self-awareness and emotional regulation skills. Art therapy through painting has demonstrated notable improvements in reducing anxiety, depression, and mood fluctuations among students with mental health challenges. Through artistic creation, individuals are able to identify and release their emotions (Xu, 2025). For older adults, home-based art therapy techniques including drawing, mandalas, painting, and collage can support mental well-being and facilitate emotional expression (Albañil-Delgado, 2020).

Visual arts can be beneficial for patients experiencing chronic pain. Art therapy has demonstrated positive effects on pain perception, mood, stress, and quality of life, functioning as an effective distraction strategy. For individuals with persistent pain, maintaining a visual arts journal has shown potential benefits in expressing and managing their pain experiences, with colors and written expressions employed to represent emotions and ideas (Lou, 2022). Programs integrating creative arts within healthcare contexts have contributed to the recovery of young women exposed to social adversity and trauma. These initiatives have facilitated healing not only by promoting social inclusion and creating a "safe" environment but also through the direct therapeutic benefits inherent in the artistic processes themselves (Brooks, 2020).

Calming Paintings and Visual Arts

The use of visual arts in hospital settings can positively influence patients' psychological well-being (Foster, 2025). In particular, calming or nature-themed artworks have been shown to reduce anxiety and depression (Nanda, 2011), lower heart rate, improve mental health outcomes, and serve as effective attentional distractions (Foster, 2025). Patients generally prefer landscapes and natural scenes, which foster a sense of calm, whereas abstract art may provoke anxiety in some individuals (Nanda, 2011). Additionally, visual artworks can contribute to creating a safe environment, support patients' sense of identity, and enhance overall patient satisfaction (Nielsen, 2017).

Colors, Light, and Environmental Design

Environmental design factors including visual arts, colors, lighting, and overall spatial arrangements are critically important for psychological well-being in healthcare settings. Positive environmental modifications can beneficially influence health outcomes. Specific elements such as natural ventilation, daylight, and biophilic design features (e.g., plants and natural landscapes) have been shown to enhance mental health, bolster resilience, and accelerate recovery (Chowdhury, 2025). Visual arts and sensory components contribute to patients feeling welcomed and less stressed. Architectural design is particularly significant in mental health care environments.

11. Supporting Emotional Expression through Art-Making

Art-based interventions and creative expression function as coping mechanisms that promote emotional healing, reduce stress, and enhance psychological well-being. Such activities can support emotional expression, self-awareness, and social connectedness (Oruç, 2025). Patients participating in artistic activities have reported increased self-esteem, decreased feelings of isolation, and enhanced opportunities for emotional expression (Skali, 2025).

Environmental art design can provide a channel for patients to release emotions and divert attention from negative affective states such as anxiety and depression (Zhang, 2025). Structured creative interventions have been shown to improve both emotional expression and overall psychological well-being (Oruç, 2025). In pediatric settings, visual art activities can enhance the well-being of children and their families while also facilitating communication processes (Ullán, 2021).

12. Music and Sound Therapy

Music therapy has demonstrated a range of positive physiological and psychological effects on anxiety, depression, and sleep disturbances. It is particularly noteworthy as a non-pharmacological intervention. Evidence indicates that music therapy can significantly reduce anxiety levels (Huang, 2020; Ba, 2024; Zhang, 2023; Zhou, 2025). Specifically, it has been shown to alleviate anxiety in adults with chronic obstructive pulmonary disease (COPD) and in patients undergoing hemodialysis (Huang, 2020; Ba, 2024). Among adolescents with anxiety disorders, piano-based music therapy has produced substantial improvements in anxiety symptoms, with effects observed to persist even one year post-intervention (Zhang, 2025). Music therapy alleviates anxiety by modulating mood through perceptual pathways. It has been found to be significantly more effective than control conditions in reducing depressive symptoms (Ba, 2024; Zhang, 2023; Zhou, 2025). Decreases in depression scores have been observed in patients undergoing hemodialysis as well as in individuals with mild COVID-19 (Ba, 2024; Zhang, 2023). Among individuals with post-traumatic stress disorder (PTSD), music relaxation interventions have been associated with significant reductions in depression levels (Blanaru, 2012). Piano-based music therapy has also improved depressive symptoms in adolescents with anxiety disorders (Zhang, 2025). Music can mitigate depressive symptoms by reducing sympathetic nervous system activity and serving as a distraction. Furthermore, music therapy significantly enhances subjective sleep quality.

Music therapy has been shown to improve sleep quality in patients with chronic obstructive pulmonary disease (COPD), individuals with mild COVID-19, and adolescents with depression (Huang, 2020; Ba, 2024; Zhang, 2023; Zhou, 2025). Among individuals with post-traumatic stress disorder (PTSD), music relaxation has led to significant improvements in both objective and subjective sleep efficiency (Blanaru, 2012). Music can exert beneficial effects on sleep by promoting muscle relaxation and facilitating mental disengagement from intrusive thoughts. The effects of music therapy on sleep are largely mediated by its anxiolytic properties and mood-regulating capacity. Additionally, music

therapy has been associated with significant improvements in both systolic and diastolic blood pressure (Huang, 2020). By reducing sympathetic nervous system activity, music can lower blood pressure, heart rate, and respiratory rate.

The Healing Effects of Natural Sounds (Rain, Flowing Water, Birdsong)

Natural soundscapes particularly birdsong, flowing water, and wind play a significant role in regulating heart rate variability, reducing arousal, and enhancing stress adaptation. Auditory stimuli derived from nature and culture, such as flowing water and classical music, when combined with specific visual features, can promote positive moods, regulate mood disorders, and enhance psychological well-being (Weng, 2024). In a study conducted on postoperative patients, music incorporating natural sounds (water and birdsong) was found to be effective in reducing pain and anxiety levels, although its effect was somewhat less pronounced compared to aromatherapy (Amini, 2018).

The Use of Slow-Tempo Music in Pain Reduction

Music can serve as a non-pharmacological approach to pain management (Naderi, 2014). Slow-tempo, relaxing music (60–80 beats per minute) in particular may exert significant effects on pain, stress, and anxiety in critically ill patients (Widiastuti, 2023). Listening to music has been shown to significantly reduce pain and anxiety in burn patients (Naderi, 2014). Furthermore, music has demonstrated efficacy in managing pain and anxiety during uncomfortable procedures, such as nasal bone fracture reduction (Ortega, 2019). In patients undergoing bone marrow aspiration and biopsy, music has also been found to reduce pain and anxiety levels while enhancing overall comfort (Şahan, 2024). Music interventions have demonstrated statistically significant effects in reducing pain intensity, pain-related emotional distress, and vital signs, including heart rate, blood pressure, and respiratory rate (Lee, 2016). However, in a study involving older adults receiving mechanical ventilation, slow-tempo music interventions did not yield statistically significant reductions in delirium duration, pain, or anxiety symptoms (Khan, 2025).

Music therapy and breathing exercises can exert beneficial effects in reducing patients' anxiety and pain during medical procedures such as angiography. In patients undergoing coronary angiography, both the breathing exercise and music-listening groups demonstrated reductions in anxiety scores and significant decreases in pain scores compared to the control group (Gauthier, 2024). Mindfulness-based interventions focused on music listening can also reduce pain intensity and anxiety in patients experiencing chronic pain and anxiety. Slow-breathing techniques, either in conjunction with biofeedback or independently, can be effective in regulating physiological arousal in contexts such as music performance anxiety and may be particularly beneficial for musicians with

elevated anxiety levels. In intensive care patients, music selected by the patient has been shown to reduce both anxiety and exposure to sedative medications (Chlan, 2013).

Dance/Movement Therapy (DMT)

Dance/Movement Therapy (DMT) is an approach that enhances bodily awareness and offers potential benefits for patients with movement limitations (Koch, 2015; Verreault, 2017). DMT can facilitate individuals' understanding and perception of their own bodies. For instance, in a feasibility study with young adults on the autism spectrum, a DMT intervention utilizing mirror-based techniques was observed to improve body awareness (Koch, 2015). Similarly, in a study involving traumatized women refugees, sessions focused on bodily movement, mirror techniques, and body-awareness exercises provided opportunities to enhance body awareness (Verreault, 2017).

In these therapies, an integrated methodology encompassing movement, emotion, cognition, and social dimensions is employed, with nonverbal therapeutic approaches such as awareness techniques, bodily movement, and behavioral interventions emerging as common factors. Existing literature does not provide detailed, direct evidence for patient populations with specific movement limitations. However, the inherently movement- and body-focused nature of DMT suggests potential benefits for such cases. Notably, it has been shown to enhance social skills, self–other differentiation, and overall well-being in individuals on the autism spectrum (Koch, 2015). Furthermore, it has been suggested that DMT can complement the verbal limitations of cognitive-behavioral therapy, thereby supporting nonverbal forms of expression and participation in individuals with restricted mobility.

Breathing Exercises and Gentle Body Movements

Interventions incorporating breathing exercises and gentle physical movements can effectively enhance both the physical and mental health of patients and caregivers (Milbury, 2017; Gupta, 2025). Mind–body practices such as yoga have been shown to improve symptom management and quality of life in cancer patients and their caregivers. These programs typically include breathing exercises, gentle movements, and guided meditations. Yoga programs designed for patients with high-grade gliomas and their family caregivers have demonstrated improvements in cancer-related symptoms, sleep disturbances, and mental quality of life (Milbury, 2017). Similarly, a dual-level Tibetan yoga program for lung cancer patients and their caregivers has shown promising preliminary outcomes regarding quality-of-life measures (Milbury, 2015). Studies involving breast cancer patients have demonstrated that yoga improves quality of life, physical functioning, and fatigue during radiotherapy.

Additionally, yoga including pranayama, gentle Hatha and restorative asanas, and meditation has been found to be an effective intervention for enhancing sleep quality in cancer patients (Mustian, 2013). The integration of yoga for patients, caregivers, and healthcare staff in intensive care units (ICUs) can support physical rehabilitation, mental resilience, and emotional balance. For patients, breathing exercises and gentle assisted movements may reduce pain, enhance relaxation, and support respiratory function (Gupta, 2025). Mind-body therapies incorporating video-assisted instruction and breathing exercises can significantly reduce anxiety levels and improve physiological stability in patients undergoing upper gastrointestinal endoscopy. In caregivers of individuals with dementia, self-administered gentle yoga and yogic breathing exercises can alleviate caregiver burden and improve stress-related biomarkers (Balasubramanian, 2023). Therapeutic Chinese practices such as Qigong and Tai Chi promote health and vitality through gentle exercises integrating breath, body, mind, and sound (McCaffrey, 2003).

Mindfulness-Based Dance/Movement Therapy (MBDMT) has been demonstrated as an effective and promising therapeutic approach for reducing pain intensity and depression scores in patients with chronic headaches. This therapy identifies nine therapeutic mechanisms, including a safe therapeutic environment, mindfulness skills, body awareness, relaxation, self-regulation, and acceptance (Majore-Dūšele, 2021).

Dance-based mindfulness interventions have been associated with improvements in body awareness, emotional regulation, stress reduction, self-compassion, social connectedness, and overall well-being. Aerobic dance, particularly mindfulness-based aerobic dance, may reduce anxiety more rapidly and effectively in policewomen (Liu, 2025). Movement-based classes, such as Pilates, can enhance mindfulness, and these gains are directly correlated with other well-being metrics, including self-regulatory self-efficacy, perceived stress, and mood.

Dance/Movement Therapy (DMT) can serve as a rehabilitative tool for neurodegenerative disorders. Classical Indian dance forms, such as Odissi, have shown potential as a rehabilitation modality to support social, cognitive, and emotional development in populations with autism spectrum disorder (Dawn, 2024). Dance programs have demonstrated significant benefits not only for physical health—enhancing balance, strength, and flexibility in older women—but also for mental and emotional well-being, including reductions in depression, increased self-esteem, and improved emotional stability. Dance involves the psychotherapeutic use of movement to promote emotional, social, cognitive, and physical integration, aligning with neuroscientific principles that connect

physical activity, emotional regulation, and neuroplasticity. It has been suggested that dance holds therapeutic potential for enhancing neurological and cognitive functions, supporting mental health and emotional well-being, while also delivering physical health benefits such as improvements in cardiovascular fitness, muscle strength, flexibility, balance, and coordination.

13. Folklore and Ritual

Folklore and ritual can serve as foundational elements in creative therapies. These approaches enable individuals to connect with their cultural roots and to express themselves through traditional narratives and practices. Folkloric stories, myths, and customs provide a rich symbolic language that helps individuals ascribe meaning to their experiences. Such narratives allow personal challenges to be situated within broader cultural or universal contexts, fostering a sense of connectedness and reducing feelings of isolation. Rituals offer structured and meaningful methods for coping with specific emotional or psychological states. For example, mourning rituals can provide a structured framework for individuals experiencing loss to express and process their emotions. Such rituals facilitate the externalization of internal experiences and foster a sense of connection with the community. When folklore and ritual are combined with creative forms of expression such as art, music, dance, or storytelling they become powerful tools for exploring and transforming one's inner world. This can be particularly beneficial for individuals who may be less receptive to conventional talk therapies. In nursing practice, understanding patients' cultural backgrounds and belief systems allows for the use of therapeutic arts in a culturally sensitive manner, thereby supporting more personalized and effective care. For instance, respecting a patient's cultural rituals and integrating them into the healing process can enhance psychological well-being and improve adherence to treatment. Traditional healing practices and cultural beliefs may also shape patients' perceptions of healthcare and influence treatment preferences. Therefore, it is essential for nurses to recognize, understand, and integrate these cultural elements into care (Pepa, 2000; Pinkoane, 2005).

14. Masks, Puppets, and Therapeutic Role-Playing

In the field of nursing, masks, puppets, and theatrical techniques can be utilized to create community-based performances. These methods serve as effective strategies for health education and health promotion. For example, in a nursing graduation course, puppet theatre was employed as a teaching strategy to improve children's oral health. Nurses and nursing technicians have also formed a puppet theatre group called "Art in Health" to explore novel approaches to care

by combining scientific knowledge with humanizing elements such as joy and playfulness. This experience encompassed four stages: sensitivity, concretization, integration, and presentation. Dramatization and puppet theatre have been identified as highly effective instructional strategies in first aid and accident prevention courses for elementary school children. These approaches can be integrated into nursing practice to enhance health awareness within communities and to convey educational messages in a more engaging and memorable manner (Rampaso, 2011; Sousa, 2012; Andraus, 2005).

15. Animal-Assisted Therapeutic Approaches

Animal-Assisted Therapeutic Approaches (AATA) are therapeutic interventions involving animals aimed at enhancing individual well-being and are considered complementary to conventional medicine (Pandey, 2024; Himanshu, 2023). These approaches have been reported to improve cognitive functioning, attachment, character development, and learning processes. AATA is employed as a non-pharmacological intervention for individuals with Alzheimer's disease. Interaction with animals has been reported to reduce behavioral disturbances, stress, and mood disorders, stimulate cognitive functioning, and provide psychosocial support. A study conducted with patients with mild to moderate Alzheimer's disease demonstrated that animal-assisted therapy led to improvements in both cognitive function and mood (Santaniello, 2020).

Furthermore, AATA has been reported to exert positive effects on depression, as well as psychiatric and neurological disorders, demonstrating stress- and anxiety-reducing effects while supporting emotional activation (Pandey, 2024; Himanshu, 2023). In children with autism spectrum disorder, interaction with animals in naturalistic settings has been shown to reduce social anxiety and stereotypical behaviors, enhance joint attention, eye contact, emotion recognition and expression skills, and increase social interaction initiatives (Dnistrianska, 2025).

In children and adolescents with special educational needs, animal-assisted programs have been reported to contribute to physical development, with dogs and horses frequently employed for conditions such as autism, cerebral palsy, and attention-deficit/hyperactivity disorder (Kovács, 2024). From a general well-being perspective, therapies involving cats have been shown to reduce loneliness and stress, dog-assisted interventions positively impact emotional states and overall well-being, horse-assisted interventions benefit individuals with cognitive and motor impairments, and dolphin-assisted therapy has shown promise for conditions such as autism and cerebral palsy (Szewczyk, 2023).

16. Literature and Storytelling (Narrative Nursing)

Narrative nursing is an emerging approach aligned with humanistic care that has been shown to effectively improve health outcomes for both patients and nurses. This approach can influence nurses' cognition, self-efficacy, and social support. Factors affecting the implementation of narrative nursing include social support, attitudes, knowledge, and the professional development environment of nurses. Among nurses in China, the practice of narrative nursing is at a moderate level and may be influenced by both personal and environmental factors. Nurse managers should prioritize specialized training and foster supportive environments to enhance the practice of narrative nursing (Zhang, 2024).

Narrative therapy can be effective in alleviating occupational stress among nurses and promoting positive health behaviors. ADDIE-based narrative nursing education programs may enhance nurses' narrative nursing competencies and the quality of humanistic care, thereby reducing work-related stress and encouraging healthy behaviors (Li, 2023). A narrative nursing intervention may produce positive outcomes for patients undergoing laparoscopic myomectomy, including the reduction of negative emotions, enhancement of nursing satisfaction, and acceleration of postoperative recovery. This intervention can alleviate postoperative anxiety and depression while increasing patient satisfaction (Long, 2025). Narrative research is increasingly gaining prominence in nursing and related healthcare literature and may contribute to the development of clinical knowledge. Nurses' narratives can illustrate how they apply virtues, professional judgment, and practical wisdom in addition to scientific knowledge and experience. Digital storytelling workshops can provide positive experiences for nurses by emphasizing themes of healing, human connection, and nursing pedagogy.

Storytelling

Sharing personal stories and transforming them into a narrative form serves as a mechanism for making experiences meaningful and manageable. This process can function as a tool for coping with challenging experiences and may facilitate reconciliation through the rewriting of personal narratives. Studies among medical students have demonstrated that sharing personal experiences, as well as stories of illness and suffering, can have a therapeutic function (Valestrand, 2024).

Poetry

Artistic approaches such as digital storytelling and "found poetry" can be employed to understand the experiences of patients living with advanced-stage cancer and to express their emotional impact. These creative interventions have

the potential to enhance emotional expression and promote psychological well-being (Sitter, 2025).

Narrative Identity

By integrating life history, autobiographical memories, and self-concept, narrative identity constructs a coherent account of an individual's past. These narratives become self-defining memories that provide continuity and purpose throughout the life course. A healthy narrative identity combines the specificity of memories with adaptive meaning-making, fostering insight and well-being (Singer, 2013).

Therapeutic Approaches

Narrative therapy enables individuals to "rewrite" their life stories by focusing on positive interpretations, which can be particularly helpful in fostering a constructive sense of identity in the treatment of depression (Seo, 2015). In medical education, having students document and share patients' life histories encourages them to perceive patients not merely as diagnostic entities but as holistic human beings (Garrison, 2011).

Identity Development and Recovery

Life story narration serves as a mechanism through which experiences are given meaning and the content of identity is constructed. In particular, among disadvantaged populations, sharing life stories can emerge as a central component of identity development and can influence healthcare experiences. The life narratives of individuals diagnosed with mental illness illustrate how narrative identity is shaped while simultaneously serving as a resource for personal recovery (Thomsen, 2023).

17. Drama and Role-Playing Techniques

In nursing education, drama and role-playing techniques are recognized as effective pedagogical approaches for enhancing students' professional knowledge and skills, providing significant contributions to empathy, communication, self-efficacy, and clinical competencies. Role-playing is identified as a powerful method for improving nursing students' clinical skills, self-efficacy, communication abilities, and levels of empathy (Maghsoodi, 2025). In mental health simulations, role-playing with standardized patients has been reported to enhance knowledge, confidence, attitudes, and competencies while reducing anxiety (Zhang, 2025). The use of role-playing methods in cardiopulmonary resuscitation (CPR) training has been shown to enhance students' self-efficacy more effectively than traditional approaches (Khaledi, 2024). This approach also strengthens communication skills and empathy; experiencing the patient role has been reported to increase levels of empathy and

altruism (Basit, 2023), while role-playing in geriatric settings has been shown to improve communication, constructive thinking, emotional awareness, and the sense of empathy. Role-playing emerges as a method that enhances student performance and satisfaction in courses on patient education principles (Ahmady, 2021) and also facilitates the integration of theoretical knowledge with practice (Benko, 2023). Drama techniques are employed to enhance nursing students' interpersonal skills, empathy, emotional intelligence, and communication, making learning more engaging and enjoyable while fostering self-confidence, creativity, responsibility, and collaboration. Additionally, drama strengthens professional training by contributing to the development of communication-based skills such as empathy, awareness, and socialization (Dertli, 2024). Overall, drama and role-playing techniques improve nursing students' professional competencies, communication abilities, and levels of empathy, better preparing them for clinical practice. Research is recommended on standardized frameworks and interdisciplinary collaborations to optimize the effectiveness of these methods.

18. Mindfulness

In nursing, mindfulness is an important approach employed to enhance the mental health, professional development, and quality of patient care for both nursing students and practitioners. This method aims to cultivate individuals' abilities to focus on the present moment, observe without judgment, and regulate their emotions (Lee, 2025; Salem, 2025). Given the challenges inherent in nursing education, students often experience high levels of stress, anxiety, and depression; mindfulness-based interventions have been shown to reduce perceived stress, increase mindfulness levels, and produce significant improvements in students' anxiety, stress, and depressive symptoms. Programs such as Reflective Mindfulness and Emotional Regulation Training (RMERT) have been shown to enhance students' self-awareness, understanding, and emotional regulation skills. Mindfulness-based courses, in turn, have been reported to increase positive feelings of accomplishment, reappraisal abilities, and empathy while reducing negative emotions (Salem, 2025; Lee, 2025). Additionally, mindfulness training supports nursing students in developing skills for supportive communication, emotional intelligence, and humanistic care, thereby contributing to strengthened empathy and patient-centered care. Mindfulness has also demonstrated positive effects on academic performance and clinical competence, with the dimensions of "mindful action" and "non-judgment" being directly associated with academic success. Furthermore, it helps students build resilience, cope with stressful working conditions, and cultivate a

more compassionate attitude toward themselves (Sköld, 2025). The integration of mindfulness-based interventions into nursing education has been shown to produce significant improvements in student well-being and educational outcomes, with programs such as weekly 45-minute face-to-face group sessions potentially enhancing participation. However, while the long-term benefits of mindfulness training are acknowledged, further research is needed to strengthen the generalizability of the findings and to determine the most effective duration and methods of implementation (Sköld, 2025).

19. Mandala

Mandala, in the field of nursing, refers to the activity of coloring or creating circular designs with intricate patterns, employed to support individuals' mental and emotional well-being and regarded as a form of art therapy (Alves, 2024). This approach provides various psychological and physical benefits for both nursing students and patients. Studies conducted with nursing students have shown that mindfulness-based mandala activities are effective in reducing anxiety levels and enhancing psychological well-being; specifically, a three-session intervention for students returning to clinical practice post-COVID-19 demonstrated a significant reduction in anxiety (Ozturk, 2022).

Mandala coloring therapy has also been shown to reduce academic stress levels and contribute to stress management, particularly among first-year nursing students (Apriyana, 2020). In clinical settings, mandala is regarded as an effective intervention for alleviating anxiety associated with chronic illness; a pilot study conducted in hemodialysis and psychiatric day hospital settings demonstrated that mandala coloring significantly reduced patients' anxiety levels (Alves, 2024). Among cancer patients, it has been reported as a low-cost, non-pharmacological nursing intervention that can decrease the severity of chemotherapy-induced acute nausea and enhance comfort (Çelik, 2024). Additionally, mandala art therapy for mothers of children with special needs has been shown to improve comfort and resilience, suggesting that nurses could beneficially implement such programs in collaboration with special education institutions (Özsavran, 2023). In the postpartum period, mandala activities combined with technology-based breastfeeding programs have been shown to enhance mothers' breastfeeding self-efficacy and mother-infant bonding (Ozturk, 2023). In nursing practice, mandalas have also been utilized to represent specialized nursing terminology for individuals with chronic kidney disease, suggesting a potential role in integrating professional nursing language (Menezes, 2020). Mandala coloring therapy has been reported as potentially effective in alleviating cognitive impairments and enhancing cognitive function among

psychiatric patients (Li, 2025). Overall, mandala activities offer valuable complementary interventions that support stress and anxiety management among nursing students in educational settings while enhancing patient comfort, resilience, and overall well-being in clinical practice. It is recommended that nurses integrate this art therapy approach into care processes (Özsavran, 2023; Çelik, 2024).

20. Meditative Art

In the field of nursing, the concept of Meditative Art is typically associated with practices such as mindfulness, art-making, or expressive art therapy, and is employed both to support the well-being of nurses and to enhance the quality of care delivered to patients. Art-making and expressive art therapy are regarded as significant approaches in nursing care for promoting person-centeredness, assessing health outcomes, and supporting healthcare professionals' well-being (Vaartio-Rajalin, 2020). Specifically, in the field of psychiatry, group art therapy has been reported to reduce the severity of psychopathology, enhance functioning, and improve quality of life in patients with schizophrenia when applied alongside pharmacological treatment. These findings may serve as a guide for psychiatric nurses in implementing art therapy interventions (Utas-Akhan, 2023).

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Chapter 5

Hematological Changes and Hemostatic Disorders: Current Approaches to Liver Diseases

Hatice TERZİ [1]

1. Introduction

The liver is a vital organ with close, bidirectional relationships with the hematopoietic system, in addition to its metabolic and detoxification functions. As the primary center of hematopoiesis during embryonic development, the liver plays a critical role in maintaining hematological homeostasis in adulthood, including regulating iron metabolism, thrombopoietin synthesis, production of coagulation and fibrinolysis proteins, synthesis of complement system components, and immune response regulation (1-4). Therefore, acute or chronic liver diseases affect not only hepatic functions but also erythrocyte, leukocyte, and platelet counts and hemostatic mechanisms to varying degrees, leading to various hematological changes (5).

Hematological disorders seen in liver diseases exhibit a wide clinical spectrum depending on the etiology, stage, and complications of the disease. Anemia, thrombocytopenia, and leukopenia are the most common hematological findings. They can develop as a result of the combined effect of numerous mechanisms, including hypersplenism due to portal hypertension, chronic inflammation, nutritional deficiencies, gastrointestinal bleeding, bone marrow suppression, viral infections, and drug toxicities. Thrombocytopenia, in particular, is one of the most frequently observed hematological abnormalities in patients with cirrhosis and is a significant issue directly affecting clinical decision-making before interventional procedures.

In recent years, understanding of hemostatic changes associated with liver diseases has changed significantly. While cirrhosis was once considered a clinical picture with a prominent bleeding tendency, the concept of "rebalanced hemostasis" is now accepted because procoagulant and anticoagulant factors change simultaneously (1, 3, 6). This approach shows that bleeding and thromboembolic event risks should be assessed together in patients with liver disease; it also shows that venous thromboembolism, especially portal vein

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thrombosis, is more common than previously thought (6, 7). Furthermore, it has been understood that conventional coagulation tests such as prothrombin time (PT) and international normalized ratio (INR) do not reliably reflect the risk of bleeding alone, and more comprehensive assessment methods such as viscoelastic tests (TEG and ROTEM) have begun to gain increasing importance in clinical practice (7).

Accurate assessment of hematological changes in liver diseases is crucial not only for diagnosis but also for treatment planning, preparation for interventional procedures, determining transfusion strategies, and managing thrombosis prophylaxis. Today, the widespread adoption of Patient Blood Management (PBM) principles, which aim to reduce unnecessary transfusions and use blood products more rationally, requires close collaboration between hematology and hepatology specialists in the multidisciplinary management of patients with liver disease (4, 7).

This section will comprehensively address hematological changes in liver diseases, including pathophysiological mechanisms; erythrocyte, leukocyte, and platelet abnormalities; hemostatic changes; thrombotic and hemorrhagic complications; and current diagnostic and treatment approaches. This review will also cover recent concepts that have gained prominence in the literature, such as "rebalanced hemostasis," thrombopoietin receptor agonists, viscoelastic testing, and patient blood management, to provide a holistic perspective.

1.1. The Relationship Between the Liver and the Hematopoietic System

The relationship between the liver and the hematopoietic system is a dynamic, bidirectional interaction that begins during embryonic development and continues throughout life. Starting in the second trimester of fetal life, the liver serves as the primary hematopoietic organ, facilitating the proliferation and differentiation of the erythroid, myeloid, and megakaryocytic cell lineages until bone marrow hematopoiesis is fully established. (8, 9). Although hematopoietic activity is largely transferred to the bone marrow after birth, the liver continues to play a central role in maintaining hematological homeostasis. Hepatocytes synthesize thrombopoietin, the primary regulator of megakaryocyte proliferation and platelet production, while liver-derived hepcidin supports erythropoiesis by regulating systemic iron metabolism through control of iron absorption and release from macrophages (10, 11). In addition, the liver is the primary organ where most of the components of the anticoagulant and fibrinolytic systems—such as antithrombin, protein C, protein S, and plasminogen—are synthesized, along with coagulation factors such as fibrinogen, prothrombin, and factors V, VII, IX, X, and XI (1, 12). In addition, it makes a significant contribution to

maintaining hematological and immunological balance through functions such as the synthesis of complement proteins, the regulation of the acute-phase response, and—via Kupffer cells, an important component of the reticuloendothelial system—the removal of aging red blood cells, iron recycling, and the clearance of microorganisms from the circulation (1, 9, 13). As a result, structural and functional abnormalities in acute or chronic liver diseases affect not only metabolic processes but also erythropoiesis, thrombopoiesis, leukocyte function, the immune response, and hemostatic mechanisms, leading to a wide range of hematological changes (2).

1.2. The Role of the Liver in Hematological Homeostasis

The liver is a metabolic and immunological organ that plays a central role in maintaining hematological homeostasis. Although adult hematopoiesis occurs primarily in the bone marrow, the liver plays essential roles in erythropoiesis, thrombopoiesis, iron metabolism, and hemostasis regulation (7, 9). Hepatocytes synthesize thrombopoietin (TPO), the primary regulator of megakaryocyte development and platelet production, and it also contributes to maintaining hematopoietic stem cells (10, 14). The liver also synthesizes hepcidin, the primary regulator of systemic iron metabolism. Hepcidin controls intestinal iron absorption and iron release from macrophages by inhibiting ferroportin, maintaining the iron balance necessary for erythropoiesis (15, 16).

The liver is also the primary site of fibrinogen, prothrombin, and many coagulation factors, as well as natural anticoagulants such as antithrombin, protein C, and protein S. Therefore, impaired liver function affects both coagulation and anticoagulation mechanisms simultaneously, leading to a complex hemostatic change now defined as “rebalanced hemostasis (7, 17). In addition, the liver plays a significant role in maintaining hematological and immunological balance by removing aging red blood cells via Kupffer cells, recycling iron, synthesizing complement, and regulating the immune response (18). For this reason, structural and functional abnormalities in liver disease constitute the fundamental pathophysiological mechanisms underlying anemia, thrombocytopenia, leukopenia, and hemostatic disorders (2, 7).

1.3. Epidemiology

Hematologic disorders associated with liver disease are a significant cause of morbidity and mortality worldwide. Along with the increase in the global prevalence of chronic liver disease and cirrhosis, the incidence of anemia, thrombocytopenia, leukopenia, and hemostatic disorders is also steadily rising. (2, 19). Thrombocytopenia is the most common hematologic abnormality in

patients with cirrhosis, occurring in approximately 70–80% of patients, while anemia occurs in 60–75%; leukopenia, by contrast, develops in patients with more advanced disease and is often associated with hypersplenism (20). Today, the increasing prevalence of chronic viral hepatitis, as well as metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-related liver disease, and hepatocellular carcinoma, has further heightened the clinical significance of hematologic complications in this patient population (21). For this reason, the early detection and appropriate management of hematological changes in liver diseases are critical not only for improving patients' quality of life but also for reducing complications related to bleeding, thrombosis, and interventional procedures (2, 7).

2. Hematological Functions of the Liver

2.1. Embryonic hematopoiesis

Embryonic hematopoiesis is a dynamic process that occurs in successive anatomical regions and supports the development of hematopoietic stem cells and the formation of mature blood cells. In the human embryo, hematopoiesis begins in the yolk sac (vitelline sac) with primitive erythropoiesis around the third week of pregnancy. Subsequently, definitive hematopoietic stem cells that arise in the aorto-gonadal-mesonephric (AGM) region enter the circulation and migrate to the fetal liver. Beginning in the 6th–7th weeks of pregnancy, the fetal liver becomes the primary hematopoietic organ where the proliferation and differentiation of the erythroid, myeloid, and megakaryocytic cell lineages occur throughout the second trimester. During this period, the microenvironment created by hepatocytes, stromal cells, and sinusoidal endothelial cells supports hematopoietic stem cell proliferation and differentiation through stem cell factor (SCF), thrombopoietin (TPO), erythropoietin (EPO), and various cytokines. In the third trimester of pregnancy, hematopoietic activity gradually shifts to the bone marrow, and after birth, the bone marrow becomes the primary site of physiological hematopoiesis. Although the liver largely loses its hematopoietic function in adulthood, it continues to play a critical role in maintaining hematological homeostasis by producing thrombopoietin, regulating iron metabolism, and synthesizing hematopoietic growth factors (9, 22).

2.2. Iron metabolism

Although the liver is not the primary site of hematopoietic cell production in adulthood, it performs critical metabolic and endocrine functions that regulate hematological homeostasis. Foremost among these is the control of iron metabolism. Hepcidin, synthesized in hepatocytes, is the primary regulatory

hormone of systemic iron metabolism. Hepcidin binds to the ferroportin receptor on enterocytes and macrophages of the reticuloendothelial system, causing its internalization and degradation and limiting intestinal iron absorption and iron release from macrophages into the circulation. During inflammation, interleukin-6 (IL-6) increases hepcidin synthesis, while hypoxia, iron deficiency, and increased erythropoietic activity suppress hepcidin expression. While this mechanism plays a key role in maintaining the iron balance needed for erythropoiesis, abnormalities in hepcidin synthesis in chronic liver diseases contribute to clinical conditions such as functional iron deficiency or iron overload (15, 16, 23).

The liver is also an important site of hematopoietic growth factor synthesis. Thrombopoietin (TPO), secreted by hepatocytes, is the primary regulator of megakaryocyte proliferation, maturation, and platelet production. Recent studies have shown that TPO not only regulates platelet production but also plays a significant role in maintaining the self-renewal capacity of hematopoietic stem cells. In contrast, erythropoietin (EPO)—the primary regulator of erythropoiesis—is synthesized mainly in renal peritubular fibroblasts during adulthood; the liver is a major site of EPO production, particularly during fetal life, and contributes only to a limited extent in adulthood. Nevertheless, the liver is indispensable for maintaining normal erythrocyte production because its metabolic functions support the regulation of iron metabolism, TPO synthesis, and erythropoiesis (10, 14, 24).

Another key component of the liver's hematological functions is regulating the hemostatic system. Hepatocytes synthesize the majority of coagulation factors—including fibrinogen, prothrombin, and factors V, VII, IX, X, XI, and XII—and are also the primary site of production for antithrombin, protein C, and protein S, which are key components of the natural anticoagulant system, as well as for proteins of the fibrinolytic system. In addition, the liver synthesizes many complement components—including C2, C3, C4, C5, and others—which regulate the innate immune response, opsonization, and inflammation. Therefore, impaired liver function leads not only to decreased coagulation factors but also to changes in anticoagulant mechanisms and complement activity, resulting in multifaceted hematological consequences such as a tendency to bleed, increased risk of thrombosis, and susceptibility to infections. Today, clinicians evaluate this condition within the framework of "rebalanced hemostasis" in patients with liver disease. (7, 17, 25).

3. Pathophysiology

The hematological changes that develop in liver diseases are not attributable to a single mechanism but result from numerous interrelated pathophysiological processes, such as portal hypertension, hypersplenism, decreased thrombopoietin synthesis, bone marrow suppression, chronic inflammation, nutritional deficiencies, alcohol use, viral infections, and drug toxicity. (2, 7). Although these mechanisms vary by disease etiology, cirrhosis stage, and comorbidities, the most common hematological findings are anemia, thrombocytopenia, leukopenia, and hemostatic disorders. In particular, as portal hypertension develops, congestion and sequestration in the spleen increase; consequently, hypersplenism develops, accelerating the peripheral destruction of red blood cells, white blood cells, and platelets. While hypersplenism is one of the most important causes of thrombocytopenia in chronic liver diseases, decreased hepatic thrombopoietin production and suppression of platelet production in the bone marrow also play significant roles in thrombocytopenia (7, 10, 20).

In chronic liver diseases, ongoing inflammation is a key mechanism underlying hematologic disorders. Elevated levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and other proinflammatory cytokines stimulate hepcidin synthesis, leading to iron retention in the reticuloendothelial system and functional iron deficiency, which can result in chronic disease anemia (15, 16). In addition, malnutrition—which is common in patients with advanced-stage liver disease—along with deficiencies in folate, vitamin B12, iron, and other micronutrients, adversely affects erythropoiesis, while chronic alcohol consumption can directly cause bone marrow toxicity, leading to suppression of cells in the erythroid, myeloid, and megakaryocytic lineages. Alcohol is also associated with macrocytosis, sideroblastic changes, and platelet dysfunction. (7, 9).

Certain medications used to treat chronic infections and liver diseases—particularly viral hepatitis—also contribute to the development of hematological abnormalities. Hepatitis B and, in particular, the hepatitis C virus are associated with various hematologic complications, such as immune-mediated thrombocytopenia, bone marrow suppression, and cryoglobulinemia. In addition, interferons, ribavirin, immunosuppressive agents, chemotherapeutic agents, and certain antiviral drugs can cause dose-dependent cytopenias (7). In conclusion, the hematological abnormalities observed in liver diseases reflect a complex, multifactorial pathophysiological process in which not only the loss of liver function but also changes in the portal circulation, immunological mechanisms, inflammation, nutritional deficiencies, and treatment-related effects all play a role (20).

4. Changes in Red Blood Cells

Anemia is one of the most common hematological complications of chronic liver disease and is observed in approximately 60–75% of patients with cirrhosis. Numerous mechanisms play a role in its development, including acute or chronic gastrointestinal bleeding, hypersplenism due to portal hypertension, chronic inflammation, nutritional deficiencies, bone marrow suppression, hemolysis, and drug-induced toxicity (2, 7). Anemia is often multifactorial, and multiple mechanisms may coexist in the same patient. Therefore, accurate anemia classification and identification of underlying causes are essential for planning an appropriate treatment strategy (26).

Iron-deficiency anemia develops from chronic gastrointestinal blood loss in chronic liver diseases, particularly esophageal and gastric variceal bleeding, portal hypertensive gastropathy, and gastric antral vascular ectasia (GAVE). In addition, chronic inflammation-driven increases in hepcidin synthesis contribute to functional iron deficiency and anemia of chronic disease. Malnutrition, which is common in patients with advanced liver disease, can lead to folate and vitamin B12 deficiencies, thereby disrupting megaloblastic erythropoiesis. In addition, chronic alcohol use plays a significant role in the development of macrocytosis by adversely affecting folate metabolism, in addition to causing direct bone marrow toxicity (15, 26).

Although less common in liver disease, hemolytic anemias are also clinically significant. Spur cell anemia (acanthocytic hemolytic anemia), which is seen particularly in advanced-stage decompensated cirrhosis, is a severe form of hemolysis resulting from changes in the lipid composition of the erythrocyte membrane and is considered an indicator of poor prognosis. Zieve syndrome, which is seen in alcohol-related liver disease, is a rare clinical condition characterized by hemolytic anemia, transient hyperlipidemia, and jaundice. In addition, macrocytosis is one of the laboratory findings frequently observed in liver diseases—even in the absence of anemia—due to mechanisms such as alcohol use, folate deficiency, and reticulocytosis. Therefore, when evaluating anemia in patients with chronic liver disease, the diagnostic approach should integrate red blood cell indices, peripheral smear, iron parameters, vitamin levels, and hemolysis markers (2, 7).

Changes in erythrocyte morphology in chronic liver diseases are laboratory findings that provide important clues for diagnostic evaluation. The morphological changes observed in the peripheral blood smear result from numerous pathophysiological mechanisms, including abnormalities in erythrocyte membrane lipid composition, oxidative stress, hypersplenism, nutritional deficiencies, and hemolysis (9). Particularly in advanced-stage

cirrhosis and alcohol-related liver disease, changes in the cholesterol-to-phospholipid ratio in the erythrocyte membrane reduce cell deformability, leading to characteristic erythrocyte shape abnormalities. Therefore, careful evaluation of the peripheral blood smear is important for recognizing hematologic complications associated with liver disease (2, 3).

One of the most common morphological changes in red blood cells observed in liver diseases is the formation of target cells. These cells develop because the red blood cell membrane surface area increases relative to its volume and are frequently observed, particularly in cholestatic liver diseases and cirrhosis. An acanthocyte, by contrast, is a red blood cell with irregular projections of varying lengths; it forms due to an increased cholesterol-to-phospholipid ratio in the membrane and is a key indicator of hemolytic anemia that develops in advanced stages of liver disease. A condition characterized by a predominance of acanthocytes is called spur cell anemia and is considered an indicator of poor prognosis due to severe hemolysis. In contrast, stomatocytes are cells in which the central pallor appears slit-like due to changes in erythrocyte membrane permeability and are observed particularly in liver diseases associated with chronic alcohol use. (2, 27, 28).

Howell–Jolly bodies may appear in the peripheral blood smear after decreased splenic function or splenectomy. These inclusions consist of DNA remnants from the erythrocyte nucleus and are normally removed from the circulation by a functional spleen. While marked hypersplenism in liver diseases generally prevents detection of Howell–Jolly bodies, their presence in the peripheral blood smear in patients who have undergone splenectomy or in cases with functional hyposplenism is an important finding indicating loss of spleen function (29). Evaluating these morphological changes alongside clinical and laboratory data significantly contributes to the differential diagnosis of hematological complications of liver disease and to determining their prognosis.

5. Changes in Leukocytes

Although leukopenia is less common than thrombocytopenia and anemia in chronic liver diseases, it is a clinically significant hematological disorder, particularly in cases of cirrhosis where portal hypertension and liver failure have progressed. The prevalence of leukopenia in patients with compensated cirrhosis is reported to be about 23%, and thrombocytopenia and leukopenia together constitute the two most common forms of dual cytopenia (2). A primary mechanism underlying leukopenia is leukocyte sequestration in the spleen due to splenomegaly and hypersplenism associated with portal hypertension. However, the direct myelotoxic effects of chronic alcohol use, viral infections, folate and

other micronutrient deficiencies, systemic inflammation, bone marrow suppression, and toxicity from interferon, immunosuppressive agents, or certain antiviral drugs may also contribute to decreased white blood cell count (30).

Although neutropenia is the most significant component of leukopenia in terms of infection risk, infection susceptibility in patients with cirrhosis cannot be explained solely by a decrease in absolute neutrophil count. In advanced liver disease, circulating neutrophils may have impaired chemotaxis, adhesion, phagocytosis, degranulation, reactive oxygen species production, and intracellular pathogen-killing capacity (31, 32). In addition, chronic inflammatory stimulation can cause neutrophil functional exhaustion, delayed apoptosis, and impaired pathogen response. Consequently, an effective antimicrobial response may be inadequate even in patients with normal or elevated white blood cell counts. While a drop in the absolute neutrophil count below 500/mm³ significantly increases the risk of serious bacterial and fungal infections, the risk of infection in cirrhosis also rises independently of neutrophil count (30, 31).

This clinical picture, which develops in cirrhosis, is currently defined as cirrhosis-associated immune dysfunction. This syndrome is a dynamic immune disorder characterized by the coexistence of systemic inflammatory activation and deficiencies in both innate and adaptive immune responses. Key components include reduced synthesis of complement and acute-phase proteins in the liver, impaired phagocytic capacity of Kupffer cells, decreased monocyte and macrophage function, changes in natural killer cell activity, inadequate T- and B-lymphocyte responses, and loss of intestinal barrier integrity (31, 32, 33).

Bacterial translocation, driven by portal hypertension, intestinal dysbiosis, and increased mucosal permeability, leads to persistent immune activation and, in later stages, immune paralysis, facilitating infection (33).

Bacterial infections occur in about one-fourth of patients with cirrhosis who are hospitalized for acute decompensation; spontaneous bacterial peritonitis, urinary tract infections, pneumonia, spontaneous bacteremia, and skin and soft tissue infections are the most common clinical presentations (33). Susceptibility to fungal and viral infections also increases, particularly with advanced-stage disease, intensive care admission, broad-spectrum antibiotic use, and acute or chronic liver failure. The development of an infection can exacerbate inflammation and portal hypertension, triggering acute decompensation, hepatic encephalopathy, kidney damage, circulatory failure, and multiple organ failure; therefore, it is one of the major determinants of mortality in patients with cirrhosis (31, 33).

In conclusion, when assessing infection risk in patients with chronic liver disease, peripheral white blood cell and neutrophil counts alone should not be used. The stage of liver disease, the degree of portal hypertension, history of previous infections, malnutrition, invasive procedures, hospitalization, antibiotic exposure, and concomitant organ failures should all be evaluated together. It should be kept in mind that classic signs of infection, such as fever and leukocytosis, may be masked by immune dysfunction; in cases of unexplained encephalopathy, renal dysfunction, hypotension, or sudden clinical deterioration, perform an early, comprehensive evaluation for infection (31, 33).

6. Changes in Platelets

Platelet abnormalities are among the most common hematological disorders in chronic liver diseases, and thrombocytopenia is generally considered one of the earliest laboratory findings of cirrhosis (2). A decrease in platelet count is closely associated with the progression of liver disease and the severity of portal hypertension. However, thrombocytopenia is a complex process that no single mechanism can explain. Hypersplenism, decreased thrombopoietin synthesis, bone marrow suppression, immune mechanisms, and increased platelet consumption all contribute to thrombocytopenia (2, 20, 30).

Splenomegaly and hypersplenism associated with portal hypertension are among the leading causes of thrombocytopenia. Increased sequestration and destruction of platelets in the enlarged spleen markedly decrease the peripheral platelet count (20). In addition, due to parenchymal damage in the liver—the primary site of thrombopoietin synthesis—thrombopoietin production decreases, and megakaryocyte proliferation and platelet production are suppressed (10, 14). Chronic alcohol use, hepatitis B and C infections, iron, folate, and vitamin B12 deficiencies, as well as certain antiviral, chemotherapeutic, and immunosuppressive medications, contribute to thrombocytopenia by exerting a suppressive effect on the megakaryocytic lineage in the bone marrow. In addition, antiplatelet autoantibodies and immune-mediated platelet destruction—which can develop particularly in chronic hepatitis C and autoimmune liver diseases—may also contribute to thrombocytopenia (20, 30).

In patients with chronic liver disease, significant abnormalities develop not only in platelet counts but also in platelet function. Platelet adhesion, activation, aggregation, and granule release are influenced by factors such as endothelial dysfunction, elevated nitric oxide levels, inflammation, and uremia (1). However, recent studies show that cirrhosis is not characterized solely by decreased platelet function; rather, primary hemostasis is significantly compensated by markedly increased von Willebrand factor (vWF) levels and decreased ADAMTS13

activity. Consequently, despite a low platelet count, many patients can maintain primary hemostatic balance, and platelet count alone cannot predict bleeding risk. This approach is a fundamental component of the concept of "rebalanced hemostasis" as defined in liver diseases (3).

Thrombocytosis is much rarer in chronic liver diseases than thrombocytopenia. However, reactive thrombocytosis may develop in early-stage chronic liver diseases, during acute inflammatory processes, in iron-deficiency anemia, or following a splenectomy (2). In addition, an increase in platelet count has been reported in some malignancies, such as hepatocellular carcinoma, due to tumor-derived cytokine release. When thrombocytosis is detected in patients with liver disease, in addition to investigating secondary causes, a differential diagnosis should also be performed to rule out concomitant myeloproliferative neoplasms (9).

7. Hemostatic Changes

In liver disease, hemostasis should not be viewed solely as a bleeding disorder caused by decreased clotting factors. A decrease in procoagulant factors is accompanied by a decrease in natural anticoagulants such as protein C, protein S, and antithrombin, as well as an increase in factor VIII and von Willebrand factor (vWF) levels. As a result of these reciprocal changes, a dynamic and fragile equilibrium—defined as "rebalanced hemostasis"—is established; however, this equilibrium can easily shift toward bleeding or thrombosis due to additional factors such as infection, acute kidney injury, portal hypertension, and invasive procedures (3, 34). For this reason, patients with cirrhosis should not be viewed solely as individuals at risk for bleeding; they should also be closely monitored for venous and portal vein thrombosis (3, 35).

In patients with liver disease, prothrombin time and the international normalized ratio (INR) reflect only a decrease in procoagulant factors; however, they cannot assess changes in the natural anticoagulant system—such as protein C, protein S, and antithrombin—platelet-vWF interaction, or fibrinolytic activity (35, 36). Furthermore, the INR has been standardized for treatment monitoring in patients taking vitamin K antagonists but has not been validated to assess hemostatic disorders associated with liver disease. Therefore, an elevated INR alone does not predict bleeding risk, and routine plasma transfusion is not recommended solely to correct the INR (35, 36).

Thrombin formation tests performed with the addition of thrombomodulin in patients with liver disease show that thrombin formation is largely preserved, and in some cases even increased, particularly in patients with compensated cirrhosis (37). This condition is attributed to the combined effect of increased factor VIII

levels and decreased levels of protein C, protein S, and antithrombin (3, 34, 37). In primary hemostasis, vWF levels increase significantly because of endothelial activation and reduced hepatic clearance, while ADAMTS13 activity—the physiological regulator of vWF—decreases. The combination of elevated vWF and reduced ADAMTS13 may contribute to a thrombotic tendency by promoting platelet adhesion (37).

In liver diseases, the fibrinolytic system also changes significantly. While levels of plasminogen, α2-antiplasmin, and thrombin-activated fibrinolysis inhibitor (TAFI) decrease, levels of tissue-type plasminogen activator (t-PA) may increase (34, 38). These changes may lead to a hyperfibrinolytic state in some patients and a hypofibrinolytic state in others. Hyperfibrinolysis is associated with low fibrinogen levels, early clot lysis, and oozing-type bleeding after the procedure. However, an elevated D-dimer level alone does not establish a diagnosis of hyperfibrinolysis and must be evaluated alongside clinical findings (35, 38). In conclusion, hemostatic assessment in patients with liver disease should not be based solely on INR; it should be performed alongside platelet count, fibrinogen levels, clinical status, and, when necessary, viscoelastic tests (36).

8. Thrombotic Complications

In liver diseases, particularly cirrhosis, the risk of not only bleeding but also thromboembolic events increases due to altered hemostasis. Decreased levels of protein C, protein S, and antithrombin, along with increased levels of factor VIII and von Willebrand factor (vWF), combined with endothelial dysfunction and portal hypertension, are the primary mechanisms contributing to thrombosis (3, 39). For this reason, patients with liver disease should not be considered "self-anticoagulated" individuals, contrary to what was previously believed. Portal vein thrombosis (PVT) is the most common thrombotic complication in cirrhosis and is associated with slowed portal blood flow, portal hypertension, and hypercoagulability. PVT can exacerbate the symptoms of portal hypertension, cause intestinal ischemia, and adversely affect surgical outcomes, particularly in liver transplant candidates (39, 40). Thrombosis can extend from the portal vein to the splenic and mesenteric veins, or it can develop in isolation within these vessels. While splenic vein thrombosis is associated with segmental portal hypertension and gastric varices, mesenteric vein thrombosis can lead to life-threatening complications such as intestinal ischemia and infarction (39, 41).

Thrombotic events in patients with liver disease are not limited to the splenic venous system. It has been shown that the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) is higher than in the general population.

Therefore, in hospitalized patients with cirrhosis, prophylaxis against venous thromboembolism should not be neglected when indicated, after the risk of bleeding has been carefully assessed (42). While Doppler ultrasound, contrast-enhanced computed tomography, and magnetic resonance imaging are the primary diagnostic methods for thrombotic complications, treatment should be tailored to each patient, considering liver function, the extent of thrombosis, and bleeding risk (39).

9. Bleeding Complications

Bleeding associated with liver disease is not solely due to a decrease in coagulation factors; portal hypertension, thrombocytopenia, platelet dysfunction, endothelial changes, and disruption of rebalanced hemostasis all play a role (3, 39). Clinically, the most significant bleeding complication is esophagogastric variceal bleeding. Variceal bleeding is primarily a consequence of portal hypertension and is more closely associated with portal pressure than with elevated INR or platelet count. Acute variceal bleeding is one of the most serious life-threatening complications in patients with cirrhosis, and early vasoactive therapy, endoscopic intervention, and an appropriate resuscitation approach are of fundamental importance in reducing mortality (43).

Mucosal bleeding not associated with portal hypertension (epistaxis, bleeding gums, and ecchymoses on the skin and mucous membranes), by contrast, is more commonly associated with thrombocytopenia, platelet dysfunction, and hyperfibrinolysis, which may be observed in patients with advanced-stage disease (35). However, because laboratory abnormalities alone do not predict bleeding risk, clinical evaluation should always take precedence (3).

In patients with liver disease, the risk of bleeding must be assessed on an individual basis prior to interventional procedures. Current guidelines state that paracentesis has a low risk of bleeding and do not recommend routine adjustment of platelet counts or INR levels (40). Similarly, transjugular intrahepatic portosystemic shunt (TIPS) procedures can be performed safely at experienced centers, and the benefit of prophylactic plasma transfusion—intended solely to correct elevated INR levels—has not been demonstrated before the procedure (39). However, liver biopsy is among the procedures that carry a higher risk of bleeding, particularly when performed percutaneously; therefore, platelet count, fibrinogen levels, the procedure technique, and the patient's overall clinical condition should be evaluated together. In high-risk cases, transjugular biopsy may be preferred as a safer alternative (39, 40).

10. Hematological Findings Associated with Liver Diseases

The type and severity of hematological changes in liver diseases vary by underlying etiology and disease stage. However, anemia, thrombocytopenia, leukopenia, and hemostatic disorders are findings commonly observed in nearly all chronic liver diseases (3, 39). In viral hepatitis, cytopenias may develop as a result of chronic inflammation, hypersplenism, and antiviral treatments. While hepatitis C infection is particularly associated with immune thrombocytopenia, cryoglobulinemia, and B-cell lymphoproliferative disorders, thrombocytopenia due to portal hypertension is common in advanced stages of hepatitis B and C infections (39, 44).

In metabolic dysfunction-associated steatotic liver disease (MASLD/NAFLD), hematological changes are generally mild in the early stages; however, as fibrosis progresses and cirrhosis develops, thrombocytopenia and coagulation disorders become more pronounced. Conversely, MASLD is also associated with an increased risk of venous thromboembolism and cardiovascular events due to chronic inflammation and endothelial dysfunction (45). In alcohol-related liver disease, macrocytic anemia, folate deficiency, bone marrow suppression, and pancytopenia due to alcohol's direct myelotoxic effect may be observed. Additionally, thrombocytopenia and platelet dysfunction are important mechanisms that increase the risk of bleeding (3, 46).

Because autoimmune hepatitis may occur in conjunction with other autoimmune diseases, it may be associated with immune-mediated hematologic disorders such as autoimmune hemolytic anemia, immune thrombocytopenia, and, more rarely, Evans syndrome (47). In primary biliary cholangitis (PBC), anemia most often presents as anemia of chronic disease or concomitant iron deficiency, while in patients with advanced disease, thrombocytopenia may develop due to hypersplenism. Primary sclerosing cholangitis (PSC), by contrast, may cause anemia through chronic inflammation and nutritional deficiencies linked to inflammatory bowel disease; as the disease progresses, cytopenias may develop due to portal hypertension (39, 48).

Hematological findings may be diagnostic indicators in metabolic liver diseases. In Wilson's disease, Coombs-negative intravascular hemolytic anemia—resulting from oxidative damage to the erythrocyte membrane caused by free copper—is characteristic, particularly in cases of acute liver failure (49). In hereditary hemochromatosis, while red blood cell parameters are generally preserved despite iron overload, thrombocytopenia and leukopenia may occur in advanced stages due to hypersplenism following cirrhosis (49).

In acute liver failure, despite a rapid decline in coagulation factors, platelet dysfunction, hyperfibrinolysis, and widespread endothelial activation, hemostasis

can be largely maintained through rebalancing. Therefore, an elevated INR alone does not reflect the risk of bleeding; patients may experience thrombotic complications as well as bleeding (50). Cirrhosis is a chronic liver disease in which hematological changes are most prominent. Thrombocytopenia, anemia, and leukopenia may develop because of hypersplenism associated with portal hypertension, decreased thrombopoietin synthesis, chronic inflammation, nutritional deficiencies, and bone marrow suppression. In addition, the risk of bleeding and thrombosis increases simultaneously due to a rebalancing of hemostasis (3, 39, 50).

11. Before and After Transplantation

Prior to liver transplantation, hematologic disorders are most often related to the natural course of end-stage liver disease. Thrombocytopenia, anemia, and leukopenia are common due to hypersplenism from portal hypertension, decreased thrombopoietin synthesis, chronic inflammation, nutritional deficiencies, and bone marrow suppression (39, 51). Although a marked improvement in cytopenias may be observed following the resolution of portal hypertension after transplantation, hematologic abnormalities may persist or recur due to immunosuppressive therapy, infections, and graft dysfunction (39, 52). Thrombotic complications in the early post-transplant period—particularly hepatic artery thrombosis and portal vein thrombosis—rank among the most significant vascular complications in terms of graft loss and mortality. Systemic venous thromboembolic events, such as deep vein thrombosis and pulmonary embolism, may also occur. Surgical technique, endothelial injury, hemostasis rebalancing, and immobilization are the primary factors contributing to thrombosis. Therefore, assess thrombosis and bleeding risk together, and administer individualized thromboprophylaxis (39, 40).

Although lifelong immunosuppressive therapy following liver transplantation is the primary approach to preventing graft rejection, it can also cause hematologic toxicity. Calcineurin inhibitors, mycophenolate mofetil, and azathioprine may contribute to anemia, leukopenia, and thrombocytopenia. In addition, immunosuppression significantly increases the risk of opportunistic infections and lymphoproliferative disorders (52, 53).

Cytomegalovirus (CMV) infection is one of the most common opportunistic viral infections following liver transplantation. CMV infection can cause febrile illness and tissue invasion, as well as leukopenia, neutropenia, and thrombocytopenia due to bone marrow suppression. It also increases the risk of acute rejection, secondary bacterial and fungal infections, and other opportunistic

infections. For this reason, antiviral prophylaxis or preemptive treatment is recommended for high-risk patients (54).

One of the most serious hematologic complications that can develop after transplantation is post-transplant lymphoproliferative disease (PTLD). The majority of PTLD cases are associated with the Epstein–Barr virus (EBV), and severe immunosuppression is the most significant risk factor. The clinical presentation can range from benign polyclonal lymphoid proliferation to aggressive lymphoma. While reducing immunosuppression is the cornerstone of treatment, rituximab and chemotherapy may be administered depending on disease extent and histopathological subtype (55).

12. Diagnostic Approach

The evaluation of a patient with cirrhosis and anemia should be based on the principle that anemia cannot be attributed to a single cause. In the initial stage, examine a complete blood count, erythrocyte indices, reticulocyte count, and peripheral blood smear. Assess iron, ferritin, transferrin saturation, vitamin B12, and folate levels, as well as renal function. Because ferritin is an acute-phase reactant, normal or elevated levels with chronic inflammation and hepatocellular damage do not rule out iron deficiency; interpret them with transferrin saturation and clinical findings (56, 57). With regard to gastrointestinal bleeding, esophagogastric varices, portal hypertensive gastropathy, gastric antral vascular ectasia, and peptic ulcers should be investigated. If you find reticulocytosis, elevated indirect bilirubin and lactate dehydrogenase, low haptoglobin, or acanthocytes on a peripheral blood smear, consider hemolysis and spherocyte anemia associated with advanced cirrhosis (56, 57).

In patients with thrombocytopenia, first rule out pseudothrombocytopenia; evaluate the platelet count course, spleen size, signs of portal hypertension, and other cell counts together. The primary causes of thrombocytopenia in cirrhosis are splenic sequestration, decreased thrombopoietin synthesis, bone marrow suppression, infections, medications, and immune mechanisms (39, 58). In cases of isolated, sudden, or unexpectedly severe thrombocytopenia, investigate alternative causes such as immune thrombocytopenia, drug-induced thrombocytopenia, sepsis, disseminated intravascular coagulation, and thrombotic microangiopathy. Consider a bone marrow examination in cases of unexplained pancytopenia, abnormal peripheral blood smear findings, or cytopenias inconsistent with the severity of liver disease.

Do not use INR and prothrombin time alone to assess bleeding risk, because these tests do not reflect decreased natural anticoagulants, platelet-vWF interaction, or fibrinolysis (35, 39, 40). The assessment should consider a history

of active bleeding, bleeding during previous procedures, the type of procedure, platelet count, fibrinogen level, renal failure, infection, and the degree of disease decompensation. Since variceal bleeding is primarily due to portal hypertension, an elevated INR is not a direct indicator of the risk of variceal bleeding. Routine administration of fresh frozen plasma solely to correct the INR is not recommended prior to low-risk procedures (35, 39, 40).

Assessment of thrombosis risk should be based on the assumption that patients with liver disease are not "naturally anticoagulated." A history of previous venous thromboembolism, immobilization, malignancy, infection, central venous catheter use, obesity, surgery, and transplantation should be systematically assessed. With regard to portal vein thrombosis, reduced portal blood flow, advanced portal hypertension, hepatocellular carcinoma, and a history of splenic vein thrombosis are significant risk factors (42). If the patient has abdominal pain, new-onset or worsening ascites, gastrointestinal bleeding, or unexplained hepatic decompensation, evaluate the portal and mesenteric venous systems with Doppler ultrasound; for suspected or widespread thrombosis, use contrast-enhanced computed tomography or magnetic resonance imaging. Because bleeding and thrombosis risk can change, repeat the evaluation as the clinical condition changes.

13. Current Treatment

Individualize management of hematologic abnormalities in liver disease based on bleeding status, anemia etiology, procedural risk, and thrombotic risk. In acute gastrointestinal bleeding, particularly variceal bleeding, restrictive red blood cell transfusion targeting hemoglobin levels of 7–8 g/dL is recommended, with adjustments for hemodynamic instability and cardiovascular comorbidities. Excessive transfusion may increase portal pressure and rebleeding risk (43).

Treat iron deficiency with oral or intravenous iron while addressing the bleeding source. Iron status should be evaluated using ferritin, transferrin saturation, and clinical findings, as ferritin may be elevated in liver disease. Iron therapy should be avoided in significant iron overload or uncontrolled infection (57). Erythropoiesis-stimulating agents are reserved for patients with concomitant chronic kidney disease or other established indications.

In severe thrombocytopenia before elective invasive procedures, avatrombopag and lusutrombopag may reduce platelet transfusion requirements (59, 60). These agents are unsuitable for emergencies or routine low-risk procedures, while eltrombopag is generally avoided because of portal vein thrombosis risk (61).

Fresh-frozen plasma is not recommended for routine INR correction in cirrhosis because of limited efficacy and risks of volume overload and increased portal pressure (39, 40). Cryoprecipitate or fibrinogen concentrate may be considered for marked hypofibrinogenemia during severe bleeding or high-risk procedures (39). Prothrombin complex concentrate should be restricted to selected emergencies, including life-threatening bleeding or urgent vitamin K antagonist reversal (39, 40). Tranexamic acid is not routinely recommended but may be considered in selected cases of persistent bleeding with suspected hyperfibrinolysis (39).

Elevated INR alone does not contraindicate anticoagulation. According to ISTH recommendations, direct oral anticoagulants or low-molecular-weight heparin/vitamin K antagonists may be used in Child–Pugh A–B cirrhosis, whereas low-molecular-weight heparin is generally preferred in Child–Pugh C. Anticoagulation for at least six months is recommended for symptomatic or progressive portal vein thrombosis, with possible extension in transplant candidates (62). Individualize treatment according to bleeding risk, liver and kidney function, platelet count, and thrombosis characteristics.

14. Conclusion

Hematological changes in liver diseases extend beyond cytopenias and decreased coagulation factors; they result from complex pathophysiological processes that affect erythropoiesis, thrombopoiesis, primary and secondary hemostasis, and the fibrinolytic system. Today, the adoption of the concept of “rebalanced hemostasis” in cirrhosis and other advanced-stage liver diseases has highlighted the need to evaluate patients not only for bleeding but also for thromboembolic complications.

In recent years, viscoelastic testing, thrombopoietin receptor agonists, advanced imaging methods, and new biomarkers have driven significant advances in diagnostic and therapeutic approaches; in addition, artificial intelligence-based decision support systems have shown promising results for personalized risk assessment. However, the current approach relies less on laboratory parameters and more on the patient’s clinical condition, combined assessment of bleeding and thrombosis risk, and individualized, multidisciplinary treatment. With future prospective studies and the introduction of new biomarkers into clinical practice, it will be possible to predict hematologic complications in liver diseases more accurately and develop targeted treatment strategies.

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Chapter 6

Artificial Intelligence in Periodontology: Current Applications, Clinical Potential, and Limitations

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Abstract

Advances in artificial intelligence technologies have enabled the development of new applications for diagnosis, disease classification, risk assessment, and treatment planning in periodontology. This book chapter aims to evaluate the current applications, clinical potential, and limitations of artificial intelligence in periodontology based on the existing scientific literature. The applications of machine learning and deep learning methods in the detection and measurement of radiographic alveolar bone loss, staging and grading of periodontitis, identification of furcation involvement and periodontal bone defects, and assessment of dental plaque and gingival inflammation using intraoral images are discussed. In addition, multimodal imaging systems, prediction of periodontal disease progression and tooth loss risk, treatment decision support, digital patient monitoring, and the clinical use of large language models are examined. Current research indicates that artificial intelligence systems can achieve high performance in certain diagnostic and prognostic tasks and have the potential to support clinical assessment processes. However, limited diversity of datasets, methodological differences, a lack of independent external validation, and insufficient evidence regarding actual clinical outcomes restrict the translation of these systems into routine practice. Patient data privacy, algorithmic bias, transparency, and clinical responsibility are also key considerations. In conclusion, although artificial intelligence represents an important technology capable of supporting clinical decision-making processes in periodontology, it should not replace comprehensive periodontal examination and clinician assessment. Future multicenter, prospective studies focusing on clinical outcomes are essential to determine the reliable and effective use of these technologies.

Keywords: Artificial intelligence, Periodontology, Deep learning, Periodontal diagnosis, Clinical decision support

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1. Introduction

Periodontitis is a chronic inflammatory disease associated with the interaction between a dysbiotic microbial biofilm and the host immune-inflammatory response, characterized by loss of periodontal attachment and alveolar bone. Disease progression may lead to irreversible destruction of the supporting tissues of the teeth and, in advanced cases, tooth loss. The assessment of periodontitis is based on clinical attachment loss and other periodontal examination findings, while radiographic examinations support the determination of alveolar bone levels and bone loss patterns (Tonetti et al., 2018; Persson et al., 2003). Early diagnosis, accurate determination of disease severity, and regular post-treatment monitoring are important for maintaining periodontal health.

Clinical and radiographic methods used in periodontal diagnosis may exhibit variability depending on measurement conditions and the examiner. Periodontal probing results are influenced by the applied force, probe tip diameter, and inflammatory status of the tissues, whereas radiographic bone level measurements may also be affected by the imaging modality and anatomical region (Garnick & Silverstein, 2000; Persson et al., 2003). Furthermore, the current periodontal classification system encompasses treatment complexity, disease progression rate, and risk factors in addition to the severity of tissue destruction (Tonetti et al., 2018). This multidimensional assessment process has increased interest in methods that support the integrated analysis of different clinical and radiographic data.

Artificial intelligence is increasingly being investigated because of its potential to support periodontal diagnosis and clinical decision-making processes. Machine learning methods enable the development of classification and prediction models using clinical measurements, demographic characteristics, and risk factors, whereas deep learning methods are particularly used to identify anatomical structures and assess periodontal bone loss in radiographic images. Furthermore, artificial intelligence applications have expanded beyond image analysis to include periodontal risk assessment, tooth prognosis prediction, treatment planning, and patient monitoring. In a systematic review conducted by Tichy et al. (2026), 29 studies focusing on image-based periodontal diagnosis and 65 studies using non-image data were evaluated, demonstrating the scope of these applications. However, limited dataset diversity, methodological differences, and insufficient independent external validation studies restrict the generalizability of the developed models to clinical settings (Tichy et al., 2026).

This book chapter addresses the current applications of artificial intelligence in periodontology, including periodontal diagnosis, radiographic image analysis, disease classification, risk assessment, treatment planning, and clinical decision

support. Existing studies are evaluated not only in terms of their reported algorithmic performance but also with respect to the quality of the data used, their clinical validity, and their applicability to clinical practice. In addition, the reliability, ethical limitations, and future research directions of artificial intelligence systems are discussed.

2. Fundamental Concepts of Artificial Intelligence and Methods Used in Periodontology

Artificial intelligence (AI) is a field of computer science encompassing methods aimed at performing tasks associated with human intelligence through computer systems. Machine learning (ML), a subfield of artificial intelligence, enables the development of classification and prediction models by learning patterns from data. Machine learning methods include logistic regression, decision trees, random forests, and support vector machines, whereas deep learning (DL) is particularly used to analyze high-dimensional data through multilayer artificial neural networks (Collins et al., 2024; Tichy et al., 2026). In periodontology, these approaches are being investigated for the analysis of various data types, including clinical periodontal measurements, demographic characteristics, risk factors, and radiographic images (Tichy et al., 2026).

Convolutional neural networks (CNNs) play an important role among the deep learning approaches used in periodontal image analysis. These models can perform tasks such as classification, object detection, and segmentation by learning discriminative features from images. Classification refers to assigning an image or image region to a specific category; object detection involves identifying the location of a relevant anatomical structure or finding within an image; and segmentation refers to delineating the boundaries of a relevant structure at the pixel level. In periodontology, these methods are used to detect radiographic bone loss, identify anatomical landmarks such as the cementoenamel junction (CEJ) and alveolar bone level, and characterize periodontal defects (Krois et al., 2019; Chang et al., 2020; Tichy et al., 2026).

In the development of artificial intelligence models, data quality, sample characteristics, and evaluation methods directly influence the reliability of the results obtained. During model development, data are generally divided into training, validation, and test sets. Training data allow the algorithm to learn patterns, validation data are used for model development and tuning, and test data enable the evaluation of model performance on previously unseen samples. Particularly in image-based studies, the inclusion of images from the same patient in different datasets may lead to data leakage and overestimation of model performance. Therefore, it is important to perform data splitting at the patient

level and evaluate the developed models using independent datasets obtained from different centers or patient populations (Collins et al., 2024; Tejani et al., 2024).

The performance of artificial intelligence models should be evaluated using metrics appropriate to the task being performed. Diagnostic classification studies use metrics such as accuracy, sensitivity, specificity, F1 score, and the area under the receiver operating characteristic curve (AUROC). Image segmentation studies employ metrics such as the Dice coefficient and Intersection over Union (IoU). When interpreting these values, class distribution, the reference standard, and the clinical objective of the study should be considered (Reinke et al., 2024; Maier-Hein et al., 2024). In clinical prediction models, in addition to discriminative ability, it is important to assess calibration, which reflects the agreement between predicted probabilities and observed outcomes (Collins et al., 2024). Therefore, a high value for a single performance metric does not, by itself, demonstrate that a model will provide reliable results across different patient groups or be useful in clinical practice.

3. Applications of Artificial Intelligence in Periodontal Diagnosis

3.1. Detection and Measurement of Radiographic Alveolar Bone Loss

The assessment of radiographic alveolar bone loss plays an important role in the diagnosis of periodontitis and the determination of disease severity. In conventional assessment, anatomical landmarks such as the cementoenamel junction (CEJ), alveolar bone crest, and root length are used to examine the extent and distribution of bone loss. However, the interpretation of radiographic images may vary among observers, and detailed assessment can be time-consuming, particularly for panoramic radiographs. Therefore, deep learning-based methods are being investigated for the automated detection and quantitative assessment of bone loss (Krois et al., 2019; Chiang et al., 2025).

Krois et al. (2019) developed a seven-layer convolutional neural network (CNN) model to detect periodontal bone loss in 2,001 image segments obtained from panoramic radiographs. The model's mean classification accuracy, sensitivity, and specificity were reported as 0.81. Although the mean accuracy of six dentists was 0.76, the difference between the model and the evaluators was not statistically significant ($p = 0.067$). Furthermore, model performance varied across tooth groups, with higher accuracy in molar regions and lower accuracy in incisors. These findings indicate that artificial intelligence can be used for the radiographic detection of periodontal bone loss, although diagnostic performance may vary according to anatomical region (Krois et al., 2019).

Chang et al. (2020) developed a hybrid system combining deep learning with conventional computer-assisted image processing methods to identify the alveolar bone level, CEJ, and long axis of teeth on panoramic radiographs. The system calculated the percentage of radiographic bone loss using the identified anatomical landmarks and performed automated classification at the tooth level. The Dice coefficient for identifying the alveolar bone level was reported as 0.93, while the Pearson correlation coefficient and intraclass correlation coefficient (ICC) between automated classification and radiologists' assessments were 0.73 and 0.91, respectively. These findings demonstrate that artificial intelligence methods can be used not only to detect bone loss but also to assess it quantitatively (Chang et al., 2020).

Chiang et al. (2025) evaluated the performance of artificial intelligence models in detecting marginal alveolar bone loss in a systematic review and meta-analysis encompassing 64 studies. In the 16 studies included in the meta-analysis, the pooled sensitivity was reported as 92.3%, specificity as 91.7%, and area under the receiver operating characteristic curve (AUROC) as 0.97. However, substantial heterogeneity and risk of bias were identified across the studies, and it was noted that temporal changes in bone levels and the performance of these systems under real-world clinical conditions had not been adequately evaluated. Therefore, the reported high diagnostic performance values do not, by themselves, demonstrate that these models are ready for routine clinical implementation (Chiang et al., 2025).

Current studies indicate that artificial intelligence has potential for the detection and measurement of radiographic alveolar bone loss. However, to establish the clinical applicability of these systems, they need to be validated across different imaging modalities and independent patient populations, be capable of assessing changes in bone levels over time, and integrate radiographic findings with clinical periodontal data (Chiang et al., 2025).

3.2. Classification of Periodontitis and Assessment of Disease Severity

The current classification of periodontitis is based on staging, which reflects disease severity and treatment complexity, and grading, which assesses the rate of disease progression and risk factors (Tonetti et al., 2018). Artificial intelligence-based systems are being developed to support this classification process through automated measurement of radiographic bone loss and analysis of clinical data.

Do et al. (2025) developed a YOLOv8-based system for automated staging and grading of periodontitis using 500 panoramic radiographs. The system employed three separate deep learning models to identify the alveolar bone level,

cementoenamel junction (CEJ), and teeth, and combined the percentage of radiographic bone loss with patient age, smoking status, and diabetes information. In the test dataset, the Dice coefficients for identifying the alveolar bone level and CEJ were reported as 0.95 and 0.94, respectively. However, the final staging and grading were performed using a rule-based algorithm applied to the automated measurements rather than directly by an artificial intelligence classifier (Do et al., 2025).

Ameli et al. (2024) developed a BERT model based on natural language processing (NLP) to predict the stage and grade of periodontitis using periodontal records and clinical notes from 309 patients. The model's staging and grading accuracies were reported as 77% and 75%, respectively, whereas these values were 66% and 72% in a previously unseen test dataset comprising 32 records. These findings indicate that structured and free-text clinical records, in addition to radiographic images, can be used for periodontal classification (Ameli et al., 2024).

Both studies demonstrate that artificial intelligence methods can support periodontal staging and grading by utilizing different data sources. However, the use of a rule-based algorithm for final classification in the study by Do et al. (2025) and the lower accuracy values obtained in the test data in the study by Ameli et al. (2024) indicate that the methodological characteristics and performance of these systems should be carefully evaluated. Furthermore, because comprehensive periodontal classification requires the assessment of clinical attachment loss, treatment complexity, and patient-specific risk factors in addition to radiographic bone loss, current systems should be considered clinical decision support tools rather than independent diagnostic tools (Tonetti et al., 2018).

3.3. Detection of Furcation Involvement and Periodontal Bone Defects

The identification of furcation involvement and intrabony periodontal defects is important for assessing disease severity and treatment planning. However, the superimposition of anatomical structures and the limited visualization of defect morphology on two-dimensional radiographs may complicate the assessment of these findings. Therefore, deep learning-based models are being investigated for the automated detection of furcation involvement and different periodontal bone defects on periapical radiographs (Mao et al., 2023; Valente et al., 2026).

Mao et al. (2023) developed a convolutional neural network (CNN)-based classification model using 300 periapical radiographs of teeth with and without furcation involvement. The study aimed to enhance the visibility of the furcation region through image preprocessing, adaptive thresholding, and masking

techniques, and an accuracy of up to 94.97% was reported for the model developed using a transfer learning approach. Although this finding indicates that artificial intelligence can be used for the radiographic assessment of furcation involvement, the reported performance requires validation using independent clinical datasets (Mao et al., 2023).

Valente et al. (2026) developed a YOLOv8-based object detection model to identify furcation involvement and different intrabony defect morphologies on periapical radiographs. A total of 581 images containing periodontal bone defects, selected from 7,464 radiographs, were evaluated for one-wall, two-or-more-wall, crater-like, and furcation defects. The model's overall precision, recall, and mAP@0.5 values were reported as 0.592, 0.435, and 0.504, respectively. Higher performance was achieved for furcation defects than for other defect categories, with a precision of 0.669 and an mAP@0.5 of 0.577, whereas lower performance was observed in the detection of one-wall defects. These findings highlight the potential for automated detection of different periodontal defect morphologies while demonstrating that model performance varies according to defect type (Valente et al., 2026).

Because these studies evaluated different image analysis tasks, the classification accuracy reported by Mao et al. (2023) should not be directly compared with the object detection metrics reported by Valente et al. (2026). Furthermore, because two-dimensional radiographs cannot fully represent the three-dimensional morphology of defects, radiographic findings should be interpreted in conjunction with clinical and, when necessary, surgical assessment.

3.4. Periodontal Assessment Using Intraoral Images and Multimodal Approaches

In addition to radiographic image analysis, artificial intelligence applications are being developed to detect dental plaque and gingival inflammation from intraoral photographs. Deep learning-based image analysis models enable the identification of areas of plaque accumulation and the assessment of visible signs of inflammation in gingival tissues. The ability to use images obtained through smartphones and intraoral cameras enhances the potential of these systems for oral hygiene assessment and remote patient monitoring (Moharrami et al., 2025).

Chau et al. (2023) developed a DeepLabv3+-based deep learning model for the automated detection of gingival inflammation from intraoral photographs. Of the 567 intraoral photographs, 80% were used for training and 20% for validation. Gingival regions were classified as healthy, inflamed, or uncertain areas. The model's sensitivity, specificity, and mean Intersection over Union (mIoU) for gingivitis detection were reported as 0.92, 0.94, and 0.60, respectively. Although

these findings indicate that signs of gingival inflammation can be automatically detected in intraoral images, they do not imply that image analysis can replace clinical periodontal examination (Chau et al., 2023).

Moharrami et al. (2025) examined 23 studies in their systematic review evaluating the performance of deep learning models for detecting dental plaque and gingivitis from intraoral photographs. For dental plaque segmentation, IoU values ranged from 0.64 to 0.86, with a median of 0.74, whereas for gingivitis segmentation, values ranged from 0.43 to 0.72, with a median of 0.63. Furthermore, the certainty of evidence was rated as moderate for dental plaque detection and low for gingivitis detection. These findings indicate that photograph-based artificial intelligence applications have potential, particularly for detecting dental plaque, whereas the evidence regarding the assessment of gingival inflammation remains more limited (Moharrami et al., 2025).

The integration of intraoral images with other imaging modalities offers a different approach to artificial intelligence-assisted periodontal assessment. Tan et al. (2025) developed a multimodal system called PerioAI that combines intraoral scan data with cone-beam computed tomography (CBCT) images. Evaluated using multicenter datasets comprising a total of 2,507 patients, the system enabled automated segmentation of tooth and alveolar bone structures and digital measurement of the distance between the gingival margin and alveolar bone (gingiva-bone distance, GBD). The reported measurement error of 0.040 mm demonstrates that quantitative periodontal assessments can be performed by integrating anatomical information obtained from different imaging modalities. However, because GBD is not directly equivalent to clinical probing depth or clinical attachment level, additional clinical validation is required before the system can replace a comprehensive periodontal examination (Tan et al., 2025).

These findings indicate that intraoral images can be used in artificial intelligence-assisted periodontal assessment. However, the performance of photograph-based models is influenced by factors such as image quality, lighting conditions, and the visual distinguishability of clinical findings. Multimodal approaches combining intraoral scanning and CBCT data offer additional opportunities for the combined assessment of periodontal hard and soft tissues. Nevertheless, independent validation studies and assessments of clinical validity across different patient populations are required before the digital measurements provided by these systems can replace a comprehensive clinical periodontal examination (Moharrami et al., 2025; Tan et al., 2025).

4. Artificial Intelligence in Periodontal Risk Assessment and Treatment Planning

Artificial intelligence applications in the assessment of periodontal diseases are being investigated not only for determining the current clinical status but also for predicting the risk of disease progression, tooth prognosis, and the likelihood of tooth loss (Lee et al., 2018; Santamaria et al., 2024; Furquim et al., 2025). Traditional periodontal risk assessment is based on the combined interpretation of clinical and patient-specific factors, such as clinical attachment loss, probing depth, radiographic bone loss, smoking, and diabetes (Lang & Tonetti, 2003; Tonetti et al., 2018). Machine learning methods have the potential to contribute to individualized risk assessment by analyzing the complex relationships among these variables (Furquim et al., 2025). However, predicting disease progression and predicting the prognosis of existing teeth or future tooth loss represent different clinical endpoints, requiring separate evaluations of model performance in these areas.

Lee et al. (2018) developed a convolutional neural network-based model to identify periodontally compromised teeth and predict their extraction status. In the study, which included 1,740 periapical radiographic images, the classification accuracy for periodontal status was reported as 81.0% for premolars and 76.7% for molars. For predicting the extraction status of teeth with severe periodontal destruction, the model achieved accuracies of 82.8% for premolars and 73.4% for molars. However, because extraction status was evaluated within a three-month follow-up period, these findings should not be interpreted as predictions of long-term tooth loss (Lee et al., 2018).

Lee et al. (2022) compared different machine learning algorithms using data from 2,359 teeth belonging to 94 patients to evaluate tooth prognosis in the context of multidisciplinary treatment planning. Among the models developed using 17 variables encompassing periodontal, endodontic, prosthetic, and other clinical factors, the decision tree algorithm demonstrated accuracies of 84.13% and 75.23% for the respective evaluator groups. However, because the reference standard in the study was based on the consensus prognostic assessment of experienced clinicians, the reported accuracy rates do not represent the ability to predict actual long-term tooth survival (Lee et al., 2022).

Santamaria et al. (2024) compared a traditional periodontal prognostic system with machine learning models to predict tooth loss over 10 years in patients receiving supportive periodontal care. A total of 1,626 teeth from 69 patients in London were evaluated for model development, while 2,792 teeth from 116 patients in Pittsburgh were used for external validation. Logistic regression and artificial neural network models were developed using variables such as probing

depth, tooth mobility, furcation involvement, radiographic bone loss, and periapical pathology. In the external validation cohort, the sensitivity and specificity of the traditional prognostic system for the "unfavourable prognosis" category were reported as 0.85% and 99.96%, respectively. The artificial neural network model demonstrated a sensitivity of 98.29% and a specificity of 52.26% for overall tooth loss prediction. Although these findings indicate that artificial intelligence models have potential for predicting tooth loss, they also highlight that the performance metrics of a specific prognostic category within the traditional system should not be considered directly equivalent to the overall predictive performance of machine learning models (Santamaria et al., 2024).

In addition to tooth loss prediction, the direct prediction of periodontitis progression risk is another area being investigated using machine learning. Furquim et al. (2025) developed models to predict disease progression using baseline data from a multicenter longitudinal study involving 415 participants, including 113 periodontally healthy individuals and 302 patients with periodontitis, who were evaluated every two months over a 12-month period. The study compared logistic regression, multilayer perceptron, and probabilistic graphical model approaches using clinical and demographic variables and salivary biomarkers. The probabilistic graphical model incorporating clinical measurements, salivary interleukin-1β levels, age, and sex demonstrated the highest discriminative performance (AUROC = 0.88), with a reported sensitivity of 0.55 and specificity of 0.81. These findings suggest that combining clinical parameters with biological markers may contribute to predicting the risk of periodontitis progression. However, the model's limited sensitivity and the need for external validation in independent patient populations should be considered when assessing its translation into clinical practice (Furquim et al., 2025).

Current research indicates that artificial intelligence methods may offer varying levels of predictive capability in assessing periodontal disease progression, tooth prognosis, and tooth loss risk. However, differences in data sources, prediction time horizons, reference standards, and clinical endpoints across studies make direct comparisons of reported performance metrics difficult. Furthermore, evaluating agreement with clinicians' decisions is not equivalent to predicting actual clinical outcomes. Therefore, before artificial intelligence-based risk models can be used for clinical decision support, they need to be validated in different patient populations, and their clinical benefits should be evaluated through prospective studies (Lee et al., 2018; Lee et al., 2022; Santamaria et al., 2024; Furquim et al., 2025).

5. Current Applications of Artificial Intelligence in Periodontal Treatment and Clinical Decision Support

The applications of artificial intelligence in periodontology extend beyond diagnosis and risk assessment to processes such as supporting treatment decisions, post-treatment patient monitoring, and monitoring oral hygiene behaviors. Research in this field focuses on predicting treatment outcomes from clinical data, digital patient monitoring, and interpreting clinical information through large language models (Shen et al., 2022; Rebeiz et al., 2025).

Rebeiz et al. (2025) conducted a retrospective longitudinal cohort study involving 3,347 teeth with at least 10 years of follow-up data to support periodontal treatment decisions. Different machine learning models were developed using variables such as probing depth, radiographic bone loss, furcation involvement, systemic diseases, and the type of periodontal treatment performed. The random forest algorithm demonstrated the highest performance, with an AUROC of 0.91 and an accuracy of 93%. An artificial intelligence-assisted decision-making platform was developed using data encompassing different treatment approaches, including nonsurgical treatment, corrective surgery, regenerative surgery, and root resection. However, associations identified in retrospective data do not prove that the treatment options recommended by the model are more effective than other approaches or improve patient outcomes (Rebeiz et al., 2025).

The contribution of artificial intelligence-derived periodontal measurements to clinical decision-making processes is also being investigated. Li et al. (2026) evaluated the impact of probing depth values derived from the PerioAI system, which integrates intraoral scanning and CBCT images (AI-derived probing depth, AI-PD), on tooth prognosis and treatment planning in a cross-sectional proof-of-concept study. The study examined 1,298 teeth and 7,788 measurement sites from 53 patients with periodontitis, comparing decisions based solely on panoramic radiographs with decisions incorporating both panoramic radiographs and AI-PD data. Using an assessment based on panoramic radiographs together with clinical periodontal records as the reference, agreement in prognosis decisions at the patient level increased from 77.6% to 84.7%, while agreement in treatment planning decisions increased from 78.2% to 84.3% ($p < 0.05$ for both comparisons). These findings indicate that adding artificial intelligence-derived periodontal measurements to radiographic information may improve the agreement of clinical decisions with the reference assessment. However, because the decisions were evaluated by a single periodontologist and the study had a cross-sectional design, these findings do not demonstrate improved long-term clinical success of the recommended treatments (Li et al., 2026).

Supporting oral hygiene behaviors following periodontal treatment is one of the areas in which artificial intelligence applications have been clinically evaluated. Shen et al. (2022) evaluated a smartphone camera-based monitoring system in a randomized controlled trial involving 53 patients with periodontitis, who were allocated to three groups: artificial intelligence-assisted remote monitoring (n = 16), artificial intelligence-assisted monitoring combined with healthcare professional counseling (n = 17), and a control group (n = 20). All patients received nonsurgical periodontal treatment. At the end of the three-month follow-up period, greater improvements in probing depth, clinical attachment level, and plaque index were reported in the artificial intelligence-assisted groups compared with the control group. The more pronounced clinical improvement observed in the group that also received healthcare professional counseling suggests that digital monitoring may provide benefits when combined with professional patient education (Shen et al., 2022).

Miyamoto et al. (2026) evaluated an artificial intelligence-based smartphone application over six months in 50 patients enrolled in a supportive periodontal care program. Patients received weekly personalized informational and motivational messages regarding periodontal disease risks, oral hygiene, and behavioral change. Compared with baseline measurements, significant improvements were observed in plaque index, bleeding on probing, and gingival index, whereas probing depth, clinical attachment level, and gingival recession values remained stable. However, this proof-of-concept study is insufficient to establish that the observed changes were directly attributable to the application or that the system improved long-term adherence to periodontal care (Miyamoto et al., 2026).

Large language models (LLMs) are also being investigated for their potential to support clinical decision-making in periodontal treatment planning. Mayer et al. (2026) compared a total of 11 systems, comprising nine general-purpose large language models and two retrieval-augmented platforms, using 30 synthetic periodontal clinical scenarios. Responses were blindly evaluated by six periodontologists in terms of diagnostic accuracy, patient safety, absence of fabricated information, and treatment plan completeness. Significant performance differences were identified among the systems ($p < 0.001$), and retrieval-augmented platforms generally achieved higher evaluation scores. However, depending on the platform, 3.3–46.7% of responses received low safety or quality scores for at least one criterion. These findings highlight both the potential of large language models to support clinical decisions and the risk of generating incorrect or inadequate recommendations (Mayer et al., 2026).

Current research indicates that artificial intelligence can be used in periodontal treatment for clinical decision support, patient monitoring, and the evaluation of treatment-related information. However, retrospective prediction models, short-term clinical monitoring studies, and evaluations based on synthetic cases represent different levels of evidence. Therefore, the clinical benefit of artificial intelligence applications should be assessed not only through algorithmic performance but also through their effects on patient outcomes and treatment processes. Responsibility for clinical decisions must remain with the clinician, who evaluates periodontal examination findings, current evidence, and patient-specific circumstances together.

6. Limitations, Reliability, and Ethical Issues in Clinical Practice

The use of artificial intelligence systems in periodontal diagnosis and treatment processes requires the evaluation of clinical reliability and potential effects on patient safety, in addition to high algorithmic performance. In current research, differences in dataset sizes, patient characteristics, imaging modalities, and reference standards limit the comparability and generalizability of findings. In particular, models developed using single-center or retrospective data cannot be assumed to demonstrate similar performance across different patient populations and clinical conditions. Therefore, independent external validation and evaluation under real-world clinical conditions are important steps in translating these models into clinical practice (Tichy et al., 2026; Tejani et al., 2024).

Reporting guidelines developed to ensure methodological transparency in artificial intelligence research provide a framework for evaluating studies. The Checklist for Artificial Intelligence in Medical Imaging (CLAIM), updated by Tejani et al. (2024), includes recommendations for reporting data sources, reference standards, model development processes, and performance evaluations in imaging-based artificial intelligence research. TRIPOD+AI, published by Collins et al. (2024), aims to promote transparent reporting of studies involving the development and evaluation of clinical diagnostic and prognostic prediction models. Although these guidelines can contribute to the methodological assessment of periodontal image analysis and tooth loss prediction studies, compliance with reporting guidelines alone does not establish the clinical validity or safety of a model (Collins et al., 2024).

Algorithmic errors in periodontal assessment have the potential to result in underestimation or overestimation of disease severity and inappropriate treatment decisions. Nantakeeratipat (2026) evaluated the staging and grading performance and potential algorithmic biases of GPT-4o and Gemini 2.5 Pro using 15

hypothetical periodontal clinical scenarios and 42 sociodemographic patient profiles. In diagnostically well-defined scenarios, the combined staging and grading accuracy was reported as 70.5% for GPT-4o and 33.3% for Gemini 2.5 Pro. Analyses based on age, sex, ethnicity, socioeconomic status, and access to healthcare did not identify statistically significant sociodemographic bias after correction for multiple comparisons. However, differences in prediction distributions across certain patient profiles highlight the importance of evaluating algorithmic fairness separately from diagnostic accuracy. The use of hypothetical scenarios also limits the generalizability of the findings to real-world patient assessments (Nantakeeratipat, 2026).

The evaluation of commercial artificial intelligence systems using independent patient data is also important for clinical reliability. Farooqi et al. (2026) investigated the performance of two commercial artificial intelligence systems in detecting dental caries and periodontal bone loss using clinical and radiographic records from 90 patients. For periodontal bone loss, agreement with the reference standard was reported as 78.47% and 73.89% for the two systems, respectively, while their specificities were 94.23% and 93.55%. Although these findings indicate the potential of these systems to support periodontal radiographic assessment, they do not eliminate the need for clinicians to verify diagnostic outputs. Furthermore, the single-center design and limited sample size should be considered when generalizing the findings to different clinical settings (Farooqi et al., 2026).

In addition to the clinical reliability of artificial intelligence systems, patient autonomy, data privacy, algorithmic fairness, explainability, and professional responsibility should also be evaluated from an ethical perspective. In its guidance on the development and use of artificial intelligence in healthcare, the World Health Organization (WHO, 2021) identified six fundamental ethical principles: protecting human autonomy; promoting human well-being and safety; ensuring transparency and explainability; fostering responsibility and accountability; ensuring inclusiveness and equity; and promoting systems that are sustainable and responsive to changing needs. In periodontology, these principles require the secure processing of radiographic images and clinical patient records, evaluation of algorithmic performance across different patient groups, and critical interpretation of artificial intelligence recommendations by clinicians. In particular, automation bias, which may arise from uncritically accepting algorithmic outputs, and the determination of responsibility for inappropriate treatment decisions are important considerations in clinical practice. Therefore, artificial intelligence systems should be regarded as clinical support tools used

under human supervision rather than independent decision-making mechanisms that eliminate the professional responsibility of periodontologists (WHO, 2021).

The reliable use of artificial intelligence systems in periodontology requires the combined assessment of clinical validity, data security, and ethical responsibilities beyond algorithmic performance. Therefore, independent validation, transparent reporting, and clinician oversight are fundamental requirements for translating these technologies into clinical practice.

7. Future Perspectives

One of the future areas of development for artificial intelligence applications in periodontology is the integrated analysis of radiographic images, intraoral photographs, and clinical periodontal data. Multimodal artificial intelligence systems may enable periodontal bone loss, probing depth, clinical attachment level, furcation involvement, and patient-specific risk factors to be evaluated within a single decision support system. In addition to determining the current periodontal status, this approach may contribute to predicting the risk of disease progression and treatment response at the individual level. However, the clinical validity of such integrated systems and their effects on patient outcomes have not yet been sufficiently established (Tichy et al., 2026).

The integration of large language models with current clinical guidelines and validated scientific sources represents another area with potential for advancement in periodontal decision support. Chatzopoulos et al. (2025) evaluated the responses of four large language models to 10 clinical questions related to periodontology in accordance with scientific evidence and the guidelines of the European Federation of Periodontology (EFP). The models' mean scores ranged from 6.30 to 8.29 out of 10, with GPT-4 achieving the highest mean score. However, differences in the accuracy and comprehensiveness of responses were reported among the models. In the future, the development of systems supported by retrieval of information from scientific sources may improve the currency, verifiability, and traceability of periodontal treatment recommendations. Nevertheless, the clinical reliability of these systems must be demonstrated through independent evaluations (Chatzopoulos et al., 2025).

A primary requirement for integrating artificial intelligence into routine periodontal practice is the prospective evaluation of developed systems across different centers and patient populations. Future research should focus not only on algorithmic accuracy and predictive performance but also on their effects on the consistency of clinical decisions, treatment outcomes, patient adherence, and healthcare processes. Furthermore, the ability of clinicians to understand the limitations of artificial intelligence outputs, compare recommendations with

scientific evidence, and critically question them when necessary is one of the fundamental conditions for the safe and responsible use of these technologies (Chatzopoulos et al., 2025; Tichy et al., 2026).

Conclusion

Artificial intelligence is a rapidly evolving field of research with the potential to support diagnostic assessment, disease classification, risk prediction, and treatment planning in periodontology. In particular, deep learning-based image analysis methods have demonstrated promising results in identifying radiographic alveolar bone loss, detecting periodontal defects, and evaluating intraoral images. In addition, machine learning models utilizing clinical and demographic data offer new opportunities for predicting periodontal disease progression and the risk of tooth loss. Multimodal imaging systems, digital patient monitoring applications, and large language models are further expanding the applications of artificial intelligence in periodontal clinical decision support.

However, the high algorithmic performance values reported in current research do not necessarily indicate that the clinical effectiveness and reliability of these systems have been conclusively demonstrated. Limited dataset diversity, methodological differences, a lack of independent external validation, and insufficient evidence regarding long-term clinical outcomes are among the main limitations preventing their adoption in routine clinical practice. Therefore, future studies should employ multicenter and prospective designs involving different patient populations and evaluate not only the diagnostic accuracy of artificial intelligence systems but also their effects on clinical decisions and patient outcomes.

In conclusion, artificial intelligence should be regarded not as an independent decision-making mechanism that replaces clinical judgment in periodontology, but as a complementary tool that supports diagnostic and treatment processes. The safe integration of these technologies into clinical practice depends on the development of scientifically validated models, the protection of patient data, algorithmic transparency, and continued clinician oversight.

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Chapter 7

Host Modulation in Periodontal Therapy: From Biological Mechanisms to Innovative Therapeutic Strategies

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Abstract

Periodontitis is a chronic disease characterized by progressive destruction of periodontal tissues resulting from interactions between dysbiotic biofilm and the host immune-inflammatory response. Host modulation aims to complement conventional periodontal therapy by targeting the destructive components of the inflammatory response alongside microbial control. This chapter evaluates the biological foundations of host modulation in periodontitis, pharmacological and adjunctive therapeutic strategies, and emerging experimental approaches in light of the available evidence. The biological foundations addressed include biofilm–host interactions, innate and adaptive immune responses, inflammatory mediators, matrix metalloproteinases, oxidative stress, the RANK/RANKL/OPG axis, and mechanisms of inflammation resolution. The pharmacological approaches examined include subantimicrobial-dose doxycycline, nonsteroidal anti-inflammatory drugs, bisphosphonates, statins, and metformin, while nutritional and bioactive strategies include omega-3 fatty acids, melatonin, curcumin, and probiotics. Emerging strategies, including specialized pro-resolving mediators, complement- and cytokine-targeted therapies, immune cell modulation, extracellular vesicles, and epigenetic approaches, are also discussed. Although the available evidence indicates that some adjunctive interventions may provide additional improvements in short-term clinical parameters, high between-study heterogeneity, low-to-moderate certainty of evidence, limited follow-up periods, and a lack of independent validation restrict the generalizability of the findings. The European Federation of Periodontology (EFP) S3 guideline likewise recommends against the routine use of most of the pharmacological agents examined as adjuncts to subgingival instrumentation. In conclusion, although host modulation is a biologically justified and potentially promising field, the available data are insufficient for translation into routine clinical practice. Future multicenter, long-term studies incorporating patient-centered outcomes are necessary to determine the actual clinical value of these approaches.

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1. Introduction

Periodontitis is a chronic, multifactorial inflammatory disease associated with dysbiotic dental biofilm and characterized by progressive destruction of the tooth-supporting tissues. Its principal features include clinical attachment loss, radiographic alveolar bone loss, periodontal pocket formation, and gingival bleeding (Papapanou et al., 2018). Periodontal therapy is a stepwise process encompassing improvements in oral hygiene, risk factor control, subgingival instrumentation, periodontal surgery when indicated, and supportive periodontal care. Reassessment of the treatment response guides the planning of subsequent interventions and long-term care (Sanz et al., 2020).

Host modulation is an adjunctive approach intended to reduce the destructive components of the inflammatory response alongside conventional periodontal therapy. Its biological rationale rests on considering the host response to microbial stimuli as a therapeutic target in addition to controlling those stimuli. Host modulation is therefore regarded as an approach that complements biofilm control (Preshaw, 2018). Nevertheless, the existence of a biological rationale for an intervention does not mean that it is recommended for clinical use. The clinical role of adjunctive therapies should be determined by jointly evaluating efficacy, the magnitude of benefit, safety, and the reliability of the evidence (Sanz et al., 2020).

This chapter aims to examine the biological foundations, therapeutic possibilities, and clinical limitations of host modulation in the treatment of periodontitis. The mechanisms associated with the inflammatory response and periodontal tissue destruction will first be described, followed by an evaluation of pharmacological, nutritional, bioactive, and microbiome-related adjunctive approaches and emerging therapeutic strategies. The efficacy, safety, and clinical applicability of these approaches will be discussed while distinguishing experimental findings from evidence obtained in human studies.

2. Biological Foundations of Host Modulation in Periodontitis

2.1. Biofilm–Host Interactions and Immune Dysregulation

The periodontal biofilm–host relationship is shaped by the composition and functions of the microbial community, interactions within that community, the host response, and local environmental conditions (Hajishengallis et al., 2023). Homeostasis denotes a balanced relationship between host tissues and the resident microbiota, whereas dysbiosis refers to a disease-associated imbalance

in the relative composition of the microbial community or in the effects of its members on the community (Lamont & Hajishengallis, 2015).

Studies of the human subgingival microbiota have shown that increases in bacterial biomass and diversity in periodontitis are accompanied by changes in the relative distribution of community members. The presence of certain disease-associated taxa at healthy sites and health-associated microorganisms at periodontitis sites indicates that this shift cannot be explained solely by the presence or absence of particular species (Abusleme et al., 2013). The effects of microorganisms on the community may also differ from their numerical abundance. In a mouse model, low-abundance *Porphyromonas gingivalis* altered the amount and composition of the resident microbiota, leading to inflammatory periodontal bone loss. The absence of bone loss when the commensal microbiota was absent or the relevant complement receptors were deficient demonstrated the joint involvement of the microbial community and the host response in this model (Hajishengallis et al., 2011).

The effects of interventions targeting the host response on the microbial environment have also been demonstrated experimentally. In a rat model of periodontitis, modulation of local inflammation was accompanied by changes in inflammation-related gene expression and the composition of the subgingival microbiota (Lee et al., 2016). These experimental findings link the biological rationale for host modulation not only to limiting tissue destruction but also to regulating host–microbiota interactions (Hajishengallis et al., 2011; Lee et al., 2016).

2.2. Innate and Adaptive Immune Responses

An immune network comprising neutrophils, monocyte–macrophage and dendritic cell populations, innate lymphoid cells, and various T lymphocyte subsets has been identified in healthy human gingiva. The T lymphocyte population includes $CD4^+$ cells and cells with a memory phenotype, as well as a subset consistent with $Foxp3^+$ regulatory T cells. In periodontitis, the proportion of IL-17-producing cells among $CD4^+$ T cells is increased (Dutzan et al., 2016). Resident tissue cells also contribute to the organization of this cellular network. Single-cell analysis of the human oral mucosa has demonstrated the expression of chemokines associated with neutrophil recruitment in stromal and epithelial cells. In periodontitis, the increased inflammatory response of these cells is accompanied by the accumulation of neutrophils and other leukocytes in the tissue (Williams et al., 2021).

Macrophage-associated responses differ between the inflammatory and healing phases. In human gingival samples, M1-associated markers decreased

and M2-associated markers increased following nonsurgical periodontal therapy; similar changes were observed during the resolution phase of inflammation in a mouse model. These findings demonstrate a shift in response patterns but do not establish that all macrophages directly convert from one phenotype to another (Uttamani et al., 2024). Regarding B cells, increased expression of APRIL and BLyS, together with B cell and plasma cell markers, has been detected in human periodontitis tissues. In the same study, reduced bone loss during the later stages of disease in B cell-deficient mice supported the contribution of these cells to periodontal destruction in that experimental model (Abe et al., 2015). Approaches aimed at therapeutically regulating immune cells encompass regulatory T and B cells as well as inflammation-associated cells. Further preclinical research and randomized clinical trials are required to translate these approaches into clinical practice (Junxian et al., 2023).

2.3. Inflammatory Mediators and Signaling Pathways

In periodontal inflammation, cytokines are components of the communication network linking responses that promote and limit inflammation. Accordingly, cytokine-related changes are evaluated within the relationships among different cell populations and regulatory mechanisms rather than solely as increases in individual mediators (Neurath & Kesting, 2024). Signaling pathways such as NF-κB, MAPK, and JAK/STAT participate in translating extracellular stimuli into cellular responses; their relationships with periodontal inflammation and tissue destruction are considered according to the cellular context (de Molon et al., 2026). Interactions between complement and microbial recognition receptors are important in regulating host defense. In experimental macrophage systems, the response elicited jointly by *Porphyromonas gingivalis* and C5a increased intracellular cAMP levels in a manner dependent on the C5a receptor and TLR2. In this interaction, protein kinase A activation was associated with reduced nitric oxide production and enhanced intracellular bacterial survival (Wang et al., 2010). In mouse models examining the contribution of C3, C3 deficiency was associated with reduced periodontal inflammation, bone loss, and TNF, IL-1β, IL-6, IL-17A, and IL-23 responses. The same study demonstrated that C3 contributed to the long-term persistence of the dysbiotic microbial community; intervention findings in a nonhuman primate model also provided experimental support for targeting C3 (Maekawa et al., 2014).

Lipid mediators exert different functional effects. In a rabbit model of periodontitis, administration of prostaglandin E_2 and leukotriene B_4 increased periodontal destruction, whereas resolvin E1 promoted inflammation resolution and tissue healing (Hasturk et al., 2007).

2.4. Matrix Metalloproteinases and Connective Tissue Destruction

The coexistence of proenzyme and active forms of MMP-8 and MMP-13 in human periodontitis samples indicates that activation status, as well as total enzyme abundance, should be considered when evaluating the proteolytic environment. In inflamed gingiva, MMP-8 immunoreactivity has been demonstrated in neutrophils, the sulcular epithelium, and plasma cells, whereas MMP-13 immunoreactivity has been demonstrated in the sulcular epithelium and macrophage-like cells (Kiili et al., 2002). The proportion and activity of active MMP-13 were higher at periodontal sites exhibiting clinical progression than at inactive sites (Hernandez et al., 2006).

Enzyme–inhibitor relationships may also vary according to disease activity. In human samples examined for MMP-13 and tissue inhibitor of metalloproteinases-1 (TIMP-1), total levels did not differ significantly between active and inactive sites; however, a positive relationship between the two molecules was reported at inactive sites and an inverse relationship at active sites (Hernández et al., 2007). In periodontitis tissue explants, the addition of MMP-13 increased MMP-9 activation, and a selective MMP-13 inhibitor prevented this effect, providing experimental support for an activation link between these enzymes (Hernández Ríos et al., 2009). MMP functions are not limited to tissue destruction. Greater regional alveolar bone loss in MMP-8-deficient mice with *Porphyromonas gingivalis*-induced experimental periodontitis indicated that this enzyme might also contribute to protection in that model (Kuula et al., 2009). A recent review evaluating the diverse functions of MMPs in oral health and disease likewise emphasizes the importance of considering these enzymes within their biological contexts (Atanasova et al., 2023).

2.5. Oxidative Stress and Redox Imbalance

Peripheral blood neutrophils from individuals with periodontitis exhibited greater extracellular release of reactive oxygen species (ROS) in the absence of stimulation than those from healthy controls, whereas the difference in total ROS production was not significant. Following stimulation through Fcγ receptors, both total ROS production and extracellular release were increased (Matthews et al., 2007).

Changes in oxidant–antioxidant measurements vary according to the biological sample. The total antioxidant capacity of gingival crevicular fluid was lower in individuals with periodontitis and reached control levels following nonsurgical periodontal therapy. In plasma, however, no significant differences were detected between groups at baseline or following treatment. The authors suggested that the reduction in local capacity might be a consequence of the inflammatory lesion (Chapple et al., 2007). Similarly, malondialdehyde levels were elevated in saliva and gingival crevicular fluid, whereas the difference in serum was not significant; total oxidant status was increased in all three sample types (Akalın et al., 2007). Salivary

levels of 8-hydroxy-2′-deoxyguanosine, a marker associated with oxidative DNA damage, were also higher in individuals with untreated periodontitis than in healthy controls. These levels decreased in the patient subgroup reassessed following initial periodontal therapy (Takane et al., 2002). In their therapeutic evaluation of oxidative processes, Sczepanik et al. (2020) considered antioxidant approaches as potential adjuncts to conventional therapy. Yang and Yang (2025), however, emphasized uncertainty regarding the thresholds separating physiological from pathological ROS levels, the lack of consensus on appropriate dosing, and insufficient evidence of long-term clinical efficacy.

2.6. Osteoimmunology and Alveolar Bone Resorption: The RANK/RANKL/OPG Axis

The RANK/RANKL/osteoprotegerin (OPG) axis participates in the regulation of osteoclast differentiation and bone resorption. The requirement for RANK in osteoclast development was demonstrated by arrested osteoclast development and osteopetrosis in mice lacking this receptor (Dougall et al., 1999). RANKL promotes osteoclast differentiation and the resorptive activity of mature osteoclasts, whereas OPG inhibits these effects (Lacey et al., 1998). The reduction of experimental bone loss following recombinant OPG administration further supported this regulatory function (Simonet et al., 1997). Soluble RANKL levels were higher in human periodontitis tissues than in healthy tissues, whereas the difference in OPG levels was not significant. The same study demonstrated RANKL production and the capacity to support osteoclast formation in B and T lymphocytes obtained from periodontal lesions; adding OPG to the cell culture suppressed osteoclast differentiation and resorption pit formation (Kawai et al., 2006). The cellular sources of RANKL have also been examined in experimental models. In a mouse model of periodontitis, deletion of RANKL from osteoblast-lineage cells or periodontal ligament cells markedly reduced bone loss. Deletion from T cells produced a more limited reduction, whereas deletion from B cells did not provide significant protection (Tsukasaki et al., 2018). In another mouse ligature model, loss of RANKL predominantly in osteocytes and additionally in mature osteoblasts reduced bone loss; however, bone loss was not prevented in mice lacking mature B and T lymphocytes (Kittaka et al., 2023). Based on their finding that NOD1 stimulation increased RANKL expression in osteocytes, Kittaka et al. (2023) proposed the NOD1–RANKL axis as a potential therapeutic target. This proposal is based on experimental model findings rather than an intervention with demonstrated clinical efficacy in humans (Kittaka et al., 2023).

2.7. Inflammation Resolution and Tissue Homeostasis

Inflammation resolution is a process involving the active regulation of cellular responses and mediator production. Experiments on acute inflammation have demonstrated that early leukotriene and prostaglandin production is followed by lipoxin formation alongside a reduction in neutrophil accumulation. In human neutrophils, the prostaglandin E_2-induced shift in lipid mediator production from leukotriene B_4 toward lipoxin A_4 formation has been termed "lipid mediator class switching" (Levy et al., 2001). Clearance of apoptotic cells also contributes to this regulation. In macrophages differentiated from human monocytes, phagocytosis of apoptotic neutrophils reduced IL-1β, IL-8, and TNF-α production while increasing TGF-β_1 production. The investigators demonstrated that this response was mediated through autocrine and paracrine mechanisms (Fadok et al., 1998).

In individuals examined under a diagnosis of localized aggressive periodontitis, maresin-1 production was reduced in macrophages, and the capacity to phagocytose and kill periodontal bacteria was reduced in both macrophages and neutrophils. Adding maresin-1 to the cell culture partially restored these functions; these findings arose from experimental evaluation of human-derived cells rather than treatment administered to patients (Wang et al., 2016). The relationship between resolution mediators and tissue repair has been demonstrated in animal models. In a rabbit model of periodontitis, resolvin E1 administration was associated with the formation of new cementum, periodontal ligament, and bone (Hasturk et al., 2007). In miniature pigs, a nanoformulation containing benzo-lipoxin A_4, administered as an adjunct to surgical treatment, also produced greater bone gain than surgery alone; new cementum and connective tissue fibers attached to the root surface were demonstrated (Van Dyke et al., 2015). In their synthesis of the literature, Lee and Tribble (2023) noted that the effects of resolution mediators may be accompanied by changes in oral microbiota composition and identified mediator–microbiota interactions as an area for further research.

3. Pharmacological Approaches to Host Modulation: Mechanisms and Clinical Evidence

3.1. Subantimicrobial-Dose Doxycycline and Matrix Metalloproteinase Inhibition

Subantimicrobial-dose doxycycline (SDD) has been evaluated as a systemic adjunctive therapy targeting host-derived collagenolytic activity (Sanz et al., 2020). In a multicenter, placebo-controlled study, administration of 20 mg doxycycline twice daily for nine months as an adjunct to root planing produced greater clinical attachment gain and probing depth reduction than placebo.

Treatment was generally well tolerated, and no acquisition of doxycycline resistance was reported (Caton et al., 2000).

Nevertheless, after considering the magnitude of the additional clinical benefit and the burden associated with prolonged systemic use, the EFP S3 guideline recommended against the use of SDD as an adjunct to subgingival instrumentation (Sanz et al., 2020).

3.2. Nonsteroidal Anti-Inflammatory Drugs

The biological rationale for nonsteroidal anti-inflammatory drugs (NSAIDs) rests on the suppression of prostaglandin synthesis. The original experimental evidence underlying this mechanism includes the demonstration that aspirin and indomethacin inhibit prostaglandin synthesis in lung homogenates (Vane, 1971). Both local and systemic administration have been investigated in periodontal therapy (Sanz et al., 2020). A network meta-analysis of 13 randomized studies reported additional short-term improvements in periodontal parameters with certain systemic regimens. However, the outcomes of combinations containing doxycycline or omega-3 cannot be attributed to NSAIDs alone (Li et al., 2026).

The absence of reported adverse events in the meta-analysis does not establish long-term safety (Li et al., 2026). The EFP S3 guideline recommends against the use of local or systemic NSAIDs as adjuncts to subgingival instrumentation (Sanz et al., 2020).

3.3. Bisphosphonates

Bisphosphonates, which aim to limit bone resorption, have been investigated as adjuncts to periodontal therapy through local gel formulations and systemic administration. A meta-analysis of 13 studies reported additional clinical improvements with both routes of administration; however, high heterogeneity in local applications, the small number of studies on systemic administration, and a maximum follow-up of 12 months limited the generalizability of the findings (Muniz et al., 2021).

The risk of bisphosphonate-associated osteonecrosis of the jaw should be considered when evaluating safety (Ruggiero et al., 2022). The absence of reported osteonecrosis in periodontal studies does not confirm safety when this outcome has not been systematically monitored (Muniz et al., 2021). The EFP S3 guideline recommends against the use of local or systemic bisphosphonates as adjuncts to subgingival instrumentation (Sanz et al., 2020).

3.4. Statins

The biological rationale for the use of statins in bone repair includes the promotion of bone formation alongside increased BMP-2 gene expression in cell and rodent experiments; these findings are not clinical outcomes obtained in periodontal patients (Mundy et al., 1999). A meta-analysis evaluating local statins as adjuncts to periodontal therapy reported approximately 1.4–2.3 mm of additional probing depth reduction and 1.7–2.2 mm of clinical attachment gain at six months. However, because of high heterogeneity, these values should not be interpreted as effect sizes applicable to all patients (Yoshida et al., 2026).

Although local applications were generally well tolerated, standardized protocols and long-term studies are needed (Yoshida et al., 2026). The EFP S3 guideline does not recommend local statin gels as adjuncts to subgingival instrumentation (Sanz et al., 2020).

3.5. Metformin

Experimental support for the effects of metformin on the periodontal host response includes reductions in inflammation and bone loss following oral administration in a rat model of periodontitis. At the effective dose of 50 mg/kg, AMPK gene expression increased, whereas NF-κB p65 expression and inflammatory mediator levels decreased; these findings do not directly establish the mechanism of local gel application in humans (Araújo et al., 2017). A meta-analysis of six clinical studies reported approximately 1.87 mm of additional probing depth reduction and 2.14 mm of clinical attachment gain at six months with local 1% metformin gel as an adjunct to conventional therapy. High heterogeneity, small samples, and the concentration of studies within particular research groups limited confidence in the findings (Haba et al., 2025).

Despite reports of good tolerability, the EFP S3 guideline recommended against the use of local metformin gel as an adjunct to subgingival instrumentation, emphasizing the off-label nature of the investigated gel formulation and the need for independent validation (Sanz et al., 2020).

4. Nutritional, Bioactive, and Microbiome-Related Adjunctive Strategies

4.1. Omega-3 Fatty Acids and Combination Strategies

The biological rationale for omega-3 fatty acids in periodontal inflammation is considered in relation to specialized pro-resolving mediators; however, omega-3 supplementation and direct administration of these mediators are distinct interventions (Lee & Tribble, 2023). A meta-analysis evaluating oral omega-3 supplementation as an adjunct to nonsurgical periodontal therapy reported additional clinical attachment gain and probing depth reduction based on a

quantitative synthesis of 18 studies. High heterogeneity and low-to-moderate certainty of evidence limit the interpretation of these findings (Naghsh et al., 2026).

Another review examining omega-3 use alone or in combination with low-dose aspirin did not consistently demonstrate the superiority of the combination. Differences in dose, EPA/DHA ratio, and duration of administration made it difficult to establish a standard regimen; the absence of reported adverse effects was considered insufficient to confirm long-term safety (Benincasa et al., 2026).

4.2. Antioxidants and Selected Bioactive Compounds

Melatonin and curcumin have been evaluated in clinical studies as adjuncts to periodontal therapy. A meta-analysis of 18 randomized studies of melatonin reported additional clinical attachment gain and probing depth reduction at certain follow-up periods; however, no significant additional benefit for probing depth at six months or consistent improvement in bleeding on probing was demonstrated. Prediction intervals that included the null value increased uncertainty regarding the reproducibility of the findings across clinical settings (Abusamak et al., 2026).

Local curcumin/turmeric-derived formulations provided additional probing depth reduction compared with inactive control interventions; the certainty of evidence was rated as low (Wu et al., 2026). Mild, transient symptoms were reported in melatonin studies, and incomplete safety reporting was emphasized (Abusamak et al., 2026). In curcumin studies, the lack of systematic adverse event assessment likewise limited definitive conclusions about long-term safety (Wu et al., 2026).

4.3. Probiotics, Prebiotics, and Synbiotics

A network meta-analysis encompassing 33 studies of probiotics reported additional probing depth reduction and clinical attachment gain with certain interventions. However, the certainty of evidence was very low for most comparisons, and heterogeneity in microbiological data limited quantitative synthesis. Because different microorganisms and administration regimens were used, the findings should not be generalized to all probiotic products (Mendonça et al., 2024).

In a placebo-controlled study involving individuals with type 2 diabetes and periodontal disease, the change in serum IL-6 was lower in the adjusted analysis following eight weeks of supplementation with a multi-probiotic–fructooligosaccharide combination than in the control group. This finding concerns a marker of systemic inflammation; it does not demonstrate

improvement in the subgingival microbiome or direct immune modulation in periodontal tissues. The combination design also precludes determination of the independent effect of the prebiotic component (Yarahmadi et al., 2024).

5. Emerging and Experimental Host Modulation Strategies

5.1. Specialized Mediators Promoting Inflammation Resolution

A mouth rinse containing the lipoxin analog $BLXA_4$ was evaluated in a randomized study involving 127 participants with gingival inflammation. During 28 days of administration, adverse event frequency did not differ significantly between groups, and no serious adverse events related to the investigational product were reported. Superiority over placebo in terms of the gingival index varied according to the analytical model used. The study provides short-term tolerability and preliminary efficacy data; it does not demonstrate bone regeneration or long-term disease control in periodontitis (Hasturk, Schulte, et al., 2021).

5.2. Cytokine- and Complement-Targeted Therapies

In a phase IIa human study in which the complement C3 inhibitor AMY-101 was administered by local injections, gingival inflammation and bleeding on probing decreased compared with placebo, and administration was well tolerated throughout the study. The absence of significant changes in probing depth and clinical attachment level requires that the findings be interpreted within the limits of a gingival anti-inflammatory effect (Hasturk, Hajishengallis, et al., 2021). In an animal study targeting a cytokine, local anti-IL-17A administration reduced alveolar bone loss and osteoclast activity in a mouse ligature model (Pacheco et al., 2021).

5.3. Modulation of Immune Cell Phenotypes and Functions

In a mouse model of periodontitis, local administration of TGF-β, rapamycin, and IL-2 increased the proportion of FOXP3-positive T cells among total T cells in periodontal tissues and reduced alveolar bone loss. Because the intervention began concurrently with disease induction, the study was preventive in nature. The authors stated that further clarification was needed to determine whether the bone-protective effect arose directly from regulatory T cell functions or from other cellular effects (Greene et al., 2022).

5.4. Approaches Targeting the NLRP3 Inflammasome

Osteoclast formation and alveolar bone loss were reduced in NLRP3-deficient mice. The pharmacological inhibitor MCC950 reduced osteoclast differentiation

in cell culture and, when administered systemically in a mouse ligature model, reduced the number of osteoclast precursors and bone resorption. Evaluation of the intervention in a short-term experiment beginning at disease induction limits its translation to established human periodontitis (Chen et al., 2021).

5.5. Cell-Derived Products and Extracellular Vesicles

Apoptotic extracellular vesicles derived from human periodontal ligament stem cells increased markers associated with the M2 macrophage phenotype in cell experiments; inhibition of NF-κB or S100A9 attenuated this response. Conditioned medium from macrophages that had interacted with the vesicles promoted osteogenic differentiation of periodontal ligament stem cells. Reduced inflammation and alveolar bone repair were reported following local injection in a mouse model of periodontitis; the use of human-derived cells does not mean that clinical efficacy has been demonstrated in humans (Zhang et al., 2025).

5.6. Epigenetic and Nucleic Acid-Based Strategies

The BET inhibitor JQ1 suppressed inflammatory mediator production and osteoclast differentiation in cell culture and reduced osteoclast numbers and bone loss in a mouse model of periodontitis (Meng et al., 2014). GalNAc-conjugated C3-targeting siRNA reduced hepatic C3 expression and circulating C3 levels in mice and reduced the Th17 response, RANKL expression, and bone resorption in the periodontal model. This approach is a liver-targeted systemic intervention, and dosing began before disease induction (Chen et al., 2025).

5.7. Targeted Delivery Systems and Controlled-Release Biomaterials

Local delivery systems have been used to administer the experimental interventions described above. Anti-IL-17A was delivered through controlled-release poly(lactic-co-glycolic acid) (PLGA) microparticles two days after ligature placement; the empty carrier did not limit bone loss (Pacheco et al., 2021). One-week release profiles were characterized for microspheres carrying TGF-β, rapamycin, and IL-2 (Greene et al., 2022). Both studies were based on mouse models and do not establish the comparative superiority of different delivery systems in humans (Pacheco et al., 2021; Greene et al., 2022).

6. Clinical Translation and Critical Appraisal of the Evidence

6.1. Integration with Conventional Periodontal Therapy

The EFP S3 guideline structures periodontal therapy as a stepwise process extending from biofilm and risk factor control to supportive care (Sanz et al., 2020). Donos et al. (2020) evaluated host modulators as adjuncts to nonsurgical

periodontal therapy. Accordingly, the reported gains relate to adjunctive use and do not demonstrate efficacy when these agents are used in place of mechanical therapy (Donos et al., 2020).

6.2. Patient Selection and Factors Modifying the Response

Interventions for smoking cessation and diabetes control are recommended components of periodontal therapy (Sanz et al., 2020). However, the evidence evaluated by Donos et al. (2020) excluded studies involving participants with diagnosed systemic diseases and included patient groups with differing smoking status. This review does not provide a direct recommendation for selecting a particular host modulator for patients with diabetes or those who smoke (Donos et al., 2020).

6.3. Local and Systemic Administration: Timing and Treatment Duration

Because the local and systemic interventions examined by Donos et al. (2020) involved different agents and protocols, they do not establish the superiority of either route through direct comparison. The authors considered patient adherence and the potential for adverse effects during systemic doxycycline use over several months among the clinical concerns. The review does not define a common initiation time or treatment duration applicable to all host modulators (Donos et al., 2020).

6.4. Clinical Significance and Sustainability of Treatment Outcomes

Loos and Needleman (2020) recommend evaluating periodontal treatment outcomes in terms of tooth retention, the need for retreatment, function, pain, and quality of life, alongside mean changes in clinical measurements. Jackson et al. (2025) identified deficiencies in the validity and responsiveness of instruments used to measure patient-reported outcomes. In a review of long-term periodontal interventions that was not specific to host modulation, none of the included studies reported patient-reported outcomes (Rattu et al., 2026).

6.5. Safety and Clinical Recommendations

Donos et al. (2020) emphasized that, despite reports of generally good tolerability for the local agents examined, safety requires confirmation before routine use. The EFP S3 guideline does not recommend local statin or metformin gels, local or systemic bisphosphonates, or NSAIDs as adjuncts to subgingival instrumentation. It also recommends against systemic subantimicrobial-dose doxycycline. These recommendations are based on considering the benefit–harm

balance alongside additional clinical gains when evaluating adjunctive therapies (Sanz et al., 2020).

7. Limitations of the Current Evidence and Future Perspectives

7.1. Methodological Limitations and Between-Study Heterogeneity

Differences in mechanical treatment protocols, participant characteristics, and outcome measures make comparisons among host modulation studies difficult. The concentration of data on certain local agents within the same research group and the conduct of studies in academic settings also present limitations regarding independent validation and generalizability (Donos et al., 2020). In biomarker research, variability in sampling methods, analytical techniques, and thresholds creates similar problems (Rakic et al., 2025).

7.2. Gaps in Long-Term Evidence and the Need for Standardization

Loos and Needleman (2020) emphasized the contribution of short-term studies to identifying promising treatments and the importance of long-term studies in guiding treatment decisions. Manufacturing quality and safety require verification for local host modulators (Donos et al., 2020). The authors of the AMY-101 study likewise recommended further refinement of the dose, injection frequency, and route of administration in subsequent studies (Hasturk, Hajishengallis, et al., 2021).

7.3. Challenges in Translating Preclinical Findings into Clinical Practice

Zhang et al. (2025) noted that the components responsible for the effects of the experimental vesicle therapy had not yet been identified and that safety and efficacy required confirmation through further research. The scope of early human studies may also limit translation: because participation in the AMY-101 study was based on gingival inflammation rather than periodontal destruction, the authors recommended cautious interpretation of the findings in relation to periodontitis (Hasturk, Hajishengallis, et al., 2021).

7.4. Biomarkers and Personalized Host Modulation

Studies validating host-derived biomarkers for predicting disease progression or treatment response are limited; the current synthesis does not provide a validated approach for selecting a particular host modulator (Rakic et al., 2025). The review of genetic biomarkers likewise identified no clinical test that reliably distinguishes progression from stability or predicts disease resolution. Polygenic risk scores were considered potential tools requiring future validation (Dommisch et al., 2025).

7.5. Priorities for Future Clinical Research

Adequately powered, multicenter studies conducted by independent research groups are needed (Donos et al., 2020). Clinical endpoints are recommended to encompass tooth retention, the need for retreatment, and function (Loos & Needleman, 2020). Patient-reported outcomes require measurement instruments developed with patient involvement and validated longitudinally (Jackson et al., 2025). The predictive value of biomarkers for treatment response should also be evaluated in longitudinal studies using standardized methods (Rakic et al., 2025).

8. Conclusion

Host modulation is a biologically justified approach aimed at limiting inflammatory tissue destruction in periodontitis. Although additional improvements in short-term clinical parameters have been reported for some pharmacological, nutritional, and experimental strategies, the current evidence remains insufficient because of high heterogeneity, limited follow-up periods, and low-to-moderate certainty of evidence. The EFP S3 guideline likewise does not recommend most of the agents examined for routine use as adjuncts to subgingival instrumentation. Therefore, host modulation should be regarded as a complementary field of research that requires more robust evidence for translation into clinical practice, rather than as a replacement for conventional periodontal therapy.

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Chapter 8

Contemporary Management of Impacted Third Molars: From Risk Assessment to Complication Prevention

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Abstract

Impacted third molars represent one of the most common conditions encountered in oral and maxillofacial surgical practice. Although third molar removal is among the most frequently performed dentoalveolar procedures, management is not limited to the technical act of extraction. Contemporary treatment requires careful assessment of whether intervention is indicated, evaluation of the anatomical relationship of the tooth to adjacent structures, estimation of surgical difficulty, identification of patient-specific risk factors, selection of an appropriate surgical approach, and implementation of strategies designed to minimize postoperative morbidity and potentially permanent complications [1–4]. Particular attention is required for mandibular third molars located in close proximity to the inferior alveolar canal, because injury to the inferior alveolar nerve may result in persistent sensory disturbance and significant deterioration in quality of life [5–9].

Management of asymptomatic and disease-free impacted third molars remains controversial. While established pathological conditions such as recurrent pericoronitis, nonrestorable caries, periodontal destruction, external root resorption, cystic or neoplastic lesions, and infection generally provide accepted indications for treatment, routine removal of all asymptomatic impacted third molars is not supported uniformly by international guidelines [1–4]. The decision should therefore be individualized according to the patient's age, tooth position, likelihood of future pathology, relationship with the adjacent second molar, operative risk, general health, and ability to undergo long-term clinical and radiographic surveillance. Longitudinal studies indicate that retained third molars may be associated with periodontal and carious pathology affecting adjacent second molars, although evidence remains insufficient to establish universal prophylactic removal as the preferred strategy [10–14].

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Panoramic radiography remains the initial imaging method for most patients, while cone-beam computed tomography (CBCT) is valuable when conventional imaging indicates a close relationship between the mandibular third molar and the inferior alveolar canal and when three-dimensional information is expected to alter treatment planning [5–8]. Coronectomy has become an established risk-reduction strategy for selected vital mandibular third molars with a high predicted risk of inferior alveolar nerve injury [15–20]. Contemporary complication prevention also requires attention to lingual nerve protection, atraumatic bone removal and tooth sectioning, appropriate flap design, infection prevention, effective postoperative pain and inflammation control, and early recognition of complications such as alveolar osteitis, infection, hemorrhage, nerve dysfunction, periodontal defects, and mandibular fracture [21–30].

This chapter reviews contemporary concepts in the assessment and management of impacted third molars, with particular emphasis on surgical decision-making, radiographic risk assessment, inferior alveolar and lingual nerve protection, coronectomy, operative technique, postoperative complications, and evidence-based strategies for reducing surgical morbidity.

Keywords: impacted third molar, wisdom tooth, mandibular third molar, inferior alveolar nerve, lingual nerve, coronectomy, CBCT, third molar surgery, surgical complications, alveolar osteitis.

1. Introduction

Third molars are the last permanent teeth to develop and erupt and demonstrate substantial variation in eruption timing, angulation, root morphology, and anatomical relationship with neighboring structures. When eruption is prevented by insufficient retromolar space, an abnormal eruption pathway, adjacent teeth, bone, soft tissue, or another pathological condition, the tooth may remain partially or completely impacted [1]. Mandibular third molars are particularly important in oral and maxillofacial surgery because their removal may require mucoperiosteal flap elevation, bone removal, tooth sectioning, and manipulation in close proximity to the inferior alveolar and lingual nerves.

Third molar surgery is frequently perceived as a routine procedure, but its biological and anatomical complexity should not be underestimated. Most patients recover without permanent morbidity, yet complications can range from temporary pain and swelling to persistent sensory dysfunction, severe infection, damage to the adjacent second molar, oroantral communication, or mandibular fracture [21,22]. The severity of possible complications means that successful management begins with appropriate case selection rather than surgical technique alone.

The contemporary approach has therefore shifted from the question of whether an impacted third molar can technically be removed to whether removal offers a meaningful benefit relative to the risks of intervention and retention. The 2024 American Association of Oral and Maxillofacial Surgeons clinical paper on impacted third molars recognizes several possible management pathways, including complete removal, coronectomy, and active clinical and radiographic surveillance [1]. This approach emphasizes shared decision-making and individualized risk assessment. In contrast, the National Institute for Health and Care Excellence has historically recommended that surgical removal of impacted third molars should be limited to teeth demonstrating evidence of pathology rather than being undertaken routinely for disease-free impactions [2]. These differences illustrate the continuing international debate concerning prophylactic removal.

The debate is complicated by the fact that the absence of symptoms does not necessarily indicate the absence of disease. Periodontal probing abnormalities, distal caries of the second molar, external root resorption, and radiographic pathological changes may occur in patients who describe their third molars as asymptomatic [10–13]. Conversely, many impacted teeth remain disease-free for prolonged periods, and prophylactic surgery exposes otherwise healthy individuals to immediate surgical risks. Current evidence therefore supports individualized assessment rather than a universal removal or retention policy. A

recent Cochrane review concluded that the available evidence remains insufficient to determine whether asymptomatic disease-free impacted third molars should routinely be removed or retained [3].

Age adds another important dimension to this decision. Surgical difficulty and complication rates generally increase as patients become older, particularly after completion of root formation and increasing bone density [23]. Older patients may also demonstrate established periodontal defects distal to the second molar that do not predictably resolve after third molar removal. At the same time, young patients should not undergo surgery simply because surgery is technically easier at a younger age. The decision should instead integrate expected future disease, operative risk, patient preference, and feasibility of long-term monitoring.

2. Development, Eruption, and Definition of Impaction

Third molar development begins during childhood, while crown completion, root development, and eruption extend through adolescence and early adulthood. Considerable individual variation exists, and radiographic appearance at an early age does not always predict the final position of the tooth. Changes in angulation and eruption pathway can continue during root development.

An impacted third molar is generally defined as a tooth that is unlikely to erupt into a normal functional position because its eruption is obstructed or its spatial relationship within the dental arch prevents normal emergence [1]. Impaction may be completely osseous, partially osseous, or predominantly soft tissue. The clinical relevance of these distinctions extends beyond description because the amount of overlying bone and soft tissue affects surgical access, procedure duration, postoperative inflammation, and risk of complications.

Third molar position is dynamic rather than completely static. Teeth that appear impacted during adolescence may undergo positional changes, and partially erupted teeth may subsequently achieve greater eruption or remain in a plaque-retentive position. Consequently, decisions made early in development should incorporate the possibility of future change rather than treating a single radiographic appearance as permanent.

Root development is similarly important. Removal before complete root maturation may simplify surgery in selected cases because roots may be shorter and less intimately related to the mandibular canal. However, very early intervention lacks justification when there is no reasonable prediction of future pathology. The timing of surgery should therefore reflect a balance between biological development and clinical indication rather than age alone.

3. Classification and Assessment of Surgical Difficulty

Several classification systems are traditionally used to describe mandibular third molar impaction. Winter's classification describes the angulation of the third molar relative to the adjacent second molar, while the Pell and Gregory system evaluates the relationship of the tooth to the anterior border of the ramus and the depth of impaction relative to the occlusal plane [31,32]. Although these classifications remain useful for communication and preliminary assessment, they cannot individually predict operative difficulty or complication risk.

Mesioangular impactions are frequently encountered and may create a plaque-retentive area between the third and second molars. Horizontal impactions can be technically demanding because substantial crown sectioning may be required and the tooth may contact the distal root of the second molar. Vertical impactions may be relatively straightforward when sufficient space exists but can be difficult when deeply positioned. Distoangular mandibular impactions may require greater distal bone removal and can present specific surgical access challenges.

Depth of impaction and available retromolar space also influence difficulty. A deeply positioned tooth surrounded by dense mandibular bone generally requires greater osteotomy and may increase procedure duration. Root number, curvature, divergence, hypercementosis, and proximity to the mandibular canal further modify difficulty. Patient-related factors including age, mouth opening, body habitus, bone density, systemic health, and ability to cooperate are equally important.

Traditional difficulty indices provide a structured method for preoperative assessment but have limited accuracy when used in isolation. Modern risk assessment should integrate clinical examination, panoramic and potentially three-dimensional imaging, patient characteristics, and surgeon experience rather than relying exclusively on a numerical classification score.

4. Indications for Third Molar Removal

The strongest indication for third molar removal is the presence of established pathology that cannot predictably be controlled while retaining the tooth. Recurrent or severe pericoronitis, nonrestorable caries involving the third molar, pulpal or periapical disease unsuitable for conservative treatment, periodontal destruction involving the third or adjacent second molar, external root resorption, cystic disease, tumor-associated pathology, and infection represent generally accepted indications [1,2].

Pericoronitis is particularly common around partially erupted mandibular third molars. The operculum and surrounding soft tissues may create a sheltered environment for bacterial accumulation, producing pain, swelling, trismus,

halitosis, or occasionally spreading infection. A single mild episode does not necessarily mandate removal, particularly if local factors can be corrected, whereas recurrent episodes increase the rationale for definitive treatment.

Caries is another important indication. A partially erupted third molar can create an area that is difficult to clean and may develop caries itself or contribute to distal caries in the adjacent second molar. The restorative prognosis of the second molar is particularly relevant because preventing irreversible damage to a strategically important second molar may justify intervention even when the third molar itself is asymptomatic.

Periodontal disease distal to the mandibular second molar deserves similar attention. An impacted or partially erupted third molar can alter the local periodontal environment and increase plaque retention. Longitudinal studies have demonstrated an association between retained third molars and periodontal pathology involving adjacent second molars [10,11]. However, removal itself can occasionally leave a residual periodontal defect, particularly in older patients with pre-existing attachment loss. The timing of intervention is therefore important.

External resorption of the second molar is a particularly significant radiographic finding because advanced lesions may compromise the prognosis of an otherwise healthy tooth. CBCT can be helpful when conventional imaging suggests resorption but cannot adequately demonstrate its extent. When clinically important resorption is caused by direct third molar contact, removal of the third molar is usually indicated.

Dentigerous cysts and other odontogenic pathological lesions may develop around impacted third molars, although such conditions are substantially less frequent than inflammatory or carious disease. Enlargement of the follicular space should not automatically be interpreted as cystic disease, and suspicious radiographic findings should be evaluated according to lesion morphology, size, clinical context, and, when indicated, histopathological examination.

5. The Asymptomatic Disease-Free Third Molar

Management of the truly asymptomatic and disease-free third molar remains one of the most debated areas of oral surgery. The controversy exists because both surgical removal and long-term retention carry potential disadvantages.

The argument supporting early removal is based partly on observations that surgical morbidity tends to increase with age and that a proportion of retained third molars eventually develops disease [10,23]. Longitudinal evidence has demonstrated associations between retained third molars and pathology of adjacent second molars. In one long-term cohort, retention of soft-tissue impacted

third molars was associated with a substantially increased risk of second molar pathology compared with absence of a third molar [10].

However, these observational relationships do not prove that prophylactic removal of every disease-free third molar provides a net health benefit. Surgical extraction creates immediate morbidity and carries small but real risks of permanent nerve dysfunction, infection, periodontal damage, and other complications. The Cochrane evidence base remains insufficient to support either routine removal or routine retention of every asymptomatic disease-free tooth [3].

This uncertainty explains differences among professional recommendations. NICE recommends against routine prophylactic removal of pathology-free impacted third molars and limits surgical intervention to teeth demonstrating pathological change [2]. AAOMS, while recognizing surveillance as an appropriate management option, places greater emphasis on estimating the future risk of pathology and acknowledges that operative difficulty increases with age [1].

A reasonable contemporary approach is therefore to avoid equating "asymptomatic" with "healthy" and to avoid equating "impacted" with "requires extraction." Clinical probing of the distal second molar, assessment for caries, examination of the surrounding mucosa, appropriate radiographic evaluation, patient age, tooth angulation, expected ability to maintain hygiene, and capacity for regular surveillance should all influence the decision. When retention is selected, it should represent active surveillance rather than abandonment of follow-up.

6. Effects on the Adjacent Second Molar

Preservation of the adjacent second molar is one of the most important considerations in third molar management. The second molar usually has substantially greater functional value than the third molar, and damage to its periodontal support or distal tooth structure can produce long-term consequences.

Mesioangular and horizontal mandibular third molars may create prolonged contact with the distal cervical region of the second molar. This relationship can facilitate plaque retention and increase the risk of distal caries. Recent radiographic studies continue to demonstrate significant associations between mandibular third molar position and distal pathology in adjacent second molars [12,13].

Periodontal damage may develop through a similar mechanism. Partially erupted third molars can create deep distal probing depths and inflammatory periodontal changes around the second molar even in patients without subjective

symptoms. Blakey and colleagues reported clinically significant periodontal findings in a notable proportion of patients with asymptomatic third molars [11].

Removal of the third molar does not invariably restore periodontal health. Younger patients with limited pre-existing defects generally demonstrate better periodontal recovery, while older individuals with deep intrabony defects may retain significant distal periodontal pathology after surgery. Preoperative assessment should therefore identify high-risk periodontal defects, and regenerative or periodontal treatment may be considered in selected cases.

7. Preoperative Clinical Evaluation

Clinical assessment should begin with a detailed medical and dental history. The clinician should identify systemic conditions that may influence anesthesia, infection risk, bleeding, wound healing, or postoperative medication selection. Anticoagulants, antiplatelet agents, immunosuppressive treatment, antiresorptive medications, allergies, pregnancy, and previous adverse reactions to anesthesia require particular attention.

The history of the third molar should establish whether the patient has experienced pericoronitis, pain, swelling, trismus, drainage, previous antibiotic treatment, or sensory symptoms. Previous episodes should be distinguished from pain arising from the adjacent second molar, temporomandibular disorders, or other sources.

Clinical examination should assess eruption status, periodontal probing, distal caries of the second molar, local inflammation, oral hygiene, mouth opening, mucosal condition, and anatomical access. In mandibular cases, the surgeon should also consider the position of the external oblique ridge and available buccal access. In maxillary cases, proximity to the tuberosity and clinical evidence of sinus disease may affect planning.

The patient should be informed not only about the risks of surgery but also about the risks of retention. Shared decision-making is particularly important in borderline cases in which both removal and surveillance are reasonable.

8. Panoramic Radiographic Assessment

Panoramic radiography remains the standard initial imaging examination for most impacted third molars because it simultaneously demonstrates tooth position, root morphology, adjacent structures, and the approximate relationship with the mandibular canal [1].

For mandibular third molars, radiographic assessment should examine root morphology, impaction depth, angulation, relationship with the second molar,

periodontal bone levels, follicular space, surrounding pathology, and the course of the mandibular canal.

Classic panoramic signs associated with close proximity between third molar roots and the mandibular canal include darkening of the root, diversion of the canal, narrowing of the canal, interruption of the canal's cortical border, deflection of the root, narrowing of the root, and bifid appearance of the root apex [5]. These findings do not prove direct nerve contact but may indicate the need for further evaluation.

Recent clinical studies continue to show that selected panoramic signs correlate with inferior alveolar nerve exposure or postoperative sensory disturbance [6,7]. Patient age and radiographic characteristics can therefore be combined to refine risk rather than interpreting a single panoramic feature in isolation.

9. Cone-Beam Computed Tomography

CBCT provides three-dimensional visualization of the mandibular third molar, roots, cortical plates, and inferior alveolar canal. Its major advantage is the ability to demonstrate whether a cortical boundary exists between the tooth and canal and whether the canal is buccal, lingual, inferior, interradicular, or directly contacting the roots.

CBCT should not automatically be obtained for every mandibular third molar. The additional radiation exposure and cost should be justified by an expectation that three-dimensional information may alter surgical planning or consent. Panoramic radiography remains adequate for many routine cases.

CBCT becomes particularly useful when panoramic imaging suggests intimate root-canal proximity, when root morphology is uncertain, when coronectomy is being considered, when unusual anatomy exists, or when precise localization could modify the operative approach. Contemporary studies demonstrate that CBCT can predict intraoperative exposure of the inferior alveolar neurovascular bundle with clinically useful accuracy in selected high-risk cases [6,33].

Three-dimensional imaging does not itself prevent nerve injury. Its benefit depends on whether the information leads to safer surgical decisions. CBCT should therefore be viewed as a decision-support tool rather than a routine prerequisite to extraction.

10. Inferior Alveolar Nerve Injury

Inferior alveolar nerve injury is among the most significant complications of mandibular third molar surgery because altered lower lip and chin sensation can

affect speech, eating, social interaction, and quality of life. Most postoperative disturbances are temporary, but persistent dysesthesia, hypoesthesia, anesthesia, or neuropathic pain may occur [5,21].

Risk is strongly influenced by the anatomical relationship between the third molar and the mandibular canal. Deep impaction, direct root-canal contact, interruption of canal cortication, complex root morphology, older patient age, and difficult surgical manipulation can increase risk [6–9].

The surgeon should distinguish expected short-term sensory alteration from permanent nerve injury when counseling patients. Reported frequencies vary because studies use different definitions, follow-up periods, and neurosensory tests. In routine third molar removal, permanent sensory disturbance is uncommon, but risk may be substantially higher in radiographically selected high-risk teeth.

When the tooth is closely related to the canal, excessive apical luxation should be avoided. Bone removal and tooth sectioning should be planned to create an exit path that requires minimal transmission of force toward the nerve.

If the inferior alveolar neurovascular bundle becomes visible intraoperatively, this does not necessarily mean that permanent injury has occurred, but it identifies a higher-risk situation. Detailed postoperative neurosensory documentation and follow-up are appropriate.

Persistent sensory disturbance should be evaluated systematically. Light touch, pin-prick discrimination, two-point discrimination, direction discrimination, and patient-reported dysesthesia can contribute to assessment. Early referral to a clinician experienced in trigeminal nerve injuries is appropriate when severe dysfunction, neuropathic pain, or suspected transection is present.

11. Coronectomy

Coronectomy has become an important strategy for reducing inferior alveolar nerve injury when complete extraction of a mandibular third molar would create an unacceptably high risk of nerve damage. The technique involves removal of the crown while intentionally leaving vital roots below the alveolar crest [15–20].

The biological rationale is that the most hazardous component of extraction is often mobilization of roots that are intimately associated with the mandibular canal. By retaining these roots, direct mechanical injury to the nerve can frequently be avoided.

One of the landmark randomized controlled trials demonstrated no inferior alveolar nerve injury after successful coronectomy in patients selected because of high radiographic risk, whereas nerve injuries occurred after complete extraction and after unsuccessful coronectomy in which roots became mobilized

[15]. Subsequent clinical research has supported coronectomy as an effective risk-reduction strategy in appropriately selected patients [16–20].

The tooth should generally be vital and free from pathology that requires complete root removal. Active periapical disease, significant root caries, root mobility during surgery, certain cystic or neoplastic conditions, and situations in which the retained roots themselves form part of the pathology may make coronectomy inappropriate.

Technical execution is important. The crown should be sectioned without mobilizing the roots, and residual enamel should not remain because exposed enamel can impair soft-tissue healing. The retained root surface is generally reduced sufficiently below the surrounding alveolar crest to permit osseous and mucosal coverage.

Root migration is an expected biological phenomenon rather than necessarily a complication. Retained roots frequently migrate coronally during the first postoperative years and generally move away from the mandibular canal [18]. Most patients do not require secondary surgery. When a migrated root subsequently becomes exposed or symptomatic, delayed removal may be considerably safer because the root may have moved away from the nerve.

Longer-term observational studies have continued to support the safety of coronectomy, with relatively low rates of reoperation despite measurable root migration [19]. Recent evidence also suggests that coronectomy may be feasible in selected pathological third molars situated close to the nerve, although careful case selection remains essential [20].

12. Lingual Nerve Injury

Lingual nerve injury is another potentially serious complication of mandibular third molar surgery. Because the nerve may lie immediately adjacent to the lingual cortical plate in the third molar region, relatively minor trauma can produce sensory alteration affecting the anterior tongue, taste, and oral function.

Risk can arise from lingual flap elevation, perforation of the lingual cortex, uncontrolled instrumentation, burs extending beyond the lingual plate, or tooth fragments displaced lingually. Surgical technique should therefore minimize unnecessary lingual manipulation.

Routine aggressive lingual retraction is not required for many buccal approaches. When lingual protection is considered necessary, the surgeon must weigh the potential protection against the possibility that retraction itself may produce nerve compression or traction.

The bur should remain under direct visual control, with particular caution during lingual crown sectioning. Elevators should not be directed forcefully toward the lingual plate, particularly when the cortex is thin.

As with inferior alveolar nerve injury, persistent lingual sensory disturbances warrant structured neurosensory assessment and timely referral when severe.

13. Surgical Technique

Successful third molar removal depends on creating adequate access while minimizing unnecessary tissue trauma. The surgical plan should be based on the individual tooth rather than a fixed sequence applied identically to all cases.

A well-designed mucoperiosteal flap should provide adequate visualization without excessive extension. Envelope and triangular flap designs are both commonly used. Contemporary comparative studies continue to evaluate differences in pain, swelling, and periodontal healing, but no single flap is ideal for every impaction [34].

Osteotomy should remove only the bone necessary to establish a controlled extraction path. Excessive bone removal increases tissue trauma and may compromise periodontal or mandibular integrity. In difficult mandibular impactions, controlled buccal and distal bone removal combined with tooth sectioning generally allows extraction with less force than aggressive elevation.

Tooth sectioning is particularly useful for mesioangular, horizontal, and deeply impacted molars. Separation of the crown from the roots or division of divergent roots allows individual components to be removed along favorable paths. The objective is not to minimize the number of sections but to minimize uncontrolled forces transmitted to the surrounding bone, second molar, and inferior alveolar nerve.

Copious irrigation is necessary during rotary bone removal to limit thermal injury. Instruments should remain sharp, and prolonged bur contact without adequate irrigation should be avoided.

At completion, the socket should be inspected for tooth fragments, loose bone, excessive granulation tissue, or visible neurovascular structures. Aggressive curettage close to the inferior alveolar canal should be avoided. Sharp bony margins may be smoothed when clinically necessary before irrigation and closure.

14. Age and Timing of Surgery

Age is consistently associated with the complexity and morbidity of mandibular third molar surgery. Increasing age is generally accompanied by completion of root development, increased bone density, reduced periodontal

regenerative capacity, and a greater probability that pathology has already developed.

A large prospective analysis identified age greater than approximately 25 years as a factor associated with increased complication rates after third molar surgery [23]. More recent studies similarly demonstrate clinically relevant differences in indications and complications between younger and older patients undergoing extraction [35].

These findings do not justify prophylactic extraction solely on the basis of youth. However, once a reasonable indication for removal has been established, unnecessarily postponing surgery for many years can increase technical difficulty and postoperative morbidity.

Older adults undergoing extraction deserve particularly careful assessment of second molar periodontal status, root-canal relationships, bone density, systemic medications, and healing potential.

15. Maxillary Third Molars

Maxillary third molar extraction generally presents a different risk profile from mandibular surgery. Inferior alveolar and lingual nerve injuries are not relevant, but the maxillary sinus, tuberosity, pterygoid region, and adjacent second molar require consideration.

The surgeon should assess root morphology and proximity to the maxillary sinus on preoperative imaging. Deeply positioned maxillary molars or divergent roots may increase the risk of sinus communication or displacement.

Excessive distal or superior force can fracture the maxillary tuberosity or displace the tooth into adjacent anatomical spaces. Controlled instrumentation and adequate exposure are therefore important.

Small oroantral communications may heal spontaneously when a stable clot and intact surrounding tissues are present, while larger defects may require surgical closure. The presence of pre-existing sinus disease should influence management.

Displacement of a maxillary third molar into the infratemporal or pterygopalatine region is uncommon but potentially serious. Blind attempts to retrieve a deeply displaced tooth should be avoided because they can move the tooth farther into inaccessible tissue planes.

16. Pain, Swelling, and Trismus

Pain, facial swelling, and temporary limitation of mouth opening are expected inflammatory consequences of third molar surgery rather than true complications in most cases. Their severity depends on surgical difficulty, procedure duration,

tissue manipulation, patient factors, and perioperative pharmacological management.

Postoperative pain usually reaches its greatest intensity during the early postoperative period and then progressively decreases. Nonsteroidal anti-inflammatory drugs are highly effective for most patients, often in combination with acetaminophen when additional analgesia is required.

Corticosteroids, particularly dexamethasone, are commonly used to reduce postoperative inflammatory morbidity. Contemporary randomized trials continue to demonstrate reductions in swelling, trismus, and selected pain outcomes following perioperative dexamethasone administration [36–39].

Different routes of administration have been studied, including oral, intravenous, submucosal, intramuscular, and local injection. Current evidence suggests that several routes can be effective, and the optimal technique depends on clinical setting and patient factors rather than a universally superior injection site.

A 2025 randomized clinical trial evaluating ibuprofen L-arginine and dexamethasone further demonstrated the continuing interest in multimodal pre-emptive analgesia for lower third molar surgery [40].

17. Alveolar Osteitis

Alveolar osteitis, commonly referred to as dry socket, is one of the most frequent postoperative complications following mandibular third molar removal. It is characterized by increasing postoperative pain associated with partial or complete breakdown of the socket blood clot, often accompanied by exposed alveolar bone and unpleasant taste or odor.

The pathogenesis is associated with premature fibrinolysis of the blood clot rather than conventional suppurative infection. Surgical trauma, smoking, previous pericoronal inflammation, difficult extraction, and other patient-related variables have been investigated as potential risk factors.

Treatment is primarily symptomatic. Gentle socket irrigation can remove food debris, and appropriate local dressings may provide temporary analgesia. Aggressive socket curettage is generally unnecessary and may increase trauma.

Chlorhexidine has one of the strongest evidence bases among preventive interventions. Randomized studies have demonstrated reductions in alveolar osteitis following perioperative chlorhexidine rinses or intra-alveolar gel application [41–44]. Its use should nevertheless account for patient tolerance and the rare possibility of hypersensitivity.

18. Postoperative Infection

Postoperative surgical site infection is less common than expected inflammatory swelling but remains an important complication. Infection may present with increasing pain after initial improvement, purulent drainage, persistent swelling, fever, lymphadenopathy, or worsening trismus.

A distinction should be made between expected postoperative inflammation and true bacterial infection. Routine swelling during the first several days does not itself justify antibiotic therapy.

Delayed-onset infection may occasionally occur several weeks after mandibular third molar removal, particularly when food debris accumulates in a deep residual socket or when healing is delayed.

Treatment depends on severity. Localized infections may respond to drainage, irrigation, and appropriate antimicrobial therapy when indicated. Deep-space infection, systemic features, airway concern, or failure of outpatient management requires escalation.

19. Antibiotic Prophylaxis

Routine antibiotic use in healthy patients undergoing uncomplicated third molar extraction remains controversial. Antibiotics can reduce certain postoperative infectious outcomes in selected studies, but this potential benefit must be balanced against adverse reactions, microbiome disruption, and antimicrobial resistance.

The absolute baseline risk of serious infection after uncomplicated surgery in a healthy individual is low. Consequently, universal prolonged antibiotic therapy is difficult to justify from an antimicrobial-stewardship perspective.

Patient and procedure characteristics should influence prescribing. Active infection, immunocompromise, complex surgery, extensive tissue manipulation, and specific medical indications may increase the rationale for antimicrobial therapy.

A 2024 network meta-analysis continued to find differences among antimicrobial regimens in relation to dry socket and surgical-site infection, but such analyses should not be interpreted as justification for indiscriminate antibiotic use [45].

Antibiotic therapy should complement rather than replace sound surgical technique, adequate irrigation, removal of infectious sources, and postoperative hygiene.

20. Hemorrhage

Bleeding after third molar surgery is usually controllable with local measures. Persistent bleeding may originate from soft tissue, cancellous bone, vascular structures, or systemic coagulation abnormalities.

Preoperative identification of anticoagulant and antiplatelet therapy is essential. In most patients receiving common antithrombotic medications, dental management should follow evidence-based protocols rather than routine medication discontinuation because inappropriate cessation can expose patients to thromboembolic risk.

Intraoperative control begins with accurate localization of the bleeding source. Direct pressure, suturing, local hemostatic agents, and socket packing are effective in most situations.

Profuse bleeding from the mandibular canal or an aberrant vessel requires calm, controlled management. Blind deep clamping should be avoided because it can injure neurovascular structures.

Postoperative instructions should explain how to manage minor oozing and when persistent bleeding requires professional assessment.

21. Periodontal Complications

The periodontal health of the second molar should be considered before and after mandibular third molar surgery. Deep impactions and pre-existing distal defects can leave residual periodontal pockets after extraction.

Age is particularly relevant. Younger patients tend to demonstrate greater spontaneous periodontal improvement, whereas older patients with established intrabony defects may have persistent attachment loss.

Surgical trauma to the distal second molar should be minimized. Flap elevation, bur contact, excessive distal bone removal, and forceful elevation against the second molar can contribute to periodontal or structural damage.

Selected high-risk defects may benefit from simultaneous periodontal regenerative strategies or bone grafting. AAOMS has published guidance recognizing that significant osseous defects after third molar removal may justify grafting in selected circumstances rather than as a routine procedure for every socket [46].

22. Damage to Adjacent Teeth and Restorations

The mandibular second molar can be injured directly during elevation or osteotomy. Elevators should not use a heavily restored or structurally compromised second molar as an uncontrolled fulcrum.

Bur contact may damage distal enamel or root surfaces. Direct visualization and deliberate sectioning of the third molar are preferable to forceful instrumentation close to the neighboring tooth.

Large restorations or crowns on the second molar should be discussed during consent because even careful surgery may occasionally produce restoration damage in difficult cases.

When significant distal caries or resorption is already present, treatment planning should consider the combined prognosis of the second and third molars rather than focusing on the impacted tooth in isolation.

23. Mandibular Fracture

Mandibular fracture associated with third molar surgery is rare but potentially serious. Risk may increase with deeply impacted large teeth, severe mandibular atrophy, older age, extensive osteotomy, cystic lesions, and excessive intraoperative force.

Late postoperative fractures can occur during the healing period when the mandibular angle remains temporarily weakened. Patients undergoing extensive removal should therefore receive individualized dietary and activity instructions.

The most effective preventive strategy is controlled bone removal combined with tooth sectioning rather than attempting to overcome resistance with progressively greater elevator force.

24. Displacement of Tooth or Root Fragments

Tooth fragments can occasionally be displaced into the sublingual, submandibular, pterygomandibular, maxillary sinus, infratemporal, or other adjacent spaces.

The decision to retrieve a displaced fragment immediately depends on its size, location, infection status, symptoms, and the potential morbidity of retrieval.

Repeated blind attempts can move the fragment farther from the surgical field and increase neurovascular damage. When localization is uncertain, imaging should precede additional surgery.

25. Root Retention During Conventional Extraction

Not every fractured root must be removed at all costs. A small deeply positioned vital root fragment in intimate contact with the inferior alveolar nerve may sometimes be safer to retain than to retrieve aggressively.

The decision differs from planned coronectomy because accidental root fracture was not part of the initial surgical strategy. Nevertheless, the same risk-benefit principle applies. If the root is noninfected, immobile, and its retrieval

carries a substantial probability of permanent nerve injury, intentional retention may be reasonable after appropriate documentation and patient counseling.

Roots associated with infection, mobility, significant pathology, or exposure should generally be removed when safely possible.

26. Postoperative Wound Management

At the end of surgery, the socket should be irrigated carefully and loose debris removed without excessive curettage. Primary closure should restore tissue position without producing excessive tension.

Complete airtight closure is not necessary after routine third molar removal. Excessive suturing can impair drainage and increase postoperative discomfort. The closure strategy should therefore reflect the size of the flap and defect.

Postoperative instructions should emphasize gentle hygiene, avoidance of mechanical disruption of the clot during the early healing period, appropriate analgesic use, hydration, and a gradual return to normal diet.

Smoking is undesirable because of its potential effect on healing and its association with postoperative morbidity. Patients should be advised to avoid smoking during the early postoperative period.

27. Adjunctive Biological Approaches

Autologous platelet concentrates, including platelet-rich fibrin, have been investigated for reducing pain and swelling, accelerating soft-tissue healing, improving socket bone regeneration, and reducing alveolar osteitis.

The biological rationale is attractive because platelet concentrates provide a fibrin matrix containing cellular and molecular mediators of healing. However, reported outcomes vary according to preparation method and study design.

Contemporary clinical trials continue to compare platelet-rich fibrin and platelet-rich plasma after bilateral third molar removal [47]. These adjuncts may be useful in selected cases, but routine application after every uncomplicated third molar extraction is not currently essential.

Other local interventions, including hyaluronic acid preparations, have also been investigated for postoperative pain and trismus. Recent randomized studies suggest possible benefits, but these strategies remain adjunctive rather than central to successful third molar surgery [48].

28. Neurosensory Documentation and Management

Preoperative consent should include discussion of inferior alveolar and lingual nerve injuries whenever clinically relevant. The magnitude of risk should be

individualized according to radiographic anatomy rather than communicated as an identical generic number for every patient.

If postoperative altered sensation occurs, the distribution and severity should be documented. Subjective patient descriptions should be combined with reproducible clinical testing when possible.

Many neuropraxic injuries improve spontaneously during the first weeks or months. Progressive recovery is reassuring, whereas complete anesthesia, severe dysesthesia, neuropathic pain, or absence of improvement deserves earlier specialist assessment.

Delayed referral can reduce therapeutic options in potentially repairable severe nerve injuries. Consequently, persistent sensory disturbance should not be dismissed solely because nerve injury is a recognized complication of surgery.

29. Informed Consent and Shared Decision-Making

Informed consent for third molar treatment should extend beyond obtaining a signature. The patient should understand the reason for recommending intervention, reasonable alternatives, expected postoperative recovery, material complications, and the implications of retention.

For a low-risk tooth with established recurrent pathology, the balance may clearly favor extraction. For an asymptomatic deeply impacted tooth in intimate contact with the inferior alveolar canal, surveillance or coronectomy may represent reasonable alternatives.

Coronectomy requires its own consent discussion because retained roots may migrate, may occasionally become exposed, and can require future removal. Conversely, the purpose of leaving the roots is to reduce the risk of nerve damage.

When surveillance is selected, patients should understand that retention is not equivalent to a guarantee that future disease will not occur. Periodic reassessment is part of the management plan.

30. Follow-Up of Retained Third Molars

Retained third molars should undergo active clinical and radiographic surveillance appropriate to individual risk. There is no universally applicable fixed imaging interval for every patient.

Clinical review should assess changes in symptoms, eruption, periodontal probing around the adjacent second molar, caries, mucosal inflammation, and oral hygiene.

Radiographic reassessment is appropriate when clinical changes occur or when the expected risk of silent pathology justifies monitoring. Repeated imaging without a clinical rationale should be avoided.

The decision to continue surveillance should be revisited as the patient ages because the relationship between the risks of future disease and the risks of surgery can change over time.

31. Future Developments in Risk Prediction

Digital imaging and artificial intelligence are increasingly being investigated for third molar risk assessment. Automated algorithms can identify mandibular canals and third molars, quantify proximity, and potentially assist in selecting cases that require CBCT or specialist management.

A 2024 study demonstrated automated detection and quantitative assessment of the relationship between the inferior alveolar nerve and mandibular third molars on CBCT [49]. Other recent investigations have used deep learning to evaluate the topographic relationship between mandibular third molars and the canal on panoramic images or CBCT [50,51].

Deep-learning models have also been developed to predict inferior alveolar nerve injury directly from imaging data. Although promising results have been reported, multicenter validation and improved interpretability are necessary before these tools can replace experienced clinical assessment [52].

The likely future role of artificial intelligence is therefore as an adjunct to surgical judgment rather than an autonomous decision-maker. Risk prediction may become increasingly personalized by combining patient age, impaction morphology, imaging characteristics, surgical complexity, and clinician-related variables.

32. Conclusion

Contemporary management of impacted third molars extends far beyond routine surgical extraction. Appropriate care begins with determining whether intervention is justified and continues through anatomical risk assessment, selection of imaging, surgical planning, complication prevention, postoperative management, and long-term surveillance.

Established pathology generally provides a clear rationale for treatment, whereas truly asymptomatic disease-free third molars require individualized assessment. Current evidence does not support the assumption that every impacted third molar must be prophylactically removed, but absence of pain should likewise not be interpreted as proof of health. Periodontal disease, distal second molar caries, root resorption, and other pathological changes may develop without prominent symptoms [3,10–13].

Panoramic radiography remains appropriate as the initial imaging modality for most cases, while CBCT provides valuable three-dimensional information

when the relationship between mandibular third molar roots and the inferior alveolar canal is uncertain and additional information may alter management [1,6–8].

Protection of the inferior alveolar and lingual nerves represents a central component of mandibular third molar surgery. In teeth demonstrating an intimate relationship with the inferior alveolar canal, coronectomy provides an evidence-supported alternative to complete extraction when appropriate case-selection criteria are fulfilled [15–20]. The procedure should not be considered a surgical compromise but rather a deliberate nerve-preserving strategy.

Complication prevention depends on thoughtful surgical execution. Adequate access, conservative osteotomy, controlled tooth sectioning, avoidance of excessive elevation forces, appropriate irrigation, protection of adjacent teeth and nerves, and evidence-based postoperative management can substantially reduce morbidity. Pain, swelling, trismus, alveolar osteitis, infection, and temporary sensory disturbance remain clinically relevant, but many can be minimized through appropriate technique and perioperative management.

Ultimately, the optimal management of an impacted third molar is not determined by the radiograph alone. Treatment should reflect the patient's current pathology, future disease risk, anatomical complexity, age, systemic health, expected surgical morbidity, preferences, and ability to participate in long-term surveillance. The most contemporary approach is therefore not routine extraction or routine retention, but individualized, evidence-based and patient-centered decision-making.

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Chapter 9

Inferior Alveolar and Lingual Nerve Injuries in Oral Surgery: Diagnosis and Management

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Abstract

Injuries to the inferior alveolar nerve (IAN) and lingual nerve (LN) are among the most significant neurological complications encountered in oral and maxillofacial surgery. Although many nerve injuries are transient and recover spontaneously, persistent sensory impairment may result in numbness, paresthesia, dysesthesia, allodynia, neuropathic pain, altered taste perception, accidental biting, speech difficulties, impaired mastication, and considerable deterioration in quality of life [1–5]. These injuries most commonly occur following mandibular third molar surgery, dental implant placement, local anesthetic injection, endodontic procedures, orthognathic surgery, trauma, and other dentoalveolar interventions [1,6–9]. The clinical consequences depend on the mechanism and severity of injury, the nerve involved, the anatomical level of damage, the presence of continuity or transection, and the interval between injury and definitive management.

Early recognition and systematic neurosensory assessment are essential because management differs substantially between a mild neuropraxic injury that is likely to resolve spontaneously and a severe axonal or neurotmetic lesion requiring surgical exploration. Clinical assessment should document the anatomical distribution of altered sensation, subjective sensory complaints, and objective responses to standardized neurosensory testing. Light touch, brush directional discrimination, two-point discrimination, pin-prick nociception, thermal testing, and patient-reported sensory disturbances provide complementary information regarding different fiber populations and can be used longitudinally to assess recovery [1,10–13]. Advanced imaging, particularly cone-beam computed tomography and magnetic resonance neurography in selected patients, may provide additional information regarding the anatomical relationship between the injured nerve and adjacent structures [14–17].

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Initial management depends on the cause of injury. Implant-related compression of the IAN represents a particularly time-sensitive condition because early removal or repositioning of an offending implant may prevent continued mechanical and ischemic injury [7,18]. In contrast, many third molar-related injuries can initially be observed when nerve continuity is presumed and progressive recovery is evident. Persistent anesthesia, severe dysesthesia, neuropathic pain, suspected nerve transection, formation of a traumatic neuroma, or absence of meaningful improvement during follow-up should prompt referral to a center experienced in trigeminal nerve microsurgery [1,19–23].

Microsurgical treatment may include external neurolysis, internal neurolysis, direct epineurial or perineurial neurorrhaphy, excision of neuroma, interpositional autogenous nerve grafting, and processed nerve allografting depending on the anatomical defect and intraoperative findings [19–26]. Contemporary evidence indicates that microsurgical repair can achieve meaningful functional sensory recovery in appropriately selected patients, particularly when treatment is undertaken before prolonged denervation and central sensory changes become established [22–27]. This chapter reviews the mechanisms, diagnosis, neurosensory assessment, conservative management, pharmacological approaches, indications and timing for microsurgery, surgical techniques, prognostic factors, and long-term follow-up of IAN and LN injuries encountered in oral surgery.

Keywords: inferior alveolar nerve, lingual nerve, trigeminal nerve injury, neurosensory disturbance, paresthesia, dysesthesia, microsurgery, nerve repair, third molar surgery, dental implant.

1. Introduction

Injury to peripheral branches of the trigeminal nerve is a recognized complication of oral and maxillofacial surgical procedures. The inferior alveolar and lingual nerves are particularly vulnerable because of their intimate anatomical relationships with the mandibular dentition, alveolar bone, mandibular canal, lingual cortex, and surgical fields commonly involved in third molar removal, implant placement, orthognathic surgery, and other dentoalveolar procedures [1,6]. While the majority of postoperative sensory disturbances improve spontaneously, permanent nerve injury can have consequences that are disproportionately severe relative to the original dental procedure.

The clinical impact of trigeminal nerve injury extends beyond simple numbness. Patients may experience tingling, burning, electric shock-like sensations, pain evoked by normally nonpainful stimuli, abnormal sensitivity to temperature, reduced ability to detect food or saliva, altered speech, involuntary biting of the lip or tongue, and impaired taste when the lingual nerve is involved [2–5]. Persistent neuropathic pain can be especially disabling and may interfere with sleep, concentration, social interaction, and psychological well-being. Consequently, nerve injury should not be regarded solely as a technical surgical complication but as a condition capable of producing long-term functional and psychosocial morbidity.

Mandibular third molar surgery remains one of the most frequently reported causes of IAN and LN injury. The risk is influenced by the anatomical relationship of the tooth to the mandibular canal, impaction depth, root morphology, age, surgical difficulty, and operative technique [6,8]. Dental implant placement represents another important cause, particularly when drilling or implant placement encroaches upon the mandibular canal. A 2025 systematic review examining implant-associated IAN injury confirmed a close relationship between implant proximity to the mandibular canal and postoperative neurosensory alterations [7]. Iatrogenic injury may also arise during endodontic procedures through mechanical instrumentation or extrusion of filling materials, during orthognathic surgery because of manipulation of the mandibular canal and nerve, or following administration of local anesthetic injections [1,9].

A major challenge in nerve injury management is that patients present with a wide range of pathophysiological injuries, from transient conduction block to complete nerve transection. The natural history and optimal treatment therefore vary considerably. A mild neuropraxic lesion may recover completely within weeks, whereas severe axonal disruption may produce permanent sensory

impairment unless surgical reconstruction is performed. Accurate early diagnosis is consequently central to management.

The timing of referral is also important. Historically, patients with postoperative sensory disturbance were sometimes observed for prolonged periods in the expectation of spontaneous recovery. Contemporary practice increasingly emphasizes structured monitoring and earlier specialist referral when recovery is absent or when clinical findings suggest a severe lesion [1,19]. The objective is to avoid unnecessary surgery in patients who are recovering while simultaneously avoiding excessive delay in patients who might benefit from microsurgical intervention.

2. Relevant Anatomy of the Inferior Alveolar Nerve

The inferior alveolar nerve is a major sensory branch of the posterior division of the mandibular nerve, itself the third division of the trigeminal nerve. After branching from the mandibular nerve, the IAN descends toward the mandibular foramen and enters the mandibular canal accompanied by the inferior alveolar vessels. Within the mandible, it provides sensory innervation to the mandibular teeth and surrounding structures before dividing anteriorly into the mental and incisive branches.

The mental nerve exits through the mental foramen and provides cutaneous sensation to the lower lip, chin, and adjacent mucosa. Consequently, injury to the IAN proximal to the mental foramen frequently produces altered sensation in the lower lip and chin. Depending on the level of injury, dental and gingival sensation may also be affected.

The relationship between the IAN and mandibular third molar roots is highly variable. The canal may pass buccal, lingual, inferior, or interradicular to the roots. In some patients, cortical bone clearly separates the canal from the tooth, whereas in high-risk cases the root surface and neurovascular bundle may be in direct contact [6]. This variability explains why radiographic evaluation is essential before third molar surgery.

The IAN is also vulnerable during implant placement in the posterior mandible. The superior border of the mandibular canal may be difficult to identify accurately on two-dimensional imaging, and drilling beyond the intended osteotomy depth can injure the nerve mechanically or through compression caused by an implant placed too close to the canal [7].

During sagittal split osteotomy, the nerve may remain within the distal or proximal mandibular segment and can be stretched, compressed, or manipulated during separation and fixation. Consequently, temporary neurosensory dysfunction is common after mandibular orthognathic surgery,

although the majority of patients demonstrate substantial recovery over time [9].

3. Relevant Anatomy of the Lingual Nerve

The lingual nerve is another branch of the mandibular division of the trigeminal nerve. It provides general somatic sensation to the anterior two-thirds of the tongue, floor of the mouth, and lingual gingiva. After joining with the chorda tympani branch of the facial nerve, it also carries taste fibers from the anterior two-thirds of the tongue and parasympathetic fibers associated with the submandibular and sublingual glands.

The lingual nerve has a highly variable anatomical relationship with the mandibular third molar region. It may lie below the lingual crest, at the level of the crest, or occasionally above the lingual cortical plate. In some individuals, the nerve lies extremely close to the periosteum of the lingual third molar region, making it vulnerable during flap elevation, lingual retraction, bone removal, tooth sectioning, or displacement of fragments [1,28].

Unlike the IAN, the lingual nerve is not enclosed within a bony canal in the third molar region. This mobility provides some protection against direct injury but also makes its exact intraoperative position difficult to predict. The nerve may be damaged by direct laceration, bur injury, compression, excessive traction, crush injury, or postoperative scar formation.

Because the lingual nerve carries chorda tympani fibers, injury can affect both somatic sensation and taste. Patients may report numbness, tingling, burning pain, altered taste, metallic sensations, reduced taste perception, or unpleasant spontaneous taste phenomena. Salivary perception may also be altered. A recent systematic review of persistent lingual nerve injury emphasized that pain and gustatory disturbance form an important part of the clinical burden and should be assessed in addition to conventional somatosensory function [29].

4. Classification of Peripheral Nerve Injury

Understanding the biological severity of nerve injury is essential for estimating prognosis and selecting treatment. The classical Seddon classification divides peripheral nerve injuries into neuropraxia, axonotmesis, and neurotmesis [30]. Sunderland subsequently expanded this concept into five degrees according to the extent of structural disruption within the nerve [31].

Neuropraxia represents the mildest form of injury and is characterized by temporary conduction block without structural disruption of the axon. Myelin

abnormalities may occur locally, but the axon remains intact. Recovery is usually complete and may occur over days or weeks.

Axonotmesis involves disruption of axons while at least some supporting connective tissue architecture remains intact. Wallerian degeneration occurs distal to the injury, and recovery depends on axonal regeneration toward the sensory end organs. Because axonal growth is slow, recovery can require months and may be incomplete.

More severe Sunderland injuries involve progressive disruption of the endoneurium, perineurium, and epineurium. When intraneural fibrosis develops, regenerating axons may fail to reach their original targets and may become misdirected.

Neurotmesis represents complete interruption of nerve continuity. Spontaneous meaningful recovery is unlikely when a nerve has been completely transected without anatomical reconnection. Surgical repair is usually required if restoration of sensory function is considered appropriate.

Clinical differentiation among these injury grades is not always possible immediately after surgery. Serial neurosensory examination therefore becomes important because the pattern of recovery provides information about underlying nerve continuity and regeneration.

5. Mechanisms of Injury

Peripheral trigeminal nerve injury can result from compression, traction, crush injury, laceration, thermal injury, chemical toxicity, ischemia, or complete transection. Different dental procedures expose nerves to different combinations of these mechanisms [1].

During third molar surgery, the IAN may be compressed by roots, elevators, or bone fragments or may be directly contacted by rotary instruments. Excessive root displacement toward the canal can stretch or crush the nerve. In high-risk cases in which root grooves correspond to the canal, extraction itself may produce substantial traction on the neurovascular bundle.

Lingual nerve injury during third molar removal may result from direct bur contact, perforation of the lingual cortex, uncontrolled elevation, lingual flap manipulation, or displacement of fragments into the lingual soft tissues. Excessive retraction can also produce neurapraxic or axonotmetic injury.

Implant-associated IAN injuries commonly arise when the osteotomy or implant enters the mandibular canal or produces compression within the canal [7]. Compression can impair intraneural microcirculation and produce ischemic damage even when the nerve is not transected. Because continued compression

may worsen injury, implant-associated sensory disturbance should be evaluated urgently.

Endodontic injury may arise from overinstrumentation beyond the root apex or extrusion of irrigants, sealers, or filling materials into the mandibular canal. Chemical injury may continue even after the procedure has ended, making early recognition important.

Local anesthetic-associated injury is uncommon but can affect the lingual or inferior alveolar nerves. Proposed mechanisms include direct needle trauma, intraneural hematoma, or local anesthetic neurotoxicity. Most cases improve spontaneously, but persistent injuries have been reported [28].

6. Incidence and Epidemiology

Reported rates of IAN and LN injury vary widely because studies differ in surgical populations, definitions of sensory impairment, follow-up duration, and testing methods. Most temporary sensory alterations resolve during the first several months, while persistent permanent deficits occur much less frequently [6,8].

Third molar surgery remains one of the dominant causes of traumatic IAN injury in oral surgery. A recent 2026 systematic assessment of high-risk mandibular third molars demonstrated that the probability of postoperative IAN disturbance rises substantially when CBCT shows loss of canal cortication or other high-risk anatomical relationships [32]. Thus, pooled incidence figures should not be applied uniformly to all third molars because anatomical risk varies considerably among patients.

Lingual nerve injury is similarly associated with third molar surgery. Permanent injuries are uncommon, but even a small absolute risk becomes clinically important because third molar removal is performed so frequently. A 2025 meta-analysis evaluating permanent lingual nerve injury emphasized that persistent lesions can be accompanied by both somatosensory and neuropathic pain manifestations [29].

Dental implants represent an increasingly important source of IAN injuries as implant treatment becomes more common. Systematic evidence published in 2025 demonstrated that the likelihood of neurosensory disturbance increases as implant proximity to the mandibular canal decreases [7]. This finding reinforces the importance of accurate three-dimensional planning and conservative safety margins.

7. Clinical Presentation

The clinical manifestations of IAN and LN injury extend across a spectrum from complete loss of sensation to painful hypersensitivity. Patients may report anesthesia, hypoesthesia, paresthesia, dysesthesia, hyperesthesia, hyperalgesia, allodynia, or spontaneous neuropathic pain [1–4].

Anesthesia indicates complete loss of sensation in the affected territory, whereas hypoesthesia describes reduced sensitivity. Paresthesia refers to an abnormal but not necessarily unpleasant sensation such as tingling or pins and needles. Dysesthesia describes an unpleasant abnormal sensation and can be spontaneous or evoked.

Allodynia is pain resulting from a stimulus that would not normally be painful. Patients may experience pain from light touch, lip movement, shaving, application of cosmetics, eating, or contact with clothing. Hyperalgesia refers to an exaggerated painful response to a normally painful stimulus.

IAN injury typically affects the ipsilateral lower lip and chin and may also influence mandibular tooth sensation. Patients may describe difficulty detecting food or saliva on the lip, accidental lip biting, or altered perception during drinking.

LN injury produces symptoms involving the ipsilateral anterior tongue, lingual gingiva, and floor of the mouth. Because taste fibers travel with the chorda tympani, patients may report dysgeusia or ageusia in addition to somatosensory dysfunction [29].

Painful trigeminal neuropathy deserves particular attention because functional recovery defined purely by touch detection may not adequately capture the patient's condition. A patient may regain measurable tactile function while continuing to experience debilitating burning or electric pain. Contemporary evaluation should therefore incorporate both objective sensory testing and patient-reported symptoms.

8. Initial Assessment Following Suspected Injury

When a patient reports altered sensation following oral surgery, the first step is to establish the timing and mechanism of onset. Immediate postoperative numbness may initially be obscured by local anesthesia, whereas symptoms recognized after anesthetic resolution may provide a clearer indication of injury.

The clinician should document the surgical procedure, intraoperative events, relationship of instruments or implants to the nerve, difficulty of extraction, nerve visualization, excessive bleeding, root fracture, displacement of fragments, or other events that may explain the lesion.

The sensory distribution should be mapped carefully. Comparison with the contralateral unaffected side is useful because normal sensory thresholds vary among individuals.

Baseline documentation should be obtained as early as practical and should include both subjective complaints and objective neurosensory findings. This baseline permits subsequent assessment of recovery and can help determine whether continued observation or specialist intervention is appropriate.

Implant-associated sensory disturbances require particularly rapid investigation. If imaging demonstrates an implant encroaching upon the mandibular canal or directly compressing the nerve, continued observation without addressing the mechanical cause may allow progressive damage [7,18].

9. Neurosensory Examination

Clinical neurosensory testing provides a structured method for evaluating the severity and evolution of trigeminal nerve injury. No single test evaluates all sensory fibers, so examination generally combines several complementary modalities [10–13].

Light-touch testing evaluates the patient's ability to perceive gentle mechanical stimulation. A cotton wisp, monofilament, or other calibrated stimulus can be used. The affected and unaffected sides should be compared under standardized conditions.

Brush directional discrimination evaluates the ability to determine the direction of a moving tactile stimulus. This test requires not only stimulus detection but also spatial processing and may reveal deficits that are not apparent with simple touch.

Two-point discrimination assesses spatial resolution by determining the minimum distance at which a patient can distinguish two simultaneous contact points from a single point. Increased thresholds indicate impaired discriminative sensation.

Pin-prick testing assesses nociceptive function and is associated primarily with smaller myelinated and unmyelinated fibers. Testing should be controlled and should compare the injured side with the unaffected side.

Thermal discrimination can evaluate the patient's ability to differentiate warm and cold stimuli. This can be useful in selected patients, particularly when subjective complaints indicate temperature-related dysesthesia.

The patient's description of spontaneous and evoked symptoms should be documented alongside objective results. Pain intensity, burning, electric sensations, unpleasant tingling, hypersensitivity, taste disturbance, accidental biting, and effects on daily activities are clinically meaningful outcomes.

The Medical Research Council sensory recovery scale and other functional sensory recovery systems have been used in microsurgical outcome research. A 2024 systematic review of lingual nerve repair concluded that standardized functional sensory recovery measures provide a useful and reproducible approach to reporting postoperative outcomes [33].

10. Quantitative Sensory Testing

Quantitative sensory testing provides more standardized measurement of sensory thresholds and can characterize abnormalities in mechanical and thermal perception. It is particularly useful in research and specialist neuropathic pain practice.

Mechanical detection thresholds, mechanical pain thresholds, pressure pain thresholds, thermal detection thresholds, and thermal pain thresholds can identify sensory loss or gain of function. Such testing may help distinguish predominantly negative sensory deficits from neuropathic states characterized by sensory amplification.

Although quantitative sensory testing provides valuable information, access may be limited in routine dental practice. It should complement rather than replace careful history and conventional chairside neurosensory examination.

11. Imaging

Imaging is selected according to the suspected mechanism of nerve injury. Panoramic radiography may identify gross anatomical abnormalities, retained root fragments, implants, or endodontic material near the mandibular canal. However, it provides limited information regarding three-dimensional relationships.

CBCT is particularly useful when an implant, tooth root, displaced fragment, or foreign material may be associated with the mandibular canal. The ability to assess buccolingual position and cortical integrity provides information that cannot be reliably obtained from panoramic imaging [14].

CT may be appropriate after major trauma or when broader osseous anatomy must be evaluated.

Conventional dental imaging demonstrates bone and foreign bodies but does not directly visualize the peripheral nerve in detail. Magnetic resonance neurography has therefore attracted increasing interest for evaluating trigeminal nerve injuries. High-resolution MRI techniques may demonstrate nerve caliber, signal alteration, discontinuity, or neuroma formation in selected cases [15–17].

MR neurography is not required for every postoperative sensory disturbance, but it may be useful when clinical findings are severe or inconclusive and when surgical planning would benefit from improved anatomical localization.

12. Differential Diagnosis

Not every sensory complaint following dental treatment represents direct peripheral nerve transection. Differential diagnosis should consider persistent local anesthesia, postoperative edema, hematoma, infection, local compression, neuropathic pain, temporomandibular disorders, central neurological disease, and pre-existing sensory abnormalities.

Patients may also develop persistent idiopathic facial pain or other chronic pain conditions after dental procedures without objective evidence of major nerve disruption. Accurate diagnosis is therefore essential before recommending invasive nerve surgery.

Neuropathic pain should be distinguished from nociceptive pain caused by infection or tissue inflammation. Burning, electric shock-like pain, allodynia, and sensory abnormalities within a recognizable nerve distribution increase suspicion of neuropathic injury.

13. Natural History and Spontaneous Recovery

The likelihood of spontaneous recovery depends largely on the severity of injury. Neuropraxic injuries frequently recover within several weeks, whereas axonotmetic lesions may require months because axonal regeneration must occur along the distal pathway [30,31].

Progressive improvement in sensory territory and test results is generally reassuring. A patient who moves from anesthesia to tingling and subsequently develops improving touch discrimination may be undergoing axonal regeneration.

The absence of any meaningful improvement over time is more concerning, particularly when the initial deficit is profound. Complete anesthesia combined with severe dysesthesia or clinical evidence of nerve transection warrants earlier specialist assessment.

Lingual nerve injuries can demonstrate spontaneous recovery during the first months after third molar surgery, but severe persistent defects become less likely to recover completely without intervention as time passes [19,22].

14. Early Conservative Management

Initial conservative management should be individualized according to the presumed mechanism of injury. Patients showing evidence of a mild injury and early improvement can generally be monitored with serial neurosensory examinations.

Education is important because patients may interpret normal regenerative tingling as worsening injury. Clear explanation of expected recovery patterns can reduce anxiety while ensuring that genuine deterioration is recognized.

Trauma to anesthetic areas should be minimized. Patients with lower lip anesthesia should be warned about accidental biting and thermal injury. Those with lingual anesthesia should take care when eating because unnoticed tongue trauma may occur.

Pharmacological treatment is primarily symptom-based. Analgesics may be appropriate for acute postoperative pain, while neuropathic pain may require specific agents such as gabapentinoids, selected antidepressants, or other medications used in neuropathic pain management. Such therapy should be individualized according to medical history and symptom severity.

Corticosteroids are sometimes used in the immediate period after suspected nerve compression or edema, although high-quality evidence defining an optimal regimen is limited. Their potential benefit is theoretically greatest when inflammatory swelling contributes to acute compression.

15. Implant-Related Inferior Alveolar Nerve Injury

Implant-associated IAN injury deserves special consideration because the causative mechanical factor may remain in place after surgery. If an implant extends into or compresses the mandibular canal, delay can theoretically prolong ischemic and mechanical injury [7,18].

When significant postoperative sensory disturbance occurs immediately after implant placement, imaging should be obtained promptly. CBCT can determine the relationship between the implant apex and the canal.

When clear nerve compression or canal penetration is demonstrated, early implant removal or repositioning should be considered. Previous systematic reviews have emphasized that early diagnosis and decompression are associated with more favorable outcomes than delayed intervention in appropriately selected patients [18].

The objective is not merely to create radiographic distance from the canal but to eliminate ongoing compression before irreversible intraneural fibrosis becomes established.

Prevention is preferable. Contemporary systematic evidence demonstrates an association between implant-canal proximity and neurosensory alterations, reinforcing the importance of careful CBCT-based planning when canal location cannot be established reliably on conventional imaging [7].

16. Third Molar-Related Inferior Alveolar Nerve Injury

The majority of IAN disturbances after mandibular third molar extraction improve spontaneously. Management therefore begins with assessment of injury severity and evidence of recovery.

Radiographic high-risk signs should ideally have been recognized before surgery. In patients with close root-canal relationships, CBCT and alternative strategies such as coronectomy may reduce the probability of direct nerve injury in selected cases.

When postoperative sensory dysfunction occurs, serial examination is important. Improvement during the first weeks to months supports continued observation. Absence of improvement, painful dysesthesia, or findings suggesting severe axonal disruption should prompt specialist referral.

The possibility of retained root or bone fragments compressing the canal should be investigated when the clinical history suggests a mechanical cause.

17. Lingual Nerve Injury Following Third Molar Surgery

Third molar removal remains a major cause of lingual nerve injury. The mechanism may involve direct laceration, compression, traction, bur injury, lingual cortical perforation, or postoperative scar formation [28].

A patient with immediate dense anesthesia of half of the anterior tongue following a technically difficult procedure involving lingual manipulation deserves careful follow-up. Taste should be assessed in addition to general sensation because chorda tympani fibers travel within the lingual nerve.

A 2025 systematic assessment of persistent lingual nerve injury demonstrated that clinically important consequences extend beyond numbness and include neuropathic pain and gustatory dysfunction [29].

Many injuries improve spontaneously, but persistent severe deficits should not simply be observed indefinitely. Evidence from microsurgical outcome studies indicates that repair can provide meaningful sensory recovery in carefully selected patients [22,33].

18. Neuropathic Pain Management

Neuropathic pain following trigeminal nerve injury can be more disabling than sensory loss. Patients may describe burning pain, electric shocks, pins and needles, painful cold sensation, or severe discomfort caused by light contact.

Management should distinguish spontaneous pain from stimulus-evoked pain and should document the effect on sleep, eating, speaking, work, and emotional well-being.

Pharmacological management follows general principles for peripheral neuropathic pain. Gabapentin, pregabalin, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors may be considered according to patient-specific factors. Topical therapies may be appropriate in selected localized oral neuropathic pain conditions.

Medication alone may not be sufficient when a traumatic neuroma or ongoing mechanical compression is present. In such cases, surgical evaluation may be required.

Patients with persistent neuropathic pain often benefit from multidisciplinary management involving oral and maxillofacial surgery, orofacial pain specialists, neurology or pain medicine, and psychological support where appropriate.

19. Photobiomodulation

Photobiomodulation or low-level laser therapy has been investigated as a noninvasive adjunct for peripheral nerve recovery. Proposed mechanisms include modulation of inflammation, mitochondrial activity, axonal regeneration, and microcirculation.

A 2024 systematic review comparing low-level laser therapy and microsurgical treatment found evidence of neurosensory improvement with both approaches, although heterogeneity of protocols and outcome measures limited definitive conclusions [34].

Photobiomodulation may therefore be considered as an adjunct in selected nerve injuries, particularly when spontaneous recovery is being monitored. However, it should not delay surgical referral when clinical evidence suggests nerve transection, neuroma formation, or severe persistent dysfunction.

Standardization remains a major limitation because wavelength, energy density, treatment frequency, and duration vary considerably among studies.

20. Indications for Microsurgical Referral

The decision to refer a patient for microsurgical evaluation should be based on the severity and trajectory of the injury rather than on a rigid time point alone.

Immediate or early referral is appropriate when nerve transection is known or strongly suspected, when a foreign body or implant is compressing the nerve, when there is severe painful dysesthesia, or when the surgical event clearly involved direct nerve laceration.

Referral is also appropriate when dense anesthesia persists without meaningful improvement during serial follow-up. Progressive spontaneous recovery can justify continued observation, whereas a static profound deficit becomes increasingly concerning.

The development of a painful traumatic neuroma is another indication for specialist evaluation. Neuroma pain may be triggered by palpation or movement and can cause severe functional impairment.

21. Timing of Microsurgery

The optimal timing of microsurgical repair remains debated. The biological argument for early intervention is that prolonged denervation can lead to distal end-organ changes, intraneural fibrosis, cortical reorganization, and chronic neuropathic pain.

Historical clinical series have demonstrated an association between prolonged delay and less predictable recovery, particularly for lingual nerve repair [19,22].

Contemporary systematic reviews continue to support timely assessment while acknowledging that meaningful recovery can still occur after delayed repair. A 2024 systematic review of lingual nerve repair reported high rates of sensory improvement following surgery, although the precise influence of treatment delay remained difficult to quantify because of heterogeneity among studies [33].

More recent 2026 evidence examining timing and outcomes of permanent lingual nerve injury similarly supports microsurgical repair as an effective treatment while emphasizing individualized decision-making rather than an absolute universal deadline [35].

In clinical practice, the objective is therefore to identify severe nonrecovering injuries early enough that specialist assessment and potential repair are not unnecessarily delayed.

22. Principles of Microsurgical Exploration

Microsurgical exploration is performed under magnification with fine instrumentation designed to minimize additional nerve trauma. The injured nerve is exposed through an approach determined by its anatomical location.

The surgeon assesses nerve continuity, external scarring, intraneural fibrosis, neuroma formation, degree of tissue loss, and the condition of proximal and distal nerve segments.

When nerve continuity is preserved but the nerve is compressed within scar tissue, external neurolysis may be sufficient. When fibrosis extends between fascicles, internal neurolysis may be considered in selected cases.

If a neuroma has formed, the abnormal segment may need to be excised until healthy fascicular architecture is identified.

The resulting defect determines whether direct repair is feasible or an interpositional graft is required.

23. Direct Neurorrhaphy

Direct neurorrhaphy is preferred when healthy proximal and distal nerve ends can be approximated without tension. Tension-free repair is fundamental because excessive traction can impair microcirculation and increase scar formation.

Epineurial suturing is commonly used for trigeminal nerve reconstruction. Fine microsutures approximate the epineurium while minimizing foreign material and intraneural trauma.

Perineurial or grouped fascicular repair may be considered when fascicular anatomy is clearly identifiable, although the small size and complex internal architecture of oral sensory nerves can limit such techniques.

Direct repair is most feasible when the defect after removal of damaged tissue is short.

24. Autogenous Nerve Grafting

When a tension-free direct repair cannot be achieved, an interpositional graft may be required.

The sural nerve has historically been one of the most frequently used donor nerves because adequate graft length can be obtained and its caliber is suitable for many reconstructive applications. However, harvesting creates a second surgical site and permanent sensory alteration in the donor territory.

Other autogenous sensory nerves can be considered depending on the required length and surgeon preference.

The graft should be slightly longer than the measured defect to permit tension-free coaptation. Both graft-host junctions require meticulous microsurgical repair.

Functional recovery after grafting depends on axonal regeneration through two coaptation sites and the graft itself, making outcomes generally less predictable than direct repair when direct repair is technically possible.

25. Processed Nerve Allografts

Processed nerve allografts have emerged as an alternative to autogenous nerve grafts in selected sensory nerve defects. These grafts provide an acellular extracellular matrix scaffold through which regenerating axons can grow.

The principal advantage is avoidance of donor-site morbidity. The technique may also reduce operative time because no donor nerve harvest is required.

Clinical series have reported favorable functional sensory recovery after processed allograft reconstruction of IAN and LN defects [24–26].

Nevertheless, outcomes depend on defect length, injury chronicity, patient factors, quality of the proximal and distal nerve segments, and surgical technique. Comparative high-quality evidence remains more limited than would be desirable for establishing superiority over autogenous grafting.

26. Conduits and Other Reconstructive Materials

Synthetic or biological nerve conduits can be used to bridge small defects or protect a coaptation site. Conduits provide an enclosed environment intended to guide axonal growth and reduce extraneural scar formation.

Their role in long trigeminal nerve gaps is more limited because axonal regeneration across substantial distances requires adequate vascular and cellular support.

Various collagen-based tubes, vein grafts, and other biomaterials have been studied. Their optimal role continues to evolve as peripheral nerve tissue engineering advances.

27. Microsurgical Management of Lingual Nerve Injury

Lingual nerve repair commonly involves excision of a traumatic neuroma followed by direct neurorrhaphy or interpositional grafting.

Surgical access must provide adequate visualization while protecting the submandibular duct and surrounding tissues. Magnification is essential because the lingual nerve may be surrounded by dense scar tissue after previous third molar surgery.

Outcomes are generally favorable when appropriate candidates are selected. A 2024 systematic review concluded that lingual nerve repair produces high rates of sensory improvement, with much of the recovery occurring during the first postoperative year [33].

Long-term evaluation should include taste and neuropathic pain in addition to tactile testing because return of general sensation does not necessarily imply complete recovery of all lingual nerve functions.

28. Microsurgical Management of Inferior Alveolar Nerve Injury

IAN microsurgery is anatomically different because much of the nerve lies within the mandibular canal. Access may therefore require removal of cortical bone and exposure of the canal.

The injured segment may be approached intraorally, and the nerve can be decompressed, explored, or reconstructed depending on findings.

Implant-associated injuries may require removal of the offending implant before or during nerve exploration. Endodontic foreign material within the canal may similarly require decompression.

A 2025 systematic review of surgical strategies for iatrogenic IAN injuries concluded that multiple repair approaches can produce meaningful sensory improvement, although heterogeneity in patient selection and outcome measurement limits direct comparisons [36].

29. Prognostic Factors

Outcome depends on several interacting factors. The severity of the original injury is fundamental. A mild compression injury has a much better spontaneous prognosis than complete transection.

Timing can influence recovery, particularly when severe lesions are left untreated for prolonged periods. However, delayed surgery does not automatically imply treatment failure, and some patients can improve after later repair.

Patient age may influence regenerative capacity, although age should not be used as an isolated contraindication.

The presence of neuropathic pain may indicate complex injury and central sensory processing changes. Pain outcomes should therefore be considered separately from simple tactile recovery.

Defect length also affects reconstructive outcomes. Longer defects may require grafting and longer regenerative distances.

The condition of the distal nerve bed and target sensory receptors is relevant, especially after prolonged denervation.

30. Functional Sensory Recovery

The objective of nerve repair is not necessarily restoration of perfectly normal preinjury sensation. Clinically meaningful functional sensory recovery is often a more realistic outcome.

Functional recovery generally implies return of useful protective and discriminative sensation without disabling pain.

Patients should be counseled realistically before microsurgery. Improvement may continue for many months because axonal regeneration and cortical adaptation are gradual.

Taste recovery after lingual nerve repair may differ from somatic sensory recovery because chorda tympani fibers constitute only one component of the nerve.

31. Follow-Up After Nerve Injury

Follow-up should be systematic rather than based solely on the question of whether the patient “feels better.”

The same neurosensory tests should ideally be repeated at successive visits so that changes can be compared objectively.

The mapped area of altered sensation should be recorded. Reduction in the affected area can provide evidence of recovery even before discrimination thresholds normalize.

Subjective symptoms should also be monitored. Decreasing numbness accompanied by increasing unpleasant tingling may represent regeneration but can also evolve toward neuropathic pain.

Taste disturbance should be reassessed in lingual nerve injuries.

Follow-up intervals should reflect injury severity. A severe static deficit requires closer observation and earlier specialist consideration than a mild improving paresthesia.

32. Follow-Up After Microsurgery

After microsurgical repair, patients should understand that immediate sensory recovery is not expected because axons must regenerate through the repaired nerve.

Early postoperative assessment focuses on wound healing and protection of the repair. Subsequent follow-up evaluates the progressive return of sensation.

Tingling or altered sensation developing within the denervated territory may indicate regeneration.

Objective tests should be repeated at standardized intervals. Functional sensory recovery frequently evolves over the first postoperative year and may continue thereafter [33].

Failure to improve should prompt evaluation for recurrent scar formation, neuroma, graft problems, or other causes.

33. Prevention of Inferior Alveolar Nerve Injury

Prevention begins with appropriate preoperative imaging and risk assessment.

During mandibular third molar surgery, panoramic signs suggesting close canal-root proximity should alert the surgeon to increased risk. CBCT may be justified when three-dimensional information is expected to alter management.

Coronectomy represents an important preventive option for selected high-risk third molars because it avoids removal of roots closely associated with the IAN.

During implant placement, adequate safety distance from the mandibular canal should be maintained. CBCT-based planning is particularly important when anatomy is uncertain or when available vertical bone height is limited.

Surgical guides can improve positional accuracy but should not eliminate independent verification of drill depth and anatomical landmarks.

Excessive apical pressure during osteotomy should be avoided.

34. Prevention of Lingual Nerve Injury

Lingual nerve protection during third molar surgery depends primarily on controlled instrumentation and avoidance of unnecessary lingual trauma.

Rotary instruments should remain under direct visualization and should not penetrate the lingual cortical plate.

Excessive uncontrolled elevator forces toward the lingual aspect should be avoided.

The role of lingual flap retraction remains debated. Retraction may protect the nerve from direct instruments in some techniques, but manipulation itself can produce traction or compression. Surgical approach should therefore be selected according to anatomy, impaction, and surgeon experience.

Adequate crown and root sectioning can reduce the need for forceful elevation and thereby decrease the risk of displacement or lingual injury.

35. Informed Consent

Nerve injury is a material complication of several oral surgical procedures, particularly high-risk mandibular third molar extraction and posterior mandibular implant placement.

Consent should be individualized rather than providing every patient with the same generic estimate.

Patients with high-risk anatomy should understand the possibility of temporary and permanent altered sensation and should be informed of reasonable alternatives such as coronectomy or surveillance when appropriate.

The possibility of neuropathic pain should be discussed because persistent nerve injury may produce symptoms beyond simple numbness.

For lingual nerve injury, potential taste disturbance should also be explained.

Clear documentation of the preoperative discussion is important, but meaningful consent requires patient understanding rather than a signature alone.

36. Psychological and Quality-of-Life Considerations

Persistent trigeminal nerve injury can produce substantial psychological distress. The discrepancy between a relatively minor original dental procedure and a persistent neurological complication may be particularly difficult for patients to accept.

Patients may become hypervigilant regarding oral sensations and may experience anxiety regarding permanent disability.

Chronic neuropathic pain can contribute to sleep disturbance, depression, social withdrawal, and impaired occupational function.

The clinician should acknowledge these consequences rather than focusing exclusively on neurosensory test scores.

Multidisciplinary support may be appropriate in patients with severe chronic pain or major psychological impact.

37. Emerging Regenerative Approaches

Research into peripheral nerve regeneration continues to explore growth factors, stem cells, bioengineered conduits, extracellular matrix scaffolds, platelet concentrates, electrical stimulation, and pharmacological enhancement of axonal regeneration.

Tissue-engineered constructs may eventually improve regeneration across larger nerve defects while avoiding donor-site morbidity.

Photobiomodulation remains among the more clinically accessible adjuncts, although treatment protocols require better standardization [34].

Future treatments may combine microsurgical reconstruction with biological modulation of axonal growth and scar formation.

38. Future Role of Imaging and Artificial Intelligence

Advances in imaging may improve both prevention and diagnosis. Automated segmentation of the mandibular canal on CBCT can support surgical planning and potentially reduce anatomical interpretation errors.

Artificial intelligence algorithms are increasingly capable of identifying the canal, teeth, and surrounding anatomical structures on three-dimensional imaging.

The eventual clinical value of these systems will depend on external validation, integration with surgical workflows, and demonstration that improved image interpretation actually reduces nerve injury.

Magnetic resonance neurography may also become increasingly relevant for direct assessment of peripheral trigeminal nerves, especially in patients being considered for microsurgical intervention.

39. Clinical Decision-Making

Effective management of trigeminal nerve injury requires integration of mechanism, severity, symptoms, serial neurosensory findings, imaging, and time course.

A patient with mild improving paresthesia after third molar extraction can often be monitored conservatively.

A patient with immediate profound anesthesia after placement of an implant penetrating the mandibular canal requires urgent imaging and consideration of decompression.

A patient with persistent lingual anesthesia, taste loss, and painful dysesthesia without improvement should be referred for specialist microsurgical assessment.

The decision is therefore not simply between observation and surgery. Management represents a continuum in which treatment changes according to biological evidence of recovery and the functional burden experienced by the patient.

40. Conclusion

Inferior alveolar and lingual nerve injuries are uncommon but potentially life-altering complications of oral surgical and dental procedures. Their consequences extend well beyond simple numbness and may include

dysesthesia, neuropathic pain, altered taste, functional impairment, accidental soft-tissue trauma, and deterioration in quality of life [1–5].

Successful management begins with prevention. Accurate anatomical assessment, appropriate radiographic evaluation, recognition of high-risk third molars, careful implant planning, controlled surgical technique, and use of nerve-preserving alternatives such as coronectomy can reduce avoidable injury.

When nerve injury occurs, early documentation and structured neurosensory assessment are essential. The distribution of the deficit, subjective symptoms, objective sensory testing, and serial evidence of recovery provide the foundation for clinical decision-making.

Many neuropraxic and mild axonotmetic lesions recover spontaneously and do not require surgery. However, severe anesthesia, painful dysesthesia, suspected transection, persistent nonrecovering deficits, traumatic neuroma, or ongoing mechanical compression should prompt early specialist referral.

Microsurgical techniques including neurolysis, direct neurorrhaphy, autogenous grafting, and processed nerve allografting can provide meaningful functional sensory recovery in appropriately selected patients [22–26,33,36]. Contemporary evidence particularly supports microsurgical repair of persistent lingual nerve injuries, while emphasizing the importance of individualized timing and standardized assessment of outcomes.

Long-term management should focus not only on measurable sensory recovery but also on neuropathic pain, taste function, daily activity, and patient-reported quality of life. The optimal contemporary approach is therefore preventive, diagnostic, restorative, and patient-centered, with timely transition from observation to specialized microsurgical care when spontaneous recovery becomes unlikely.

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