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Integration of Immunology in a Systems-Based Osteopathic Medical Curriculum

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Abstract: Immunology is an important component of the medical curriculum. It provides a foundation for understanding the cellular and molecular processes by which the body protects itself from external substances and the immunological responses that contribute to the development of many illnesses. The inclusion of immunology in an osteopathic medical curriculum is essential to understanding the body's defense systems as well as the alignment of osteopathic concepts with immunology. By encompassing innate and adaptive immunity, immunology reflects the interconnectedness of the body's systems and the foundation for self-regulation inherent in osteopathy. A problem facing medical educators is determining how to facilitate students' learning of immunological concepts in a way that will help them retain and apply the material throughout their clinical years and beyond. This paper aims to provide an immunology education framework designed to effectively integrate immunology topics across the preclinical courses of an osteopathic medical curriculum. Drawing insights from an extensive review of the literature and current medical curricula, we propose an integrative curriculum model that broadly incorporates fundamental concepts of immunology across multiple disciplines and systems-based courses horizontally as well as vertically over the preclinical years using clinical presentations and laboratory findings and further connecting them to osteopathic principles. This integrative curriculum will augment medical students' understanding of immunology, making them better able to connect core concepts with clinical applications and enhance their application of immunological concepts in osteopathic patient care in alignment with the NBOME guidelines. Using the proposed integrative medical curriculum may better prepare medical students for providing holistic medical care and guidance to their future patients.

Keywords: immunology; osteopathic; medical; curriculum; systems-based; NBOME

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1. Introduction

Immunology is a branch of biomedical science that focuses on the study of the immune system responsible for defending the body against infectious and other harmful foreign substances. It consists of two branches of immunity, innate and adaptive, comprising an array of host defense mechanisms and cells. These defensive cells are displayed at all corners of the body, withholding a few immune-privileged areas such as the brain, eyes, uterus, and testes, and utilize not only the primary circulatory system to transverse the different organ systems but also a unique lymphatic system [1]. This highway system for immune cells allows for the communication and integration of the host defense at common junctions called lymph ducts and nodes. However, this pathway can also be used by tumors to metastasize, infections to spread, and as a means for autoimmune diseases and other pathologies to arise. As such, this confluence and unity of different body systems highlight one of the fundamental tenets of osteopathic medicine.

Immunology holds significance in an osteopathic medical school curriculum for several reasons. Immunological concepts mirror the principles of osteopathy, which value the body as a connected unit that can self-heal and self-regulate. The immune system is one of the main ways the body can maintain this homeostasis. In the context of the osteopathic five models, immunology encompasses the respiratory–circulatory and metabolic-energy models [2,3]. These two philosophies care for efficient arterial supply, venous and lymphatic drainage, effective cellular metabolic processes, energy expenditure, and exchange involving immune regulation and control [1,3,4]. A compromise of this homeostasis may give rise to a diseased state.

The osteopathic principles and patient care practices involve manipulations to remove mechanical impediments to homeostasis, improve circulation, and relieve congestion by improving venous and lymphatic drainage, restoring efficient metabolic processes, alleviating inflammation and infection, and repairing normal immune system functions [4]. These require an understanding of the basis of pathogenesis, often related to foreign invaders of the body or autoantigens generated from the body's tissues. Thus, knowledge of immunology is crucial for diagnosing and managing diseases.

The National Board of Osteopathic Medical Examiners (NBOME) identifies foundational knowledge related to the microbiologic and immunologic bases of health and disease as a required element for osteopathic physicians and requires them to demonstrate effective application of clinical science knowledge in immunology and allergies pertaining to the primary care-oriented focus of osteopathic medical practice (NBOME COMLEX-USA Master Blueprint, https://www.nbome.org/assessments/comlex-usa/master-blueprint/competency-domains/applied-osteopathic-medical-practice-knowledge/, accessed on 24 May 2023). As such, osteopathic medical students need to grasp the principles of immunology to comprehend how the immune system functions in health and disease and apply the learned information in clinical contexts. According to the American Association of Colleges of Osteopathic Medicine (AACOM), there are currently 41 accredited colleges of osteopathic medicine in the United States, delivering instruction at 66 teaching locations in 35 states. In the current academic year, these colleges are educating more than 35,000 future physicians, which is 25% of all U.S. medical students [5]. However, as reported in 2022, only 2 out of 44 osteopathic medical programs in the United States require upper-division biology science courses, and among these, only one has immunology as a prerequisite [6]. Overall, 18.6% of all U.S. medical schools recommend immunology as a prerequisite for medical school enrollment, but none deem the completion of the course as necessary.

Medical students find immunology abstract and challenging to learn regardless of their backgrounds, and most find it difficult to relate to clinically, adding to the confusion of where everything connects [7–11]. Also, immunology is delivered in various ways based on the medical school; variations include delivery as a stand-alone course, integrated with other topics, or as a portion within a foundational science course [6]. Elucidating the basic concepts in immunology requires extensive use of terminology. Furthermore, for the teaching of immunological concepts to be effective, instructors must be adept at integrating basic knowledge from multiple disciplines in the context of clinical observations and laboratory findings [12,13].

Over the past decade, growth in research and innovation in medical science has continued to make the latest information available on diseases, drugs, guidelines, and practices. This has led to an increase in the intensity and complexity of medical knowledge [14]. Alongside these changes, the medical curriculum has evolved significantly to accommodate the new information [15–19]. Also, the development of new and progressive teaching-learning methods and curricular changes have led to various pedagogic approaches such as problem-based, simulation-based, and team-based learning modules. For immunology, a single course presentation covering the foundational principles has remained preferable to provide an appropriate knowledge base, though some medical schools implement a more integrative approach in which immunology topics are incorporated into other courses [15]. Regardless of the approach, the curriculum should cover the minimal core concepts and

principles essential for the integration of immunology (and medical microbiology) into the practice of medicine [15]. Integration of clinical approaches and patient cases with foundational sciences has been increasingly emphasized in medical education as an essential process to better prepare medical students for applying knowledge in their field of work [9,12,13]. Assessment for immunology on both COMLEX and USMLE examinations requires learning of the subject in both foundational concepts and application in the clinical fields [20,21].

The educational concept of "integration" can be demonstrated in several ways [22,23]. One theory is that integration is the extent to which educators present knowledge, beliefs, or skills to learners [24]. Another concept of integration establishes it as a process that occurs in the learner's mind as a result of the merging of previously acquired knowledge with fresh insights and/or experiences [25]. Numerous educators define integration as an approach that informs how curricular factors are structured and arranged [23,26,27] such as vertical, horizontal, and spiral integration; interdisciplinary organ-system modules; and longitudinally integrated clinical skills courses. This paper outlines the relevant topics in immunology for a medical school curriculum, their distribution and integration vertically and horizontally across the first- and second-year organ systems-based courses, and their applications in clinical and osteopathic connections. The goal is to present an integrated curriculum structure that can be applied as a standardized model for teaching medical immunology across the U.S. osteopathic medical schools.

2. Methodology

We reviewed available literature that highlights the integration of immunology into a U.S. medical school curriculum and the expected learning outcomes for students. However, we did not find any literature that specifically focuses on the association of immunology topics with clinical sciences and osteopathic medicine in the entire systems-based preclinical curriculum. Our presentation of the integrated curriculum is derived from the literature including listings of core knowledge objectives for medical microbiology and immunology recommended by the Association of Medical School Microbiology and Immunology Chairs (AMSMIC) [23] and the current preclinical curriculum organization at California Health Sciences University–College of Osteopathic Medicine (CHSU-COM), and follows the curricular guidelines provided by the National Board of Osteopathic Medical Examiners (NBOME) handbook. Additionally, we reviewed the American Association of Immunologists (AAI) Undergraduate Immunology Toolkit [28] to ensure the core concepts were included and proper scaffolding was established for clinical connections and applications throughout the curriculum. We identified topics in immunology that are appropriate for the systems-based course and that align with the osteopathic applications pertinent to the course being covered. We systematized the topics into eleven tables; Table 1 represents immunology topics covered in the foundational course (Host Defense Mechanisms) and related clinical correlations, and Tables 2–10 represent the integration of immunology in the clinical presentation categories (in Dimension 2 as defined by NBOME) with specific systems-based topics assessed in each category. Lastly, Table 11 represents the incorporation of immunology concepts in the teaching of osteopathic principles and practices.

Table 1. Integration of immunological concepts corresponding to the foundations in biomedical sciences.

Foundational Knowledge in Immunology		
Topics	**Core Concepts**	**Clinical Correlations**
Cells and organs of the immune system	Development and maturation of white blood cells. Bone marrow, thymus, spleen, lymph nodes, MALTs. Development of T and B cells.	Leukocytosis, leukopenia, hepatosplenomegaly, aplastic anemia, developmental stasis in hematological malignancy, genetic immune deficiency.
Innate immune system	Physical barriers to infection. Physiological barriers to infection. Cells of the innate immune response (neutrophils, macrophages, dendritic cells, NK cells) and their functions in recognition of microbes, cytokine production, and destruction of microbes. The phagocytic barrier to infection. Recognition of microbes by phagocytic cells. Major components of the inflammatory response. Local and systemic effects of the inflammatory response. Key inflammatory cytokines and their roles. Functional role of cell adhesion molecules (selectins, integrins). Chemotactic factors involved in inflammatory cell recruitment. The complement system: pathways, components, and their functions.	Inflammation, neutrophilia, septic shock, disseminated intravascular coagulation (DIC), deep vein thrombosis (DVT), anaphylaxis, myeloperoxidase deficiency, chronic granulomatous disease (CGD), Chediak-Higashi syndrome, severe congenital neutropenia, complement deficiencies, leukocyte adhesion deficiency types I and II, paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome, hereditary angioedema without urticaria.
Adaptive immune system	Specificity, diversity, specialization, self-activation, memory. Cells involved in the adaptive immune response (T cells, B cells, antigen-presenting cells). Clonal selection of T and B cells. Phases of adaptive immune response –recognition, activation, effector, contraction, and memory. Basic effector functions of T and B cells in an immune response.	Central and peripheral tolerance, naturally and artificially acquired active and passive immunity, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), severe combined immunodeficiency (SCID).
Antigens and Antibodies	Antigen, antigenic determinant, epitope, and hapten. Fundamental difference between B cell and T cell epitopes. Basic structure of the immunoglobulin molecule, including the major Ig fragments (Fab, Fc) and regions (hinge, variable, hypervariable). Structures and functions of the major classes and subclasses of immunoglobulins.	Vasculitis, arthritis, hemolytic disease of the newborn (erythroblastosis fetalis), hyper IgM syndrome, hyper IgE syndrome, selective IgA deficiency, common variable immunodeficiency (CVID).
Antigen Receptor Diversity MHC, Antigen Processing and Presentation	Molecular genetic mechanisms of generation of antibody diversity. Isotype switching and its functional significance. Somatic hypermutation and its functional significance. Crosstalk between innate and adaptive immunity. Essential characteristics of humoral and cellular immunity. T and B cell activation and the role of antigen-presenting cells. Functions of MHC molecules in antigen presentation and cell-cell interactions in the immune system. Major structural features of the MHC gene products. Tissue distribution of class I and class II MHC.	Multiple myeloma, chronic lymphocytic leukemia (CLL), hemochromatosis, ankylosing spondylitis, reactive arthritis, IBD, acute anterior uveitis, Addison disease, myasthenia gravis, Grave disease, psoriasis, severe allopurinol (gout treatment) hypersensitivity, hypersensitivity to abacavir (HIV antiviral agent), severe hypersensitivity to carbamazepine, celiac disease, hay fever, Goodpasture syndrome, lupus, Type 1 diabetes.

Table 1. *Cont.*

Foundational Knowledge in Immunology		
Topics	**Core Concepts**	**Clinical Correlations**
B and T lymphocyte activation	Activation of T cells (e.g., the interactions between APCs and T cells leading to T cell activation). Functional role of the T cell accessory protein CD4 and CD8 in recognition of antigen and T cell activation. Mechanism of superantigen activation of T cells. Mechanism of antigen-induced B lymphocyte activation. Compare and contrast the effects of T-independent and T- dependent antigens on B cell activation. Lymphocyte Tolerance and Selection. Regulation of Lymphocyte Activation Response Cytokines. Effector T cell populations and their activation requirements. The process by which effector CTLs recognize target cells.	Bare lymphocyte syndrome-I, bare lymphocyte syndrome-II, HSV-I recurrence, necrotizing fasciitis, toxic shock syndrome, T-B+NK+ SCID, T cell signaling defects, DiGeorge syndrome (q22 deletion syndrome), acquired immune deficiency syndrome (AIDS), Chai and Lataie disease, Bruton's tyrosine kinase (BTK) deficiency or X-linked agammaglobulinemia (XLA), Wiskott–Aldrich syndrome (WAS), immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome Fas or FasL deficiency aka autoimmune lymphoproliferative syndrome (ALPS), Perforin deficiency aka familial hemophagocytic lymphohistiocytosis, Arthus reaction.
Regulation of Immune Response	Role of Fas and Fas ligand in CTL-mediated lysis of target cells. CTL-mediated cell lysis, the role of perforin. Role of NK cells in mediating lysis of virally infected target cells.	
Cellular Immunity	Functional differences between innate and adaptive immune responses. Roles of CD4+ and CD8+ T cells in the adaptive immune response to viral infection. Role of CD4+ T cells in activation of macrophages.	
Immunity to Microbe and Vaccines	CTL-mediated cell lysis, the role of perforin. Immune response to extracellular bacterial infections. Immune response to intracellular bacterial infections. Delayed type hypersensitivity as it relates to host responses against intracellular bacteria. Mechanisms of immune evasion by pathogens. Types of vaccines (inactivated, attenuated, recombinant vaccines, DNA vaccines). Primary versus secondary immune responses to vaccines and microbes. Mode of action of adjuvants and examples of adjuvant materials.	

Table 1. *Cont.*

Foundational Knowledge in Immunology		
Topics	**Core Concepts**	**Clinical Correlations**
Diseases of the immune system	Immunopathologic mechanisms of hypersensitivity, allergies, and asthma: Gell and Coomb's classification of hypersensitivity. Pathophysiologic mechanisms associated with Type I (IgE)-mediated injury. Primary effector mediators released by mast cells. Pathologic changes in tissues during anaphylactic reactions –acute phase reaction and late phase reaction. Effect of mediators on target organs with clinical expression of allergic reactions. Therapeutic modulation of type I hypersensitivity. Clinical expression of anaphylactic reactions and diagnosis via skin tests, RAST, immunoassays, etc. Allergic asthma Bronchial wall changes that occur in asthma Treatment considerations of various forms of asthma Type II and type III hypersensitivity reactions Compare immunopathology of Goodpasture's syndrome and Lupus Drug-induced type I and II hypersensitivity Erythroblastosis fetalis Mechanism and histopathology of Arthus reaction Type IV cell-mediated hypersensitivities Basis for and examples of contact hypersensitivity Tuberculin reaction Autoimmunity: Organ-specific autoimmune diseases Systemic autoimmune diseases Autoimmune diseases mediated by autoantibodies Autoimmune diseases mediated by T cells Basic therapeutic intervention used to treat autoimmune diseases	Hypersensitivities, allergies and asthma, hay fever, autoimmune hemolytic anemia, systemic anaphylaxis, Goodpasture syndrome, lupus, drug-induced type I and II hypersensitivity, erythroblastosis fetalis, serum sickness, Arthus reaction, contact dermatitis, multiple sclerosis, type-I diabetes, transplant rejection, tuberculin reaction, myasthenia gravis, thrombocytopenic purpura, pemphigus vulgaris, pernicious anemia, rheumatic fever, post-streptococcal glomerulonephritis, hypersensitivity pneumonitis.
Transplantation Immunology	Immunologic basis of graft rejection Principle of first set and second set rejection Autograft, isograft, allograft and xenograft Role of CD4 and CD8 T cells in graft rejection Non-self MHC molecules as the major molecular targets in graft rejection Hyperacute, acute, and chronic rejection and the immunological reactions involved Tests used to measure tissue histocompatibility Areas of clinical organ transplantation Approaches to prolonging graft survival (immunosuppressive drugs, mAbs, immune modulators) Mechanism of inhibition of T cell activation used by several drugs The special immunological complexities that can be associated with bone marrow transplantation	Transplant rejection reactions (hyperacute rejection, acute cellular rejection, acute humoral rejection, chronic rejection), Graft-Versus-Host Reaction (GVHR), GVHD.

Table 1. *Cont.*

Foundational Knowledge in Immunology		
Topics	**Core Concepts**	**Clinical Correlations**
Immunodeficiencies	Congenital versus acquired immunodeficiency Presentation and pathophysiology associated with severe combined immunodeficiencies A condition associated with DiGeorge Syndrome B cell defects, including X-linked agammaglobulinemia, Hyper-IgM Syndrome, Common variable immunodeficiency, and selective IgA deficiency Phagocytic defects, including chronic granulomatous disease, leukocyte adhesion deficiencies, and Chediak-Higashi syndrome Acquired immunodeficiencies and their causes (AIDS, drug-induced, radiation-induced) Immunological abnormalities associated with HIV infection	Bruton's tyrosine kinase (BTK) deficiency or X-linked agammaglobulinemia (XLA), Wiskott–Aldrich syndrome (WAS), immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, SCID, DiGeorge syndrome.
Applied Immunology: Immunotherapeutics	Antibody therapy Use of immunosuppressive drugs Use of bone marrow transplantation Use of IVIG Potential therapeutic roles of cytokines or antibodies specific for cytokines and/or their receptors	Immunosuppression treatments in tissue transplants, inflammatory conditions, autoimmune diseases.
Immunodiagnostics	ELISA, Western blotting, flow cytometry, immunofluorescence staining, RIA, etc.	General principles and applications of each test in clinical diagnosis and management, point-of-care testing (POCT).

Table 2. Integration of immunological concepts corresponding to community health, patient presentations related to wellness, and genetics.

Community Health, Patient Presentations Related to Wellness and Genetics	
Topics/Core Concepts	**Clinical Correlations**
Epidemiology	Public health risks: Infection outbreaks, epidemics, endemics, pandemics, bioterrorism.
Vaccination and immunization programs	Inactivated vaccines: Live-attenuated vaccines, mRNA vaccines, Subunit, recombinant, polysaccharide, and conjugate vaccines, toxoid vaccines, viral vector vaccines, CDC vaccine schedules, antitoxins, antigen-allergy desensitization, immunosuppressive therapy in managing autoimmune disorders and cancer, the influence of immunology knowledge on healthcare, the impact of vaccines on health, economics, and social perspectives.
Herd immunity	Protection of infants, immunocompromised, and elderly patients, transmission rate, and outbreak control
Immunogenetics	HLA-typing, hereditary immunodeficiencies, diagnostics, blood transfusion reactions, genetic predisposition, resistance to infections, prospects of immunological education and research in developing countries.
Personalized medicine and precision health	Combination therapy in cancer based on immunological profiles reduced healthcare-associated pathogen resistance, reduced polypharmacy, and adverse drug reactions.
Immunological responses to occupational/ environmental factors	Smoking, pollution, radiation, and sunscreen, contaminations, industrial chemicals/irritants on chronic pulmonary, integument, organ diseases, foreign body reactions, pet/animal-related reactions, and other environmental allergic reactions.
Community-based interventions for promoting immunological health and wellness	Social determinants of health: Education level, nutrition, exercise, etc. Education: Sanitation efforts, chronic disease outcomes, cancer outcomes, genetic testing and counseling, STD testing and counseling. Nutrition: Impact of food quality on metabolic diseases, diabetes, and cardiovascular diseases, inflammation related to cultural/ethnic food preferences.

Table 3. Integration of immunological concepts corresponding to the musculoskeletal and integumentary system.

Musculoskeletal and Integumentary System	
Topics/Core Concepts	**Clinical Correlations**
Autoimmunity and immunopathology of the musculoskeletal and integumentary system	Rheumatoid arthritis, juvenile rheumatoid arthritis, reactive arthritis, scleroderma, systemic lupus erythematosus, Sjogren syndrome, ankylosing spondylitis, acute and chronic inflammatory dermatoses (dermatomyositis, myositis, etc.), blistering diseases (dermatitis herpetiformis), bullous diseases (pemphigus, bullous pemphigoid), panniculitis, vitiligo, hidradenitis suppurativa.
Inflammatory and non-inflammatory diseases	Inflammatory diseases of joints, adhesive capsulitis, bursitis, tendonitis, osteosis, polymyalgia rheumatica, JIA, osteoarthritis, fibromyalgia, vasculitis, gout, CPPD, FMF.
Skin allergies	Food medication-related, aeroallergens, autoimmune disease, immunodeficiency, infection, IgE-driven mast cell degranulation and histamine release, use of antihistamines in allergy control, angioedema.
Immunologic skin lesions	Psoriasis, lichen planus disease, scleroderma, tick bites, lice infestation (pediculosis), urticaria, dermatitis (allergic, contact, atopic), eczema, fungal infections, candidiasis, tinea capitis, tinea corporis, viral infections (varicella, herpes, enteroviruses, pityriasis rosea, bacterial and other opportunists, acne and related conditions (rosacea, acne vulgaris, acneiform skin lesions), systemic diseases, disseminated gonorrhea, secondary syphilis, lupus, Kawasaki disease, hair and nail related conditions, folliculitis.
Laboratory test findings	Allergen sensitivity test with wheal formation, fungal and bacterial cultures, skin and muscle biopsy, eosinophilia, serological markers (rheumatoid factor, anti-cyclic citrullinated peptide antibodies), inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), incorporation of immunological assays (immunofluorescence, enzyme-linked immunosorbent assay) for the detection of specific autoantibodies and immune complexes.
Pharmacology of immunomodulators	DMARDs, corticosteroids, TNF-alpha and other interleukin inhibitors, biologics, antihistamines.

Table 4. Integration of immunological concepts corresponding to the circulatory and hematologic system.

Circulatory and Hematologic System	
Topics/Core Concepts	**Clinical Correlations**
Autoimmune diseases and red blood cell disorders	Immune-complex deposition, rheumatic valvular heart disease, autoimmune hemolytic anemia, autoimmune platelet disorders (idiopathic immune thrombocytopenia (ITP) and thrombotic thrombocytopenic purpura (TTP), autoimmune clotting factor disorders (acquired hemophilias), antiphospholipid syndrome, autoimmune cytopenia, warm and cold agglutinations.
Transfusion medicine and hematopoietic stem cell transplantation	Blood type reactions, ABO and Rh groups, graft-versus-host disease (GVHD), immune reconstitution syndrome, acute and chronic rejections.
Immune deficiencies and infectious origins	Agammaglobulinemia, autoimmune cytopenia, myocarditis, pericarditis, infective endocarditis, peripheral arterial disease (PAD), infection-related diseases, circulatory inflammation and diseases, atherosclerosis, arteriosclerosis (foam cells, macrophages), peripheral vascular disease/blood vessel disorders, shock (septic, anaphylactic), human immunodeficiency virus infection and AIDS.
Neoplastic disorders and other hematological malignancies	Leukemias, lymphomas, lymphatic system disorders, lymphadenopathy, lymphedema, plasma cell dyscrasias, amyloidosis, multiple myeloma.
Laboratory test findings	Peripheral blood smears, human immunodeficiency virus testing (antibody, antigen, viral load), clinical HIV viral load test, CD4 count, interpretation of complete blood count, neutropenia, neutrophilia, serology.

Table 5. Integration of immunological concepts corresponding to the respiratory system.

Respiratory System	
Topics/Core Concepts	**Clinical Correlations**
Pulmonary defenses	Nasopharynx: Nasal hairs, turbinates, mucociliary apparatus. Oropharynx: Saliva, cough, bacteria interference, complement production. Trachea/Bronchi: Cough/epiglottic reflexes, mucociliary apparatus, dendritic cells, bronchus-associated lymphoid tissues (BALT), IgG/IgM/IgA, airway surface liquid (lysozyme, lactoferrin, secretory leukocyte proteinase inhibitor, antimicrobial peptides). Terminal airways/alveoli: Lining fluid (surfactant, fibronectin, immunoglobin, complement, free fatty acid, iron-binding proteins), alveolar macrophages, interstitial macrophages, neutrophils, dendritic cells, BALT.
Autoimmune diseases	Sarcoidosis, small cell lung cancer, bronchial asthma, allergic rhinitis, hay fever, pulmonary fibrosis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis, Goodpasture syndrome.
Paraneoplastic syndromes	Lambert-Eaton myasthenic disease, paraneoplastic cerebellar degeneration, paraneoplastic encephalomyelitis, paraneoplastic sensory neuropathy, paraneoplastic dermatomyositis.
Infection-related diseases	Tuberculous granuloma, aspergillosis, pneumonia (viral, bacterial, fungal).
Hypersensitivity reactions	Extrinsic allergic alveolitis, chronic hypersensitivity pneumonitis, pulmonary Langerhans cell histiocytosis, berylliosis, pneumococcosis.

Table 6. Integration of immunological concepts corresponding to the endocrine system and metabolism.

Endocrine System and Metabolism	
Topics/Core Concepts	**Clinical Correlations**
Autoimmune diseases	Hashimoto thyroiditis, Grave disease, Addison disease, type 1 diabetes, Cushing disease, euthyroid sick syndrome, autoimmune adrenalitis, primary adrenal insufficiency, autoimmune hypothyroidism, silent lymphocytic thyroiditis, Riedel thyroiditis, postpartum thyroiditis, atrophic thyroiditis, De Quervain thyroiditis, hypoparathyroidism.
Immunological regulations	Role of pro-inflammatory cytokines- IL-1, IL-6, TNF-alpha, etc. Promotion of hypothalamic-pituitary-adrenal (HPA) axis, fever, secretion of catecholamines. Inhibition of hypothalamic-pituitary-thyroid (HPT) axis, hypothalamic-pituitary-gonadal (HPG) axis.
Autoimmune flare-ups due to heat/UV exposure	Systemic lupus erythematosus (SLE) or Lupus, psoriasis, arthritis.
Heat-sensitive conditions	Multiple sclerosis, thyroid disorders.

Table 7. Integration of immunological concepts corresponding to human development, reproduction, and sexuality.

Human Development, Reproduction, and Sexuality	
Topics/Core Concepts	**Clinical Correlations**
Innate immune disorders	Intrauterine infections.
Cellular and antibody deficiencies	Post-exposure antigen testing.
Rh isoimmunization/incompatibility	Clinical Rh screening, hemolytic disease of the neonate (HDN), maternal IgA against necrotizing enterocolitis in preterm infants.
Immunity development	Development of child immunity during the COVID-19 pandemic, early exposure to germs, and lasting benefits.
Non-neoplastic disorders	Lichen sclerosis.
Autoimmune conditions	Antiphospholipid syndrome (APS), autoimmune oophoritis, SLE.

Table 8. Integration of immunological concepts corresponding to the nervous system and mental health.

Nervous System and Mental Health	
Topics/Core Concepts	**Clinical Correlations**
Autoimmune diseases: Antibody-mediated attack on central and peripheral nervous structures Paraneoplastic antibody production	Guillain-Barre syndrome, multiple sclerosis, optic neuritis, transverse myelitis, neuromyelitis optica, spasticity, paraneoplastic encephalitis, acute disseminated encephalomyelitis, Bell's palsy, myasthenia gravis, Lambert-Eaton myasthenic syndrome.
Infectious Diseases: Opportunistic CNS infection and malignancy CSF fluid analysis Molecular mimicry	HEENT infections (viral, bacterial, fungal, systemic, central nervous system), sinusitis, encephalitis, meningitis, toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy, *Campylobacter jejuni* infection.

Table 9. Integration of immunological concepts corresponding to the genitourinary and renal systems.

Renal System	
Topics/Core Concepts	**Clinical Correlations**
Autoimmune diseases	Sjogren disease, Goodpasture syndrome, Alport syndrome, IgA nephropathy, idiopathic nephrotic syndrome, post-streptococcal glomerulonephritis, pelvic inflammatory disease, renal vasculitis (ANCA-associated), renal ischemia.
Infection-related diseases	Post-streptococcal glomerulonephritis, pelvic inflammatory disease (PID).
Genital lesions	Inflammatory and neoplastic causes, local or systemic, male or female excoriations and infestations.
Bacterial toxin-related diseases	Hemolytic uremic syndrome, toxic shock syndrome.

Table 10. Integration of immunological concepts corresponding to the gastrointestinal system and nutritional health.

Gastrointestinal System and Nutritional Health	
Topics/Core Concepts	**Clinical Correlations**
Autoimmune diseases	Pernicious anemia, intrinsic factor, celiac disease, ulcerative colitis, Crohn's disease, MALT lymphoma.
Infection-related diseases	Secretory diarrhea, viral hepatitis, MALT lymphoma due to *Helicobacter pylori.*
Food allergies	Allergic eosinophilic esophagitis, food protein-induced proctocolitis, food protein-induced enteropathy, food protein-induced enterocolitis.
Malabsorption conditions	Acute and chronic diarrhea, celiac disease, Crohn's disease, Whipple disease, tropical sprue.
Immune or enzyme deficiency	Lactase, disaccharidase, steatorrhea, irritable bowel syndrome (IBS), short-bowel syndrome, Crohn's disease

Table 11. Integration of immunology concepts in osteopathic medicine.

Integration of Immunology in Osteopathic Medicine	
Topics/Core Concepts	**Correlation with Osteopathic Principles and Practices**
Five osteopathic models of treatment	Metabolic Energy Respiratory-Circulatory Model.
Lymphatics drainage techniques	Myofascial release (MFR), suboccipital release, Miller thoracic Pump, pedal pump (Dalrymple technique), thoracic inlet release, doming of the diaphragm, thoracoabdominal MFR, pectoral traction, rib raising, cervical chain drainage, hepatic pump, spleen pump, ischiorectal fossa release, pelvic diaphragm MFR, bladder MFR, sternal/pericardial ligaments MFR, jugular vein drainage, MOPSE protocol.
Soft tissue techniques	Lateral stretching, contralateral kneading, longitudinal kneading, cervical longitudinal traction, contralateral traction, condylar decompression, rolling, tapotement, effleurage, suboccipital inhibition, cervical paraspinal soft tissue technique, frontal sinus effleurage, maxillary sinus effleurage, trigeminal nerve decompression, auricular drainage, Galbreath technique.
Four junctions	Occipitoatlantal Junction, cervicothoracic junction, thoracolumbar junction (respiratory diaphragm), lumbosacral junction (pelvic diaphragm).
Chapman's reflex points	Neurolymphatic, gangliform, contracted, edematous, ridge-like, ropy, shotty, fibro spongy, pinhead to almond-sized palpatory viscerosomatic tissue reflex points.

3. Discussion

3.1. Foundational Knowledge in Immunology

The foundational immunology course in medical school is geared towards students' understanding of the mechanisms underlying various diseases and guiding diagnosis and treatment decisions. Students learn key immunological concepts such as how the components of the immune system are generated and organized, the mechanisms of immune responses, and the pathology of immunodeficiencies. A solid foundation in immunology that provides medical students with a comprehensive perspective on the immune system's role in health and disease will enable students to provide better patient care and offer clearer communication to patients regarding expansive health topics such as vaccinations, autoimmune conditions and their manifestations, and transplant and infusion safety.

The Host Defense Mechanisms course at CHSU-COM introduces first-year osteopathic medical students to the various elements of the immune system; students become familiar with the strategies and mechanisms employed by the immune system to evade pathogens, distinguish between self and non-self-antigens, and create long-lasting cell-mediated protection. These defense mechanisms are categorized into two major components: innate immune responses and adaptive immune responses. The course uses team-based as well as self-designated learning activities, case-based application exercises, and clinically integrated scenarios that incorporate immunological topics in infectious diseases, histopathology, and laboratory analyses. Medical students retain immunological concepts most effectively when they are engaged in assignments that provide a clinical context [23,29–31]. The course is designed to deliver the basic "core" concepts in immunology (Table 1), which are reinforced and scaffolded in the subsequent systems-based courses covered over the first and second years (Tables 2–10). In the systems-based courses, students connect the immunological principles and mechanisms with the clinical world of diagnosis and therapy of diseases relevant to the system being covered. Furthermore, the courses integrate immunological concepts into osteopathic principles and practices wherever applicable (Table 11).

Unlike the study of alternate organ systems, the immune system is not confined to one location, organ, or tissue type within the body. It is therefore logical, in the facilitation of better-quality medical education, for the teaching of immunological concepts to have significant integration and numerous clinical applications among the teachings of varying organ systems.

The General Medical Council (GMC) recommends that the medical curricula be structured to provide a balanced learning opportunity and to integrate the learning of basic and

clinical sciences so that students link theory with practice [32]. The Association of American Medical Colleges (AAMC) also emphasizes that the scientific basis of medicine should be integrated into coursework offered throughout the medical education curriculum [33]. For true integration to occur, the curriculum should reinforce the basic ideas repeatedly, building upon them until the student has grasped the full context or mechanism associated with them [34]. A continuous reinforcement of topics covered in previous courses allows for a progression in which the student first establishes a foundation of knowledge and gradually builds the ability to comprehend information of increasing levels of complexity and integration throughout the curriculum [35].

Table 1 lists several diseases that are relevant for use in clinical correlations for the integration of immunology concepts in a foundational basic science course. For example, SCID (severe combined immunodeficiency syndrome) can be used to highlight the extent and severity of disease processes that can manifest across multiple organ systems in the absence of a well-functioning immune system. SCID patients experience nutritional deficiencies due to the immune system's control of the gut microbiota. In some cases of SCID (such as the X-linked category), growth and development can also be impaired due to recurrent infections (urogenital or respiratory) and chronic inflammation (musculoskeletal and gastrointestinal systems; Tables 3 and 11).

An alternate example is the phenomenon of antibody cross-reactivity in streptococcal strains. Antigenic similarities between antibodies made against streptococcus prime the immune system to attack homologous epitopes found on myocardiocytes, a concept that can be taught alongside basic immunology as well as upper-division cardiovascular pathology topics (Table 4). Antigen-antibody interactions can also be utilized to teach the concept of "point-of-care" testing (POCT; Table 1), clinical laboratory testing carried out close to the patient care site where therapy or care is rendered. POCT covers a wide range of testing modalities, including immunoassays, flow cytometry, and enzyme-linked immunosorbent assay (ELISA) (Table 1), and offers fast test result turnaround compared to laboratory testing, with the potential to get a result rapidly so that appropriate therapy can be adopted, leading to improved clinical or economic outcomes [36].

The advances in our understanding of the immune system are leading to changes in the techniques that doctors use to treat different types of cancer and other immune-related diseases. Many cytokines and antibodies specific for cytokines and/or their receptors are now identified as potent chemotherapeutic agents [37,38]. Incorporation of immunotherapy, including novel cancer treatments and how they are used in clinical settings, is therefore essential in a medical curriculum, as students will acquire the knowledge base to treat immunologically mediated disorders, such as immunodeficiencies, hypersensitivity reactions, autoimmune diseases, tissue and organ transplants, cancers, inflammatory disorders, infectious diseases, and any other illness where immunotherapy can extend life expectancy [38]. Students will thus gain a better understanding of how immunotherapy can improve the quality of life and longevity of those who are afflicted.

3.2. Integration in Community Health, Patient Presentations Related to Wellness and Genetics

A list of immunological topics in community health, patient presentations related to wellness and genetics, and the pathologic conditions that may be used for clinical correlations are provided in Table 2.

The World Health Organization (WHO) estimates that 4 million deaths worldwide are prevented by childhood vaccination, providing a valuable arsenal for healthcare providers against adverse public health outcomes [39]. This number jumps to more than 50 million deaths that can be prevented through immunization this decade. By 2030, it is estimated that measles vaccination can save nearly 19 million lives, and Hepatitis B vaccination can save 14 million lives [40]. Therefore, integrating these public health measures and the CDC vaccine schedules into the medical school curriculum is pivotal for the future of patient education and prevention medicine.

Vaccines, invented by Edward Jenner in 1796, strive to eradicate pathogens based on their ability to induce and amplify host immune responses. More specifically, these adaptive immune responses include a cell-mediated branch of T-cells, which recognize cells infected by viruses or other intracellular pathogens through specific MHC molecules displayed on antigen-presenting cells like macrophages, dendritic cells, or B cells. Killing these infected cells through direct cytotoxicity or activating pro-apoptotic pathways is CD8+ T-cell mediated. Additionally, cytokine-meditated antibody production by mature naive B-cells, organized by CD4+ T-cells, prevents the pathogen from spreading. Similarly, when vaccines introduce antigens into the body, B-cells and T-cells work together to undergo seroconversion or the formation of antibodies against specific viral components. Inactivated vaccines, which use dead virus particles or fragments, live-attenuated, polysaccharide, recombinant, and conjugate vaccines, all rely on this method to achieve immunity. Long-term immunity to repeat infections is prevented by the production of dormant memory B-cells and class-switching from IgM to IgG antibodies. This humoral immunity confers a more robust and rapid response to the insulting pathogen, allowing the host to experience mild or asymptomatic symptoms but not preventing a blockade in transmission [41].

Some viruses, like Influenza, utilize low-fidelity replication cycles to overcome immune responses generated by vaccines. The faulty repair mechanism, coupled with a high replication rate, leads to genetic diversity in the progeny of virus particles with new epitopes no longer recognized by pre-existing memory B-cells. This process, called antigenic drift, challenges public health officials as it requires annual vaccines for novel strains of the Influenza virus. On the contrary, antigenic shift requires multiple different Influenza stains to infect an intermediate zoonotic host, commonly porcine, simultaneously. Genetic material is reassorted, creating a phenotype that enables the virus to produce hypervirulent factors, invades immune responses, and allows rapid transmission, thus leading to pandemics [42].

Major global health threats have sparked interest in developing novel, more immediate vaccine strategies. Most recently, the COVID-19 pandemic saw the advent of messenger RNA (mRNA) vaccines. This mode of immune stimulation utilizes a new method of intracellular delivery into host cells through a lipid nanoparticle. Upon entry, the exogenous mRNA translates into antigenic viral proteins displayed on host cell membranes. In SARS-CoV-2, the spike protein, which the virus uses for attachment and entry, is encoded into a self-amplifying mRNA sequence (for Pfizer and Moderna vaccines), allowing the host to use its cellular machinery to make a more native immune response to this foreign protein. Johnson and Johnson and AstraZeneca vaccines used another adenovirus vector-based method (Ad vectors), a double-stranded DNA genome encased in a protein capsid, to express in vivo vaccine antigens [43]. The application of these newly engineered vaccine delivery approaches has shown promise for future preventative measures, and it will likely play a significant role in developing future vaccines for existing and novel pathogens. Therefore, healthcare curricula must include their implications, mechanisms, and adverse effects in various clinical scenarios. Student learning objectives for this subject should focus on, but not be limited to, the following: defining terminologies, describing the principles of vaccine concepts and the historical perspective of vaccine evolution, differentiating between various vaccine types with specific examples for respective vaccine groups, identifying the safety factors of a vaccine and vaccine risk factors for specific susceptible populations, explaining the concepts of DNA/cDNA and mRNA vaccines, including the COVID-19 vaccine and its mechanism of action, and understanding the significance of age-specific vaccination schedules for specific population groups, including childhood vaccines vs. adult vaccines. Moreover, recent research highlights the importance of vaccine hesitancy and the role of social, cultural, and political factors in shaping public attitudes toward vaccination [44–48]. By incorporating these socio-behavioral aspects associated with the behavioral model in osteopathic medical education, future healthcare providers can play a vital role in promoting vaccine acceptance and advocating for evidence-based immunization practices in diverse communities.

3.3. Integration in Musculoskeletal and Integumentary System

Table 3 lists the immunological topics in musculoskeletal and integumentary systems, as well as the pathologic conditions that may be used for clinical correlations.

Integrating immunological concepts within the musculoskeletal and integumentary systems oversees a growing list of clinical outcomes at the intersection of immunology, pathology, rheumatology, and dermatology. The intricate interplay between the immune system and these organ systems plays a pivotal role in maintaining homeostasis and in the pathogenesis of various autoimmune, inflammatory, and infectious diseases. Immunological processes influence the development and progression of conditions such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus, dermatomyositis, and more [49]. As such, comprehending the immunological aspects of musculoskeletal and integumentary health is vital for inclusion in medical school curricula, as it equips future healthcare professionals with essential knowledge for diagnosing, managing, and treating a wide array of conditions, thereby enhancing their ability to provide comprehensive and effective patient care.

Rheumatoid Arthritis (RA) is a chronic autoimmune disease with various systemic complications primarily affecting the joints, resulting in increased inflammation of the synovium, painful joint swellings, and destruction [50,51]. Patients may experience pain in one or more joints, stiffness, tenderness, fatigue, weakness, and joint deformities. Additionally, environmental triggers such as smoking, infections, and hormonal factors have been implicated in disease onset and progression [50,52]. Although unknown, many proposed mechanisms of immunopathogenesis for RA have been proposed, involving a complex interplay of genetic, environmental, and immunological factors. Genome studies have identified several genetic risk loci associated with RA susceptibility, including the human leukocyte antigen (HLA) region and genes involved in immune regulation and signaling pathways [53]. In the synovium of RA patients, dysregulated immune responses involving innate and adaptive immune cells contribute to sustained inflammation and joint damage. Synovial infiltration by activated T cells, B cells, macrophages, and dendritic cells results in the production of pro-inflammatory cytokines such as TNF-alpha, IL-1, and IL-6, driving synovial hyperplasia and cartilage degradation [54]. Moreover, the formation of autoantibodies against citrullinated proteins, notably anti-cyclic citrullinated peptide (anti-CCP) antibodies, is a hallmark of RA and correlates with disease severity and progression [55]. These autoantibodies contribute to immune complex formation and complement activation, further perpetuating the inflammatory cascade within the synovium [56]. Thus, a comprehensive understanding of the immunopathogenesis of RA is crucial for future clinicians, allowing a targeted therapeutic intervention, both pharmaceutical and osteopathic.

Ankylosing spondylitis (AS) is another chronic inflammatory disease primarily affecting the axial skeleton, characterized by sacroiliitis, spondylitis, and enthesitis. The disease causes vertebrae in the spine to fuse, resulting in kyphosis, and patients present with back pain, hip stiffness, neck pain, and fatigue [57]. The immunopathogenesis of AS, like RA, involves a multifaceted interplay of causes but is primarily associated with the HLA-B27 isotype present in over 90% of AS patients [58]. HLA-B27 mediates aberrant immune responses by presenting arthritogenic peptides to CD8+ T cells, leading to inflammation at enthesis sites. Additionally, microbial infections, particularly involving Gram-negative bacteria like *Klebsiella pneumoniae*, have been implicated as environmental triggers in AS pathogenesis, potentially inducing cross-reactive immune responses via molecular mimicry [59]. Dysregulated cytokine production, notably TNF-α, IL-23, and IL-17, further contributes to inflammation, osteoclast activation, and bone remodeling in AS [60]. Moreover, dysbiosis (imbalance in gut microbiota composition) has been linked to AS, with alterations in microbial composition potentially influencing immune dysregulation and disease progression [61]. Similarly, many other immunological skin lesions and gut health are intricately linked through the concept of the gut-skin axis, which highlights the bidirectional communication between the gut microbiota, the immune system, and the skin. Disruptions in gut health, such as dysbiosis or increased intestinal permeabil-

ity (leaky gut), have also been implicated in the pathogenesis of various immunological skin disorders. For example, conditions like psoriasis, atopic dermatitis, and acne have been associated with alterations in gut microbiota composition and increased intestinal permeability [62]. Understanding the immunological mechanisms underlying these disorders is essential for elucidating disease etiology, identifying novel therapeutic targets, and advancing personalized treatment strategies.

Osteopathic manipulative medicine (OMM) can be integrated into the curriculum as an approach to the management of RA. OMM encompasses a variety of hands-on techniques, including soft tissue manipulation, stretching, and gentle joint mobilization, which are applied to restore musculoskeletal balance and optimize physiological function [63]. Studies have suggested potential benefits in reducing pain, mobilizing lymphatic drainage, improving joint mobility, and enhancing the quality of life in patients with inflammatory arthritis [64]. OMM techniques may help mitigate secondary musculoskeletal dysfunctions and compensatory patterns arising from chronic inflammation and RA joint stiffness [64]. Additionally, OMM may exert systemic effects through neurophysiological mechanisms, modulating pain perception, autonomic function, and immune responses [65]. Incorporating OMM into the multidisciplinary management of RA may offer patients a non-pharmacological adjunctive therapy that promotes holistic care.

3.4. Integration in Circulatory and Hematologic System

A list of immunological topics in the circulatory and hematologic system and the pathologic conditions that may be used for clinical correlations is provided in Table 4.

Understanding the interactions between the cardiovascular and hematologic systems is essential in immunology and medical education. These systems work closely together to ensure proper circulation, oxygenation, and immune surveillance throughout the body. Diseases affecting both systems, such as peripheral arterial disease (PAD) and thrombotic thrombocytopenic purpura (TTP), highlight the complex interplay between immunity, vascular function, and hematopoiesis. Incorporating these concepts into medical education enables future healthcare professionals to comprehensively evaluate and manage conditions that arise from dysregulation in either system.

Thrombotic Thrombocytopenic Purpura (TTP) is a rare autoimmune disorder characterized by the formation of blood clots in small blood vessels throughout the body. Deficiency of ADAMTS13, an enzyme responsible for cleaving von Willebrand factor, is a hallmark of TTP [66]. Deficient ADAMTS13 activity leads to the accumulation of ultra-large von Willebrand factor multimers, promoting platelet adhesion and aggregation and causing thrombosis. Treatment typically involves plasma exchange to remove autoantibodies and replenish ADAMTS13 levels [67]. Idiopathic thrombocytopenic purpura (ITP) is another autoimmune disorder characterized by low platelet counts due to immune-mediated destruction of platelets.

Peripheral arterial disease (PAD) is an inflammatory condition characterized by narrowed arteries that reduce blood flow to the arms and legs. This narrowing leads to atherosclerosis, a condition a condition where fatty deposits build up in the arteries, restricting blood flow and causing symptoms such as claudication [68]. Atherosclerosis is a significant risk factor for stroke and myocardial infarction. Studies have shown that M2 macrophages play a role in the regression of atherosclerosis by secreting anti-inflammatory cytokines such as IL-10 and TGF-Beta [69]. Treatments for PAD often include lipid-lowering drugs and interventions targeting M2 macrophages.

Rheumatic Fever is an infection-related immune disease that can lead to rheumatic valvular heart disease, where the heart's valves become permanently damaged. Untreated Streptococcal infections can lead to rheumatic fever, which affects connective tissues, including those in the heart [70]. Molecular mimicry is a pathogenic hallmark of this disease, in which N-acetyl glucosamine, the Group A Streptococcal epitope, and Streptococcal M Protein structurally mimic cardiac myosin [71]. This mimicry allows these antibodies to attack the heart valves and trigger an immune response involving B and T cells. The

heart's valves eventually become scarred, leaky, and non-functioning. This process can result in heart failure, bacterial endocarditis, and ruptured heart valves. Rheumatic heart disease also affects the body's connective tissues, including the heart, joints, skin, and brain, resulting in inflammation [71].

Hematopoiesis refers to the development of blood components, including red and white blood cells. Hematopoiesis occurs in the bone marrow, spleen, and liver. In addition, leukopoiesis is the production of white blood cells, and this lineage has multiple types of cells. The progenitor cell is the myeloid stem cell, which becomes myeloblasts. The myeloblast can become an immature basophil, eosinophil, or monocyte, then differentiate into a basophil, eosinophil, or monocyte, respectively [71]. The myeloblast undergoes development into a band neutrophil, which eventually matures into a neutrophil. Similarly, a lymphoid stem cell can mature into a lymphocyte. The stages of B cell development begin with lymphoid progenitor cells, resulting in early progenitor B cells, precursor B cells, immature naïve B cells, transitional B cells, and then mature naïve B cells [71]. Immature naïve B cells then migrate from the bone marrow into the spleen and lymph nodes, where they mature into effector B cells. T cell progenitors migrate from the bone marrow, enter the thymus, undergo selection, and mature into functional T cells. T cell precursors are made in the bone marrow and then migrate to the cortex of the thymus for positive selection. This process produces CD4+ and CD8+ cells, which migrate to the medulla of the thymus for negative selection [71]. The mature but naïve CD4+ and CD8+ cells migrate to the lymph nodes where they mature into helper T cells and cytotoxic T cells upon encountering the antigens. Disruptions or aberrations in this finely regulated process can lead to pathological consequences. For example, disruptions in hematopoiesis can give rise to hematological malignancies, including leukemia, lymphoma, and myeloma. In these conditions, aberrant proliferation and differentiation of hematopoietic stem or progenitor cells lead to the accumulation of malignant cells within the bone marrow and peripheral blood. These cancerous cells often disrupt normal hematopoiesis, impairing the production of healthy blood cells and causing symptoms such as anemia, thrombocytopenia, and leukopenia [72].

Both cardiovascular and hematological systems highlight the importance of recognizing connectedness within the body in a closed circuit of vessels, fostering a comprehensive approach to patient care that considers systemic and local immune responses. Studies have shown that osteopathic manipulative treatment (OMT) can enhance vascular endothelial function, reduce arterial stiffness, and improve arterial compliance, thereby promoting optimal blood flow and reducing cardiovascular risk [73]. Additionally, OMT may facilitate the mobilization of hematopoietic stem cells from the bone marrow into the peripheral blood, potentially influencing hematopoiesis [74]. Central lymphatic releases, mainly at the thoracic outlet, have proven to be most beneficial in clearing infections, normalizing circulation, and maintaining homeostasis within the body's five osteopathic treatment models.

3.5. Integration in the Respiratory System

Table 5 lists the immunology topics or concepts that may be used in the respiratory system and the pathologic conditions that may be used for clinical correlations.

In the realm of pulmonology, immunology plays a significant role in various pathologies, influencing both their development and progression. Lambert Eaton myasthenic disease is a prominent example to use for discussion of autoimmune conditions characterized by antibodies targeting voltage-gated calcium channels (VCGG) at the neuromuscular junction [75]. Additionally, small cell lung cancer cells often exhibit affected VCGGs, leading to the presence of positive VCGG antibodies. Patients typically display muscle weakness, diminished reflexes, ptosis, and no muscular atrophy [75]. Addressing the underlying small cell lung cancer malignancy is crucial for managing Lambert-Eaton symptoms effectively.

Sarcoidosis is a multi-system granulomatous disorder affecting various organs. In the lungs, granulomas are typically found in the hilar lymph nodes, interstitial spaces, and perilymphatic regions around bronchioles and pulmonary venules [76]. Granulomatous

inflammation is initiated by an inhaled antigen and mediated by CD4+ helper T cells, which release cytokines through a Th1 response. This process further promotes T cell proliferation and macrophage activation, leading to granuloma formation. Sarcoidosis can result in pulmonary interstitial fibrosis as fibroblasts deposit collagen to replace the granulomas. Histopathological examination typically reveals well-formed non-caseating epithelioid granulomas distributed in a lymphatic pattern [76]. Additionally, characteristic features such as Schaumann bodies and asteroid bodies aid in disease identification.

Goodpasture Syndrome presents as an autoimmune disorder characterized by widespread pulmonary hemorrhage and renal involvement. Autoantibodies target the non-collagenous domain of the alpha3 chain of collagen IV [77]. In the lungs, these autoantibodies contribute to the destruction of the alveolar basement membrane, leading to necrotizing hemorrhagic interstitial pneumonitis. Immunofluorescence typically reveals linear IgG staining along the alveolar septa. Histopathological examination of lung tissue often shows necrosis of alveolar walls, intra-alveolar hemorrhages, hemosiderin-laden macrophages, fibrous thickening, and hyperplasia of type 2 pneumocytes [77].

Bronchial Asthma represents a hypersensitivity reaction within the airways characterized by recurring episodes of reversible bronchial constriction. Two distinct phenotypes with differing pathologic mechanisms are recognized: Atopic (extrinsic, T2) asthma and non-atopic (intrinsic) asthma [78]. Atopic asthma involves a Type 1 Hypersensitivity reaction mediated by IgE and presents with positive allergen skin tests. This condition stems from an allergy to antigens, with Th2 lymphocytes orchestrating the inflammatory response. The exaggerated Th2 response prompts the release of cytokines such as IL-4 and IL-13, which stimulate IgE release, activate eosinophils via IL-5, and induce mucous production via IL-13.

Moreover, this reaction manifests in two distinct phases: the early-intermediate phase and the late phase. The early-intermediate phase, occurring within minutes, is attributed to the binding of IgE to mast cells, subsequently leading to the release of cytokines [78]. This cascade results in heightened mucus production, increased vascular permeability, vasodilation, and bronchoconstriction, contributing to respiratory distress. Conversely, the Late-phase reaction, occurring over hours, is characterized by inflammatory mediators stimulating the production of chemokines, which in turn recruit eosinophils, leading to epithelial damage and further bronchoconstriction [78]. Notably, individuals with atopic asthma exhibit a positive response to bronchodilators and anti-inflammatory medications.

In contrast, non-atopic asthma lacks eosinophilic inflammation and Th2 markers but exhibits abundant alveolar neutrophilic inflammation [78]. Common triggers for this phenotype include cigarette smoke, obesity, GERD, infections, and pollutants. In addition to bronchial hyperreactivity, Th1, Th17 cells, neutrophils, and cytokines such as IL-6, IL-8, and IL-17 contribute to the inflammatory process [78]. Unlike atopic asthma, non-atopic asthma shows poor responsiveness to steroids.

3.6. Integration in the Endocrine System and Metabolism

A list of immunology topics or concepts and the pathologic conditions that may be used for clinical correlations in the endocrine system and metabolism is provided in Table 6.

Understanding endocrinology and reproductive health encompasses the integration of immunological aspects into various disease conditions. For example, Type 1 diabetes is an autoimmune disorder marked by the destruction of B cells and a severe deficit in insulin production. Classified as a Type IV hypersensitivity reaction, it reflects a breakdown in self-tolerance within T cells directed against B cell antigens [79]. Antigen-presenting cells (APCs) play a crucial role in presenting these autoantigens to helper T cells, triggering the release of cytokines and the recruitment of B and T lymphocytes. Consequently, these lymphocytes cause both a direct cytotoxic and antibody-mediated effect on pancreatic B cells [79]. Histopathological analysis often reveals leukocytic infiltrates within the islets, predominantly composed of T cells, alongside a decrease in both the number and size of pancreatic islets. Genetic predisposition to Type 1 diabetes commonly involves HLA-DR3

and HLA-DR4 alleles [79]. Clinically, the classic triad of symptoms includes polyuria, polydipsia, and polyphagia. If left unmanaged, Type 1 diabetes can lead to potentially life-threatening complications such as diabetic ketoacidosis [79].

Hashimoto thyroiditis represents a type of hypothyroidism characterized by an autoimmune destruction of the thyroid gland. Notable autoantibodies involved are antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG) [80]. The impairment of TPO function inhibits the conversion of iodide to iodine crucial for thyroglobulin incorporation, leading to a deficiency in T3 and T4 release in response to TSH stimulation. Histopathological examination typically reveals painless, symmetric enlargement of the thyroid gland accompanied by extensive lymphocytic infiltration and the presence of Hurthle cells [80]. HLA subtypes DR3 and DR5 are implicated in the disease's genetic predisposition, while laboratory findings commonly exhibit elevated TSH levels alongside decreased T3/T4 levels. Additionally, Hashimoto thyroiditis predominantly affects females aged between 45 and 65 years [80]. Common symptoms indicating hypothyroidism typically involve weight gain, fatigue, intolerance to cold, dry skin, hair thinning, reduced heart rate, and feelings of depression.

Graves disease, the most prevalent cause of hyperthyroidism, arises from an autoimmune condition in which autoantibodies target thyroid proteins and TSH receptors [81]. Thyroid-stimulating immunoglobulin (TSI) binds to TSH receptors, mimicking their actions, leading to heightened T3/T4 levels and diminished TSH levels in laboratory tests. Genetic predisposition often involves HLA-DR3 and HLA-B8 alleles, with the peak incidence typically occurring between ages 20 and 40 [81].

3.7. Integration in Human Development, Reproduction, and Sexuality

Table 7 lists the immunology topics or concepts and the pathologic conditions that may be used for clinical correlations in human development, reproduction, and sexuality.

To comprehend reproductive medicine fully, one must intertwine it with the complexities of immunology. Among the notable conditions within this field is hemolytic disease of the newborn (HDN), which necessitates rhesus (Rh) screening. HDN, also known as erythroblastosis fetalis, manifests when a pregnant mother's blood type clashes with that of her unborn baby [82]. If the mother is Rh-negative and the baby is Rh-positive, her antibodies may attack the fetus, leading to manifestations of pallor, hyperbilirubinemia, hydrops fetalis, and hepatosplenomegaly in the newborn. This incompatibility arises in subsequent pregnancies, as the creation of antibodies against Rh-positive factors takes time. Therefore, it is imperative to conduct Rh screening for mothers during the initial trimester to prevent any adverse repercussions. For Rh-negative mothers, administering the drug RhoGAM at 28 weeks of gestation and within 72 h postpartum is crucial [82]. Furthermore, in managing an affected newborn, blood transfusions and expedited delivery constitute primary interventions.

Antiphospholipid syndrome (APS) is an immune-mediated condition that is prevalent among women [83]. APS is characterized by the development of arterial and venous thrombosis, as well as pregnancy loss occurring after the 10th week of gestation. Diagnostic tests such as enzyme-linked immunosorbent assay (ELISA) or functional assays may reveal the presence of specific antibodies, including anticardiolipin, anti-beta-2-glycoprotein-1, or lupus anticoagulants, alongside antiphospholipid antibodies. It is noteworthy that these antibodies can lead to a false positive result in syphilis screening [83]. Clinical manifestations of APS can affect any organ, with the involvement of three organs indicating a particularly severe condition. Diagnosis of APS requires the fulfillment of both clinical and laboratory criteria. Clinical criteria entail vascular thrombosis or adverse pregnancy outcomes, while laboratory criteria involve detecting specific antibodies. Management of APS involves the administration of medications like Warfarin or Heparin, with the choice depending on the patient's pregnancy status [83].

Prominent among non-neoplastic epithelial vulvar disorders is lichen sclerosus, an autoimmune dermatosis predominantly affecting post-menopausal women. This condition

manifests with epidermal thinning, dermal sclerosis, and chronic inflammatory infiltration in the deeper layers of the dermis [84]. Although the precise pathogenesis is yet to be fully explained, evidence suggests the presence of activated epithelial T cells within the subepithelial inflammatory infiltrate. Moreover, individuals afflicted with lichen sclerosus may face an increased susceptibility to developing squamous cell carcinoma of the vulva [84].

3.8. Integration in the Nervous System and Mental Health

Table 8 lists the immunology topics or concepts and the pathologic conditions that may be used for clinical correlations in the nervous system and mental health.

A solid foundation in immunology yields crucial insights into the initiation and pathogenesis of various neurological disorders. Although the nervous system is often regarded as one of the immune-privileged areas of the body, it remains vulnerable to various autoimmune diseases triggered by infections, paraneoplastic conditions, and general trauma [78]. Furthermore, students must acknowledge that immunocompromised individuals are especially prone to opportunistic infections affecting the central nervous system. This underscores the importance of future physicians familiarizing themselves with specialized prophylactic measures tailored for these individuals.

Understanding humoral and cell-mediated diseases is especially significant in examining the influence of immunology on the central nervous system (CNS). For example, in disorders such as Guillain-Barré syndrome (GBS), grasping the concepts of molecular mimicry and self-tolerance within the field of immunology is essential for comprehending the implications. In GBS, the immune system mounts a response against a *Campylobacter jejuni*, infection and subsequently produces self-reactive antibodies, which can then attack the gangliosides on peripheral nerves [85]. In contrast, multiple sclerosis (MS) features an immunological aberration in the activation and autoreactivity of infiltrative T-cells against myelin antigens.

Incorporating immunology into the study of the central nervous system enables students to comprehend intricacies in immune regulations, including the concept of immune-privileged sites. In clinical practice, analyzing cerebrospinal fluid (CSF) can leverage the immune system's role to discern the etiology of meningitis (viral, bacterial, fungal) based on differential responses of the immune system [85]. Pathogens face the unique challenge of breaching the blood–brain barrier (BBB) to invade the central nervous system (CNS), employing strategies that involve either compromising the barrier's integrity or subverting host immune defenses. By understanding the role of the BBB in regulating immune cell trafficking and the importance of CSF analysis in clinical practice, students can appreciate the interconnectedness of the immune system and the CNS. Additionally, immunodeficient individuals also face vulnerability to opportunistic CNS infections. For example, in HIV/AIDS, depletion of CD4+ T cells and impairment of cellular immunity compromise the body's ability to mount effective immune responses, allowing opportunistic infections like toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy (PML) to manifest in the CNS [85].

Beyond pathogen-induced immune dysfunction, the nervous system can experience paraneoplastic complications stemming from neoplasms in other regions. A comprehensive grasp of the immune system's reaction is imperative for understanding the subtleties involved in diagnosing and treating autoimmune conditions like myasthenia gravis (MG) and Lambert-Eaton syndrome (LES). These conditions may appear similar due to their shared involvement of autoantibodies targeting specific components of the neuronal signaling pathway. However, recognizing the remarkable specificity of antibody production enables clinicians to differentiate between them. In MG, the immune system generates autoantibodies against acetylcholine receptors (AChRs), resulting in impaired neuromuscular transmission that worsens with exertion. Conversely, in LES, autoantibodies target presynaptic voltage-gated calcium channels, disrupting neurotransmitter release and causing muscle weakness that improves with exertion [78]. The distinct consequences of antibody

formation also directly impact pharmacologic intervention, as treatment with cholinesterase inhibitors only alleviates MG symptoms, with no effect on LES.

3.9. Integration in the Renal System

A list of immunology topics or concepts and the pathologic conditions that may be used for clinical correlations in the renal system are provided in Table 9.

Immunology is integral to the study of the renal system as it provides insights into the mechanisms underlying the multitude of immune-mediated renal diseases, such as glomerulonephritis, urinary tract infections (UTI), kidney transplant rejection, and other autoimmune disorders. Glomerulonephritis stands out as a prime example of immune-mediated renal pathology. This collective term encompasses a diverse range of kidney diseases characterized by inflammation and injury to the glomeruli, the functional units responsible for filtering blood and forming urine. Importantly, many forms of glomerulonephritis have an immune basis, implicating aberrant immune responses in their pathogenesis [78]. For instance, post-infectious glomerulonephritis (PIGN) frequently arises following infection with certain pathogens, notably *Streptococcus pyogenes*. In PIGN, the immune system mounts an exaggerated response to antigens shared between the infectious agent and renal tissues, leading to the deposition of immune complexes within the glomeruli and subsequent inflammation and damage [85].

Furthermore, autoimmune disorders such as lupus nephritis and Goodpasture disease exemplify the ability for aberrant immune system activation to result in hypersensitivity reactions. In lupus nephritis, autoantibodies directed against self-antigens, including nucleic acids and nuclear proteins, contribute to immune complex deposition (Type III hypersensitivity) in the kidneys, culminating in renal inflammation and injury. Similarly, Goodpasture disease involves the production of autoantibodies targeting the alpha-3 chain of type IV collagen, a key component of the glomerular basement membrane [78]. This immune-mediated attack on renal tissues underpins the pathogenesis of Goodpasture disease and underscores the critical role of immunological processes in renal pathology.

Impaired immune defenses in the renal system frequently lead to UTIs, one of the most common nosocomial infections [78]. Medical students need to grasp these concepts to recognize the clinical manifestations of renal antibodies or infection-related disorders, interpret diagnostic tests, and formulate appropriate treatment strategies. In terms of infectious disease, the urinary system serves as a critical barrier against microbial invasion, with innate and adaptive immune mechanisms working in concert to thwart pathogen colonization. However, urinary tract pathogens have evolved sophisticated strategies such as adherence pili and biofilm formation to evade immune surveillance and adhere to uroepithelial surfaces, leading to treatment challenges [85].

Another illustration of the interplay between renal pathology and the immune system is evident in the dipstick test, a frequently employed diagnostic method for urinary tract infections (UTIs) [85]. The presence of leukocyte esterase, an enzyme produced by white blood cells, signifies inflammation or infection within the urinary tract. Infection-related kidney stones are also a unique consequence of microbial colonization of the renal system, as they form as a result of bacterial urease activity, which increases urinary pH and promotes the formation of struvite crystals. Immune responses to urinary tract infections may exacerbate inflammation and contribute to stone formation [78].

In the genitourinary system, the immune system protects against pathogens while maintaining tolerance to self-antigens. For example, in the male reproductive system, the testes are considered immune-privileged sites, where the blood–testis barrier prevents the entry of immune cells and antibodies. This immune privilege is essential for preventing autoimmune responses against sperm antigens. In females, the mucosal immune system in the reproductive tract helps protect against sexually transmitted infections (STIs) while also tolerating sperm and embryos during reproduction [78].

3.10. Integration in the Gastrointestinal System and Nutritional Health

Table 10 lists the immunology topics or concepts and the pathologic conditions that may be used for clinical correlations in the gastrointestinal system and nutritional health.

For medical students studying gastrointestinal (GI) tract diseases, grasping fundamental concepts like mucosal immunity and immune tolerance, food allergies, and microbial commensalism within the GI system is essential. The constant interaction between the GI tract and the external environment underscores the intricate relationship between gastrointestinal health and immune function. There is a wide array of diseases affecting the gastrointestinal (GI) system that are diagnosed based on the detection of specific antibodies (Kumar et al., 2021). Antibodies play a pivotal and diverse role in categorizing many of these diseases, often being part of the diagnostic criteria or therapeutic target. For instance, the detection of antimitochondrial antibodies (AMA) is indicative of primary biliary cholangitis (PBC), aiding in the differential diagnosis between PSC and PBC [78]. In the case of malabsorptive conditions, anti-tissue transglutaminase antibodies (anti-tTG) serve as a key marker for celiac disease, while antibodies against parietal cells are seen in the instances of autoimmune gastritis and pernicious anemia [85].

Immune tolerance refers to the ability of the immune system to recognize and tolerate harmless antigens while mounting appropriate responses against pathogens [78]. In the GI tract, immune tolerance mechanisms are crucial for preventing excessive inflammation and maintaining tissue homeostasis. When these mechanisms fail to properly function, food allergies result from aberrant immune responses to harmless dietary antigens, leading to allergic reactions. Key immunological mechanisms involved in food allergies include IgE-mediated hypersensitivity reactions such as those leading to anaphylactic shock, and T cell-mediated responses. Certain food allergens can stimulate T cell responses, resulting in delayed-type hypersensitivity reactions and chronic inflammation. [85].

Malignancies such as MALT lymphoma are yet another example of immune-related pathology that relates to immunology with both gastrointestinal and infectious diseases. H. pylori infection triggers chronic inflammation in the gastric mucosa [78]. The bacterium induces the production of pro-inflammatory cytokines, such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), by activating immune cells like macrophages and T cells. Chronic inflammation creates an environment conducive to the oncogenic transformation of lymphoid cells [85].

By delving into these specific examples, medical students can gain a deeper understanding of how immune tolerance and microbial commensalism contribute to GI health and pathology. This knowledge equips them with the tools to recognize and manage disorders arising from dysregulation of these processes, ultimately enhancing their ability to provide effective care for patients with GI-related conditions.

3.11. Integration in Osteopathic Medicine

Osteopathic medicine emphasizes a holistic approach, asserting that all body systems are interrelated and mutually affect each other [1]. The lymphatic system's crucial role in immune function makes it a vital area of focus for any healthcare provider, especially those trained in osteopathy. As described by A. T. Still, the founding father of Osteopathic Medicine, to avoid seeing a confused nature in the form of disease, it is essential to keep the lymphatics normal all the time, as manipulation of lymphatics is connected to the source of life and death [1]. The first competency domain of the NBOME guidelines holds that osteopathic physicians must demonstrate knowledge of osteopathic principles and practice, understand the physical findings of somatic dysfunction, and apply the basic skills of osteopathic manipulative treatment (OMT). The goal is to address concerns patients commonly present with, emphasizing optimizing homeostasis.

Several approaches may be adopted to enhance the integration of immunological concepts into osteopathic principles and treatment courses in the preclinical osteopathic medical curriculum (Table 11). Firstly, immune functions can be modulated by addressing somatic dysfunctions through OMT techniques grounded in metabolic energy and

respiratory-circulatory models. As the lymphatic system maintains fluid balance, defense, and nutritional transport (Hruby, 2021), improving lymph mobilization through mechanical conduction is a fundamental concept utilized in OMT to treat somatic dysfunctions [1,63]. Furthermore, understanding the interplay between the lymphatic system and the immune response and recognizing how dysfunctions in lymphatic flow may impact immune functions will enhance students' understanding of the applications of OMT techniques in promoting lymphatic drainage and potentially bolstering immune functions.

The metabolic energy model focuses on the body's metabolic processes and energy expenditure, viewing health as a balance of energy production and utilization [86]. In the context of immunology, this model recognizes the influence of metabolic pathways on immune cell functions and the body's response to infection and inflammation, which utilize an ample supply of the body's reserves. Metabolic dysregulation, often associated with conditions such as obesity, autoimmune diseases, and other chronic inflammatory conditions, can further compromise balance and predispose individuals to nonimmune-related disorders [86]. Similarly, the respiratory-circulatory model optimizes respiratory function and circulatory dynamics to maintain tissue perfusion and metabolic balance and thus support overall health and well-being. From an immunological perspective, adequate oxygenation is crucial for optimal immune cell function and the body's ability to mount an effective immune response. Hypoxia due to respiratory dysfunction or impaired circulation can impair immune cell function and compromise host defense mechanisms. Additionally, impeded lymphatic flow can result in edema, pneumonia, infections, energy loss, fatigue, ineffective metabolic processes, toxic waste buildup, inflammation, and poor wound healing. Failure to efficiently return lymph, which carries APCs and other immune cells, nutrient-rich lipids, and hydrating extracellular fluids, can lead to unnecessary exertion of metabolic needs and disrupt the balance of the metabolic energy and respiratory-circulatory models [1]. The OMT techniques targeting respiratory and circulatory mechanics aim to restore normal physiological function, enhance immune function, and support immune responses [86].

The four major anatomical transition junctions of the body: the craniocervical junction (occipitoatlantal junction), cervicothoracic junction (thoracic inlet), thoracolumbar junction (abdominal diaphragm), and lumbopelvic junction (pelvic diaphragm), play a critical role in lymphatic drainage facilitation and immune regulation and hence have significance beyond structural landmarks [87]. The NBOME guidelines for the osteopathic curriculum also instruct the screening and treatment of these four junctions.

Osteopathic manipulative medicine (OMM) utilizes a comprehensive approach that includes a variety of gentle manual techniques such as myofascial release, suboccipital release, doming of the diaphragm, and the multicenter osteopathic pneumonia study in the elderly (MOPSE) protocol to enhance fluid circulation and immune function [1]. This approach is rooted in identifying and correcting the underlying causes of lymphatic dysfunction, whether they stem from visceral, fascial, or musculoskeletal imbalances. The myofascial release technique utilizes gentle, sustained pressure to promote the movement of lymphatic fluid, improving tissue mobility and releasing restrictions within the fascia, and the suboccipital release technique stimulates the vagus nerve to target dysfunctions within the suboccipital triangle, for example, fascial headaches, temporomandibular joint dysfunction, and nausea [1]. Doming of the Diaphragm enhances lymph flow and pressure gradients, which is particularly beneficial for individuals with dysfunctional breathing patterns, including those with chronic obstructive lung diseases such as asthma, COPD, and bronchitis [1]. Osteopathic physicians employ the MOPSE protocol, a structured approach focusing on thoracic paraspinal soft tissue techniques, rib raising, diaphragmatic re-doming with direct MFR, sub-occipital decompression, cervical soft tissue techniques, MFR to the thoracic inlet, thoracic lymphatic pump activation, and pedal lymphatic pump techniques [88]. This protocol addresses somatic dysfunctions affecting respiratory excursion, autonomic activity, and pulmonary lymphatics, offering a comprehensive strategy for pneumonia management [88].

Another important technique is effleurage, which utilizes light, sweeping strokes over the skin, mainly directed toward the heart or away from extremities, to maintain optimal lymph flow and immune functions [1]. By learning these OMM techniques, students can utilize tailored interventions to enhance lymphatic drainage and improve immune functions, which may significantly benefit patients suffering from lymphedema, chronic inflammation, or recurrent infections. Moreover, in post-operative care, OMM techniques can facilitate quicker recovery by reducing surgical edema and promoting the clearance of anesthesia and other catabolic products from the body.

Similar to effleurage, counterstain is a mobilization technique used by osteopathic physicians to reduce strain and discomfort through passive body positioning. Counterstain can help alleviate abnormal neuromuscular reflexes and improve joint mobility, thus indirectly supporting immune function by reducing the mechanical stresses that can impede circulation and lymphatic flow [1]. Learning these manual medicine techniques will enable osteopathic medical students to connect the core principles of osteopathic medicine with immunology principles and apply the skills in the holistic treatment of their patients.

Beyond the manual manipulation of lymphatic vessels, osteopathic principles concerning the Chapman reflexes also emphasize lymphatic function and immunological responses. The Chapman reflexes, also referred to as neurolymphatic nodules, are gangliform-contracted lymphoid tissue nodules representing blatant, palpable tissue texture abnormalities [1]. These neurolymphatic points are located at particular body sites associated with internal organ somatic dysfunctions. As osteopathic students master the intricacies of manual manipulation, Chapman's points are theorized to represent physiological responses to lymphatic congestion.

The immune system plays a significant role in pain perception, primarily through the interaction of immune cells and inflammatory mediators that can influence nerve function and pain signaling pathways. When tissue is injured or infected, the immune system responds by sending inflammatory cells to the damaged site, which proceed to release cytokines and other chemicals that not only help in fighting off the infection or clearing the products of cellular damage but also sensitize nerve endings [1]. Although the immune response is considered localized to the region of tissue damage, the nerve endings relaying pain and sensitivity information undergo convergence at the spinal cord level, which explains the basis of Chapman point treatment.

The most well-known examples of the clinical application of Chapman's points are seen in the evaluation of a patient with occult appendicitis presenting with generalized abdominal pain. For appendicitis, the primary Chapman point is typically found near the tip of the right 12th rib [89]. This location is strategic as it corresponds to where the nerves from the appendix enter the spinal cord. Osteopathic students are taught to identify this point by palpating for a small, palpable nodule or area of increased tenderness, which represents lymphatic congestion (indicating an immune response correlated with lymphatic congestion in this region). Understanding this relationship allows osteopathic students to learn additional therapeutic avenues to manage pain, particularly in chronic conditions where inflammation and immune reactivity are crucial.

4. Conclusions

As newer pathologies are researched and their mechanisms uncovered, their ties to immunologic origins have become more evident. Dynamic and systematic integration of immunology concepts is therefore important for developing robust systems-based basic science programs in both allopathic and osteopathic medical curricula. This paper offers a conceptual framework for medical educators and program directors to integrate immunology in a body-system-based format over the courses covered during the preclinical years.

The proposed approach comprises introducing core immunology topics in a first-year foundational course emphasizing the host defense mechanisms. The concepts are then reinforced and scaffolded throughout the first- and second-year systems-based courses via integration into clinical scenarios. Furthermore, we discuss the association of immunology

concepts with osteopathic principles and practices and propose topics for the integration of these concepts into an osteopathic preclinical curriculum.

Instructors can select from the range of clinical conditions listed for each system to use for clinical correlations appropriate for the grade level and as the teaching emphasis shifts from basic immune defenses in the first-year courses to more disease-focused, pathologic mechanisms in the upper-division second-year courses. This integrative approach will enhance the students' retention and deeper understanding of the immunological concepts, thus preparing them better for the clinical years and future clinical practice. It may also help students perform better in their board examinations administered at the end of the second year.

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References

1. Seffinger, M.A. *Foundations of Osteopathic Medicine: Philosophy, Science, Clinical Applications, and Research*; American Osteopathic Association: Chicago, IL, USA, 2018; issuing body.
2. Bordoni, B. The Five Diaphragms in Osteopathic Manipulative Medicine: Neurological Relationships, Part 1. *Cureus* **2020**, *12*, e8697. [CrossRef]
3. Esteves, J.E.; Zegarra-Parodi, R.; van Dun, P.; Cerritelli, F.; Vaucher, P. Models and theoretical frameworks for osteopathic care—A critical view and call for updates and research. *Int. J. Osteopath Med.* **2020**, *35*, 1–4. [CrossRef]
4. Mein, E.A.; Richards, D.G.; McMillin, D.L.; McPartland, J.M.; Nelson, C.D. Physiological regulation through manual therapy. In *Physical Medicine and Rehabilitation: State of the Art Reviews*; Hanley and Belfus: Philadelphia, PA, USA, 2000; Volume 14.
5. American Association of Colleges of Osteopathic Medicine (AACOM). U.S. Colleges of Osteopathic Medicine [Website]. 2024. Available online: https://www.aacom.org/become-a-doctor/prepare-for-medical-school/us-colleges-of-osteopathic-medicine#:~:text=Osteopathic%20Medical%20Schools&text=There%20are%20currently%2041%20accredited,medicine%20in%20the%20United%20States) (accessed on 16 July 2024).
6. Reynolds, A.B.; Bhattacharjee, R.; Zhao, Y. Current Status of Immunology Education in U.S. Medical Schools. *Immunohorizons* **2022**, *6*, 864–871. [CrossRef] [PubMed]
7. Bansal, A.S. Medical students' views on the teaching of immunology. *Acad. Med.* **1997**, *72*, 662. [CrossRef] [PubMed]
8. Lee, A.; Malau-Aduli, B. Medical students' learning experiences and perceptions of immunology. *Int. J. Med. Educ.* **2013**, *3*, 1539.
9. Haidaris, C.G.; Frelinger, J.G. Inoculating a New Generation: Immunology in Medical Education. *Front. Immunol.* **2019**, *10*, 2548. [CrossRef] [PubMed]
10. Tomasi, A.G.; Belhorn, T.; Church, F.C. PRIME Immunology: Self-directed Introduction to Medical School Immunology. *Med. Sci. Educ.* **2021**, *31*, 1279–1282. [CrossRef] [PubMed]
11. Siani, M.; Dubovi, I.; Borushko, A.; Haskel-Ittah, M. Teaching immunology in the 21st century: A scoping review of emerging challenges and strategies. *Int. J. Sci. Educ.* **2024**. [CrossRef]
12. Kulasegaram, K.M.; Martimianakis, M.A.; Mylopoulos, M.; Whitehead, C.R.; Woods, N.N. Cognition before curriculum: Rethinking the integration of basic science and clinical learning. *Acad. Med.* **2013**, *88*, 1578–1585. [CrossRef]
13. Manglik, N.; Dudrey, E.F.; Baatar, D.; Piskurich, J.F. Immune response to bacteria: An integrated learning module to enhance preclinical students' competency in immunology. *MedEdPORTAL* **2017**, *13*, 10585. [CrossRef]

14. Bauzon, J.; Alver, A.; Ravikumar, V.; Devera, A.; Mikhael, T.; Nauman, R.; Simanton, E. The Impact of Educational Resources and Perceived Preparedness on Medical Education Performance. *Med. Sci. Educ.* **2021**, *31*, 1319–1326. [CrossRef]
15. Griner, P.F.; Danoff, D. Sustaining change in medical education. *J. Int. Assoc. Med. Sci. Educ.* **2000**, *283*, 2429–2431. [CrossRef]
16. Roberts, C.; Lawson, M.; Newble, D.; Self, A.; Chan, P. The introduction of large class problem-based learning into an undergraduate medical curriculum: An evaluation. *Med. Teach.* **2005**, *27*, 527–533. [CrossRef]
17. Rapp, D.E. Integrating cultural competency into the undergraduate medical curriculum. *Med. Educ.* **2006**, *40*, 704–710. [CrossRef] [PubMed]
18. Ramsey, P.G.; Miller, E.D. A single mission for academic medicine: Improving health. *J. Int. Assoc. Med. Sci. Educ.* **2009**, *301*, 1475–1476. [CrossRef] [PubMed]
19. Booth, J.S.; Burges, G.; Justemen, L.; Knoop, F.C. Design and implementation of core knowledge objectives for medical microbiology and immunology. *JIAMSE J. Int. Assoc. Med. Sci. Educ.* **2009**, *19*, 100–138.
20. National Board of Osteopathic Medical Examiners (NBOME). COMLEX-USA Master Blueprint (PDF). 2023. Available online: https://www.nbome.org/assessments/comlex-usa/master-blueprint/ (accessed on 24 May 2023).
21. United States Medical Licensing Association. Step 1 Content Outline and Specifications. 2022. Available online: https://www.usmle.org/prepare-your-exam/step-1-materials/step-1-content-outline-and-specifications (accessed on 7 July 2023).
22. Matinho, D.; Pietrandrea, M.; Echeverria, C.; Helderman, R.; Masters, M.; Regan, D.; Shu, S.; Moreno, R.; McHugh, D. A Systematic Review of Integrated Learning Definitions, Frameworks, and Practices in Recent Health Professions Education Literature. *Educ. Sci.* **2022**, *12*, 165. [CrossRef]
23. Brauer, D.G.; Ferguson, K.J. The integrated curriculum in medical education: AMEE Guide No. 96. *Med. Teach.* **2015**, *37*, 312–322. [CrossRef] [PubMed]
24. Harden, R.M.; Davis, M.H.; Crosby, J.R. The new Dundee medical curriculum: A whole that is greater than the sum of the parts. *Med. Educ.* **1997**, *31*, 264–271. [CrossRef]
25. Grant, J. Principles of curriculum design. In *Understanding Medical Education: Evidence, Theory, and Practice*, 3rd ed.; Swanwick, T., Forrest, K., O'Brien, B.C., Eds.; Wiley-Blackwell: Oxford, UK, 2019; pp. 71–88.
26. Wijnen-Meijer, M.; Ten Cate, O.T.J.; Rademakers, J.J.D.J.M.; Van Der Schaaf, M.; Borleffs, J.C.C. The influence of a vertically integrated curriculum on the transition to postgraduate training. *Med. Teach.* **2009**, *31*, e528–e532. [CrossRef]
27. Neufeld, V.R.; Woodward, C.A.; MacLeod, S.M. The McMaster M.D. program: A case study of renewal in medical education. *Acad. Med.* **1989**, *64*, 423–432. [CrossRef] [PubMed]
28. Porter, E.; Amiel, E.; Bose, N.; Bottaro, A.; Carr, W.H.; Swanson-Mungerson, M.; Varga, S.M.; Jameson, J.M. American Association of Immunologists recommendations for an undergraduate course in immunology. *Immunohorizons* **2021**, *5*, 448–465. [CrossRef] [PubMed]
29. Wilkerson, L.; Stevens, C.M.; Krasne, S. No content without context: Integrating basic, clinical, and social sciences in a preclerkship curriculum. *Med. Teach.* **2009**, *31*, 812–821. [CrossRef] [PubMed]
30. Kennelly, P.J.; Bond, J.S.; Masters, B.S.; Dennis, E.A.; Brenner, C.; Raben, D.M. Desperately seeking Flexner: Time to reemphasize basic science in medical education. *Acad. Med.* **2013**, *88*, 1405–1406. [CrossRef]
31. Weston, W.W. Do we pay enough attention to science in medical education? *Can. Med. Educ. J.* **2018**, *9*, e109–e114. [CrossRef] [PubMed]
32. General Medical Council (GMC). *Tomorrow's Doctors*; GMC: London, UK, 2009.
33. Association of American Medical Colleges (AAMC). *Report IV—Contemporary Issues in Medicine: Basic Science and Clinical Research*; Medical School Objectives Project; AAMC: Washington, DC, USA, 2001.
34. Bruner, J.S. *The Process of Education*; Harvard University Press: Cambridge, MA, UAS, 1960.
35. Davis, M.H.; Harden, R.M. Planning and implementing an undergraduate medical curriculum: The lessons learned. *Med. Teach.* **2003**, *25*, 596–608. [CrossRef] [PubMed]
36. Larkins, M.C.; Thombare, A. Point-of-Care Testing. [Updated 2023 May 29]. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2024. Available online: https://www.ncbi.nlm.nih.gov/books/NBK592387/ (accessed on 16 July 2024).
37. Berraondo, P.; Sanmamed, M.F.; Ochoa, M.C.; Etxeberria, I.; Aznar, M.A.; Pérez-Gracia, J.L.; Rodríguez-Ruiz, M.E.; Ponz-Sarvise, M.; Castañón, E.; Melero, I. Cytokines in clinical cancer immunotherapy. *Br. J. Cancer* **2019**, *120*, 6–15. [CrossRef]
38. Justiz Vaillant, A.A.; Nessel, T.A.; Patel, P.; Zito, P.M. Immunotherapy. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
39. World Health Organization. Immunization Coverage. Available online: https://www.who.int/newsroom/fact-sheets/detail/immunization-coverage (accessed on 16 July 2024).
40. Centers for Disease Control and Prevention. Vaccine-Preventable Deaths. Available online: https://www.cdc.gov/vaccines/vpd/about/disease-dis.html (accessed on 16 July 2024).
41. U.S. Board on Health Promotion and Disease Prevention. *Vaccine Safety Forum: Summaries of Two Workshops*; National Academies Press: Washington, DC, USA, 1997.
42. Abdelwhab, E.M.; Veits, J.; Mettenleiter, T.C. Antigenic drift and antigenic shift in influenza A viruses. *Viruses* **2023**, *15*, 125.
43. Gebre, M.S.; Brito, L.A.; Tostanoski, L.H.; Edwards, D.K.; Carfi, A.; Barouch, D.H. Novel approaches for vaccine development. *Cell* **2021**, *184*, 1589–1603. [CrossRef]

44. Dubé, E.; Vivion, M.; MacDonald, N.E. Vaccine hesitancy, vaccine refusal and the anti-vaccine movement: Influence, impact and implications. *Expert Rev. Vaccines* **2013**, *14*, 99–117. [CrossRef]
45. Larson, H.J.; Jarrett, C.; Eckersberger, E.; Smith DM, D.; Paterson, P. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: A systematic review of published literature, 2007–2012. *Vaccine* **2014**, *32*, 2150–2159. [CrossRef] [PubMed]
46. Stormacq, C.; Van den Broucke, S.; Wosinski, J. Does Health Literacy Mediate the Relationship between Socioeconomic Status and Health Disparities? Integrative Review. *Health Promot. Int.* **2019**, *34*, e1–e17. [CrossRef] [PubMed]
47. Willis, D.E.; Andersen, J.A.; Bryant-Moore, K.; Selig, J.P.; Long, C.R.; Felix, H.C.; Curran, G.M.; McElfish, P.A. COVID-19 Vaccine Hesitancy: Race/Ethnicity, Trust, and Fear. *Clin. Transl. Sci.* **2021**, *14*, 2200–2207. [CrossRef] [PubMed]
48. Kim, B.; Hong, S.; Kim, S. Are They Still Determining? Analysis of Associations among Ethnicity, Gender, Socioeconomic Status, Neighborhood Factors, and COVID-19 Vaccination. *Front. Commun.* **2023**, *8*, 1040797. [CrossRef]
49. Volkov, M. Autoantibodies and B Cells: The ABC of rheumatoid arthritis pathophysiology. *Immunol. Rev.* **2020**, *294*, 148–163. [CrossRef] [PubMed]
50. Centers for Disease Control and Prevention. Rheumatoid Arthritis (RA). Available online: https://www.cdc.gov/arthritis/basics/rheumatoidarthritis.html#:~:text=Rheumatoid%20arthritis,%20or%20RA,%20is,usually%20many%20joints%20at%20once (accessed on 24 May 2023).
51. Smolen, J.S.; Aletaha, D.; McInnes, I.B. Rheumatoid arthritis. *Lancet* **2016**, *388*, 2023–2038. [CrossRef] [PubMed]
52. Sparks, J.A.; Chang, S.-C.; Deane, K.D.; Gan, R.W.; Demoruelle, M.K.; Feser, M.L.; Karlson, E.W. Associations of smoking and age with inflammatory joint signs among unaffected first-degree relatives of rheumatoid arthritis patients: Results from studies of the etiology of rheumatoid arthritis. *Arthritis Rheumatol.* **2019**, *71*, 652–660. [CrossRef] [PubMed]
53. Okada, Y.; Wu, D.; Trynka, G.; Raj, T.; Terao, C.; Ikari, K.; Kochi, Y.; Ohmura, K.; Suzuki, A.; Yoshida, S.; et al. Genetics of Rheumatoid arthritis contributes to biology and drug discovery. *Nature* **2014**, *506*, 376–381. [CrossRef]
54. McInnes, I.B.; Schett, G. The pathogenesis of rheumatoid arthritis. *N. Engl. J. Med.* **2011**, *365*, 2205–2219. [CrossRef]
55. van Venrooij, W.J.; van Beers, J.J.B.C.; Pruijn, G.J.M. Anti-CCP antibodies: The past, the present and the future. *Nat. Rev. Rheumatol.* **2011**, *7*, 391–398. [CrossRef]
56. Holers, V.M.; Demoruelle, M.K.; Kuhn, K.A.; Buckner, J.H. Rheumatoid arthritis and the mucosal origins hypothesis: Protection turns to destruction. *Nat. Rev. Rheumatol.* **2019**, *15*, 457–466. [CrossRef] [PubMed]
57. Mayo Clinic Staff. Ankylosing Spondylitis. Available online: https://www.mayoclinic.org/diseases-conditions/ankylosing-spondylitis/symptomscauses/syc20354808#:~:text=Ankylosing%20spondylitis,%20also%20known%20as,be%20difficult%20to%20breathe%20deeply (accessed on 24 May 2023).
58. Reveille, J.D. Genetics of spondyloarthritis—Beyond the MHC. *Nat. Rev. Rheumatol.* **2017**, *13*, 404–416. [CrossRef] [PubMed]
59. Ciccia, F.; Guggino, G.; Rizzo, A.; Alessandro, R. Role of gut microbiota in the pathogenesis of rheumatic diseases. *Best Pract. Res. Clin. Rheumatol.* **2017**, *31*, 767–779.
60. Baeten, D.; Sieper, J. Ankylosing spondylitis. *Lancet* **2018**, *390*, 73–84.
61. Benjamin, J.L.; Hedin CR, H.; Koutsoumpas, A.; Ng, S.C.; McCarthy, N.E.; Prescott, N.J.; Hart, A.L. Smokers with active ankylosing spondylitis have elevated chemokine receptor6 levels in serum. *PLoS ONE* **2019**, *14*, e0215124.
62. Salem, I.; Ramser, A.; Isham, N.; Ghannoum, M.A. The gut microbiome as a major regulator of the gut-skin axis. *Front. Microbiol.* **2018**, *9*, 1–13. [CrossRef]
63. Hruby, R.J.; Hoffman, K.N.; Avian, A.A.; Hough, B. Osteopathic manipulative treatment for rheumatoid arthritis: A systematic review and meta-analysis. *Altern. Ther. Health Med.* **2018**, *24*, 18–24.
64. Cutler, M.J.; Holland, B.S.; Stupski, B.A.; Gamber, R.G. The effect of osteopathic manipulative treatment on disease severity in patients with rheumatoid arthritis: A pilot study. *J. Am. Osteopath. Assoc.* **2017**, *117*, e5–e6.
65. Orrock, P.J.; Myers, S.P. Osteopathic intervention in chronic non-specific low back pain: A systematic review. *BMC Musculoskelet. Disord.* **2013**, *14*, 129. [CrossRef]
66. Cataland, S.R.; Holers, V.M.; Geyer, S.; Yang, S.; Wu, H.M.; Soundar, E. Biomarkers of ADAMTS13 activity in thrombotic microangiopathies. *Medicine* **2018**, *97*, e12172.
67. Page, E.E.; Kremer Hovinga, J.A.; Terrell, D.R.; Vesely, S.K.; George, J.N.; Hovinga, K.R. Thrombotic thrombocytopenic purpura: Diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. *Blood Adv.* **2017**, *1*, 590–600. [CrossRef] [PubMed]
68. Fowkes FG, R.; Rudan, D.; Rudan, I.; Aboyans, V.; Denenberg, J.O.; McDermott, M.M.; Criqui, M.H. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. *Lancet* **2017**, *382*, 1329–1340. [CrossRef]
69. Bennett, M.R.; Sinha, S.; Owens, G.K. Vascular smooth muscle cells in atherosclerosis. *Circ. Res.* **2016**, *118*, 692–702. [CrossRef] [PubMed]
70. Watkins, D.A.; Johnson, C.O.; Colquhoun, S.M.; Karthikeyan, G.; Beaton, A.; Bukhman, G.; Zuhlke, L.J. Global, regional, and national burden of rheumatic heart disease, 1990–2015. *N. Engl. J. Med.* **2017**, *377*, 713–722. [CrossRef] [PubMed]
71. Rose, N.R.; Mackay, I.R. *The Autoimmune Diseases*, 5th ed.; Academic Press: Cambridge, MA, USA, 2014.
72. Doulatov, S.; Notta, F.; Laurenti, E.; Dick, J.E. Hematopoiesis: A human perspective. *Cell Stem Cell* **2012**, *10*, 120–136. [CrossRef] [PubMed]

73. Kelloway, L.; Record, E.; St Clair, N.; Wade, L.; Bedard, M.; Bezanson, J. The effects of osteopathic manipulative treatment on vascular endothelial function. *J. Am. Osteopath. Assoc.* **2017**, *117*, e6.
74. Hodge, L.M.; King, H.H.; Williams, A.G. Effects of osteopathic manipulative treatment on circulation and immunological parameters in nursing home residents: A pilot study. *J. Am. Osteopath. Assoc.* **2005**, *105*, 400–408.
75. Kesner, V.G.; Oh, S.J.; Dimachkie, M.M.; Barohn, R.J. Lambert-Eaton Myasthenic Syndrome. *Neurol. Clin.* **2018**, *36*, 379–394. [CrossRef]
76. Sève, P.; Pacheco, Y.; Durupt, F.; Jamilloux, Y.; Gerfaud-Valentin, M.; Isaac, S.; Boussel, L.; Calender, A.; Androdias, G.; Valeyre, D.; et al. Sarcoidosis: A Clinical Overview from Symptoms to Diagnosis. *Cells* **2021**, *10*, 766. [CrossRef]
77. Reggiani, F.; L'Imperio, V.; Calatroni, M.; Pagni, F.; Sinico, R.A. Goodpasture syndrome and anti-glomerular basement membrane disease. *Clin. Exp. Rheumatol.* **2023**, *41*, 964–974. [CrossRef]
78. Kumar, V.; Abbas, A.K.; Aster, J.C. *Robbins and Cotran Pathologic Basis of Disease*, 10th ed.; Elsevier: Amsterdam, The Netherlands, 2021.
79. Gillespie, K.M. Type 1 diabetes: Pathogenesis and prevention. *CMAJ* **2006**, *175*, 165–170. [CrossRef] [PubMed]
80. Radetti, G. Clinical aspects of Hashimoto's thyroiditis. *Endocr. Dev.* **2014**, *26*, 158–170. [CrossRef] [PubMed]
81. Subekti, I.; Pramono, L.A. Current Diagnosis and Management of Graves' Disease. *Acta Med. Indones* **2018**, *50*, 177–182. [PubMed]
82. Bowman, J.M. RhD hemolytic disease of the newborn. *N. Engl. J. Med.* **1998**, *339*, 1775–1777. [CrossRef] [PubMed]
83. Sammaritano, L.R. Antiphospholipid syndrome. *Best Pr. Res Clin Rheumatol.* **2019**, *34*, 101463. [CrossRef] [PubMed]
84. Kirtschig, G. Lichen Sclerosus-Presentation, Diagnosis and Management. *Dtsch. Arztebl. Int.* **2016**, *113*, 337–343. [CrossRef]
85. Goldman, L.; Schafer, A.I. *Goldman-Cecil Medicine*, 27th ed.; Elsevier: Amsterdam, The Netherlands, 2024.
86. Fusco, G.; Chen, S.W.; Williamson, P.T.F.; Cascella, R.; Perni, M.; Jarvis, J.A.; Cecchi, C.; Vendruscolo, M.; Chiti, F.; Cremades, N.; et al. Structural basis of membrane disruption and cellular toxicity by α-synuclein oligomers. *Science* **2017**, *358*, 1440–1443. [CrossRef] [PubMed]
87. Chikly, B.J. Manual techniques addressing the lymphatic system: Origins and development. *J Am Osteopath Assoc.* **2005**, *105*, 457–464. [PubMed]
88. Kuchera, M.L.; Kuchera, W.A. *Osteopathic Consideration in Systemic Dysfunction*, 2nd ed.; Greyden Press: Columbus, OH, USA, 1994.
89. Bath, M.; Nguyen, A.; Bordoni, B. Physiology, Chapman's Points. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2024. Available online: https://www.ncbi.nlm.nih.gov/books/NBK558953/ (accessed on 16 July 2024).