**Osteomyelitis**

Osteomyelitis in long bones presents a variety ofchallenges depending on the infection’s particular fea-tures (etiology, pathogenesis, extent of bone involvement, and duration) and the patient (infant, child, adult, or immunocompromised). Over the past four decades,we have made tremendous progress in treating thisdisease as the many factors that account for the occurrence and persistence of infection have been identiﬁedand a variety of antimicrobials with different spectrumsof activity against speciﬁc pathogens have been developed. Also, new operative techniques, such as Ilizarovﬁxation and muscle ﬂaps, and innovative delivery systems for antibiotics have been added to our arsenal. Inspite of these advances, however, osteomyelitis remainsdifﬁcult to treat, with considerable morbidity and costs.This article offers a basic review of the classiﬁcation, etiology, epidemiology, pathogenesis, and treatment oflong bone osteomyelitis

**CLASSIFICATION**

Osteomyelitis can be classiﬁed by duration (acute orchronic), pathogenesis (trauma, contiguous spread, hematogenous, surgical), site, extent, or type of patient. Although several classiﬁcations of osteomyelitis havebeen described by different authors, the two most widelyused in the medical literature and in clinical practice arethe classiﬁcation systems by Waldvogel et al. and Cierny et al. Under the Waldvogel system, osteomyelitis is ﬁrst described according to duration, either acuteor chronic. Second, the disease is classiﬁed according tosource of infection, as hematogenous when it originatesfrom a bacteremia or as contiguous focus when itoriginates from an infection in a nearby tissue. A ﬁnalcategory of the classiﬁcation is vascular insufﬁciency. One of the limitations of the Waldvogel classiﬁcationsystem is that it does not consider infection originatingfrom direct penetration of microorganisms into the bone, as may occur after trauma or surgery. In addition, it is an etiologic classiﬁcation system that does not readily lend itself to guiding surgical or antibiotic therapy. Because of the wide variability in the etiology of osteomyelitis, a classiﬁcation based on the pathogenesis of the disease, such as that of the Waldvogel system, has limited value in clinical practice.The second system is known as the Cierny-Mader classiﬁcation. The Cierny-Mader classiﬁcationis a clinical classiﬁcation based on anatomic, clinical, and radiologic features. It characterizes osteomyelitis as being in one of four anatomic stages. In stage 1, or medullary, osteomyelitis is conﬁned to the medullary cavity of the bone. Stage 2, or superﬁcial, osteomyelitis involves only the cortical bone and most often originates from a direct inoculation or a contiguous focus infection.Stage 3, or localized, osteomyelitis usually involves both cortical and medullary bone. In this stage, the bone remains stable, and the infectious process does not involve the entire bone diameter. Stage 4, or diffuse, osteomyelitis involves the entire thickness of the bone, with loss of stability, as in infected nonunion. The Cierny-Mader system adds a second dimension, characterizing the host as either A, B, or C. The A hosts are patients without systemic or local compromising factors.B hosts are affected by one or more compromising factors. C hosts are patients so severely compromised that the radical treatment necessary would have an unacceptable risk-beneﬁt ratio. One shortfall of this system is that by deﬁnition, the C host category is a subjective evaluation. Also not taken into account are other properties including the length of time that an infection has been able to persist, if indwelling medical devices are in the infected area, and whether it is a pediatric or teen/adult patient. Many cases of osteomyelitis may be treated with antimicrobial therapy alone.One example is seen in pediatric osteomyelitis cases where the ability of the younger patient to resorb dead bone thereby removes the devitalized surfaces where bacteria can persist in a bioﬁlm mode of growth (dis-cussed later). In addition, rapidly diagnosed infections in adults can first be treated with antimicrobial therapy because signiﬁcant areas of devitalized bone have not yet formed. Generally, however, this classiﬁcation seems to be of value in clinical practice, because it addresses the dynamic nature of the disease and adds the second dimension of the host’s physiologic, metabolic, and immunologic capabilities.

**Role of T and B lymphocytes in osteomyelitis**

T lymphocytes originate from precursor stem cells in fetal liver and bone marrow and differentiate into mature cell types after migration to the thymus. T lymphocytes may be categorized based on their distinct function into cytotoxic T lymphocytes (expressing the surface protein cluster of differentiation (CD) 8 and responsible mainly for immune defense against intracellular pathogens and for tumor surveillance) and helper T lymphocytes (expressing the surface protein CD4). In this review, we focus on CD 4+ cells. Helper T cells(naïve CD4+ T lymphocytes) are triggered when they are presented with peptide antigens by MHC (major histocompatibility complex) class II molecules, which are expressed on the professional antigen-presenting cells(APCs) surface. Both are necessary for production of an adequate immune response. T cells have on their surface T cell antigen receptors (TCR) responsible for recognition of an antigen/major histocompatibility complex (HLA complex), immunological accessory molecules Identifying HLA determinants, and adhesion molecules recognizing their counterpart ligands on APCs. Once activated, helper (CD4+) T cells can be subdivided into at least three main functional subtypes according to releasing cytokines , the Th1 subset (mainly involved in cell-mediated tissue-damaging reaction), theTh2 subset (driving B cells to produce antibodies in the humoral immune response), and Th17 cells (playing role in immune responses to infectious agents and maintenance of autoimmune diseases). Th 1 cells produce tumor necrosis factor-β (TNF- β), interferon gamma (IFN-γ), and interleukin (IL) 2,;Th 2 cells secrete mainly IL-4, IL-5, IL-6, and IL-13, and Th17 secrete IL-17. Moreover, some CD4+ T cells produce both Th1 and Th2 cytokines and have been termed Th0. Determination of Th subtype is activated during an immune response, which depends on the type of antigen and its concentration, the nature of the initial antigen-presenting cell, and, probably, on ill-defined genetic and environmental influences. Were cognize also set of T cells that can suppress these inflammatory responses, described as regulatory T cells (T regs). The particular factors beginning thyroid autoimmunity are not well known, but many potential influences have been described. Development of autoimmunity is, probably as mentioned, a process including both genetic and environmental effects. Immunologic self-tolerance is induced during the perinatal period, when immature lymphocytes in the thymus are exposed to self-antigens. At this crucial moment , clonal deletion or induced anergy of auto reactive T cells determines self-tolerance to auto antigens. However, these mechanisms are never ideal and some auto reactive cells may be normally present in their circulation. As we described above, AITD arise from a break-down of self-tolerance to thyroid antigens and this process might be induced by excessive exposure to thyroid antigens, a modified self-antigen, exposure to environment alantigens that mimic a self-antigen, polyclonal immune activation, or idiotypecross reaction of self-antigen

**B lymphocytes**

B lymphocytes develop from hematopoietic stem cells. Maturation of B cells takes place in bone marrow, ,whereas their activation occurs in the secondary lymphoid organs such as lymph nodes and the spleen. B cells represent mainly the humoral immunity. Nevertheless, their role as a cell it self is equally relevant. In practice, they are activated in patients with AITD. In Graves’ Disease, B cells play a vital role as they are the source of pathognomonic activating autoantibodies(TRAb) against thyroid-stimulating hormone receptor(TSHR). TRAb, by binding to the receptor, chronically stimulates it. TSHR is expressed on thyroid follicular cells; thus, the consequence of this chronic stimulation is an increased production and secretion of thyroid hormones T4and T3. Although the role of B cells in development of Hashimoto’s thyroiditis is not as significant as in GD, it should be mentioned that they produce autoantibodies to the thyroglobulin (Tg) and thyroid peroxidase (TPO), which are thyroid self-antigens. Antibody dependent cell-mediated cytotoxicity is a meaningful factor responsible for apoptosis of thyroid follicular cells in HT.B cells can also serve as APCs. They have a transmembrane receptor, called BCR (a surface immunoglobulin), which enables them to identify specific antigens, against which they initiate an immune response and synthesize antibodies, and present fragment s of these antigens toCD4+ T cells using MHC class II molecules. When the antigen is uncommon, B cells may be the dominant APCs as they have an ability of up-concentration antigens on the cell due to the presence of BCR in the cell membrane. T helper (Th) cells reciprocally support activation of B cells. Particular attention was paid to sequencing of thyroid antibodies and defining B cell epitopes in TSH receptor. This, in turn could enable further understanding of the pathogenesis of GD, which is a cause of triggering TSHR leading to development of this disease. However, the pace of the autoimmune reaction in AITD is usually slow, which leads its proliferation and differentiation involving many different polyclonal B and T cells. B cells exert their activity of antibody synthesis in the thyroid gland. Moreover, intense autoreactive B cell infiltration of the thyroid tissue is observed in patients withAITD. It means that the thyroid may be a major place for thyroid antibody secretion and presents a significant role in promoting persistence of AITD. Additionally, reduced serum concentration of thyroid antibody after surgical or radioiodine thyroid ablation or any other antithyroid drug treatment, is a confirmation of this finding. There are studies showing that anti-CD20 therapy efficiently depletes B cells in thyroid glands of mice with autoimmune thyroiditis, even though many of thyroid B cells do not express CD20. Moreover, the fact that the therapy using rituximab, B cell-depleting anti-CD20 antibody, induces clin-ical improvement in Graves’ ophthalmopathy, suggests acrucial role of B cell involvement and provides a base for the development of new therapeutic strategies in patients suffering from AITD [145].B cells not only participate in proinflamatory reactions.They also play a role in regulation of immune responses. Recent studies identified regulatory B (Breg) cells as specific subsets that have an ability of immune responses suppression.

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