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Postgraduate Orthopedics

4th Edition

An Exam Preparatory Manual

HIGHLIGHTS

- "All solved DNB theory questions for past 15 years"
- Allied surgical and medical sciences
- Bone and joint disorders
- Pediatric orthopedics
- Regional orthopedics (limbs and axial skeleton)

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CHAPTER 6

Miscellaneous Topics and Recent Advances

6.1 NANOTECHNOLOGY (Q1)

1. What is nanotechnology? Describe the role in orthopedics. Also, explain the recent advances in detection of periprosthetic joint infections.

Ans: Nanotechnology is a science dealing with objects functional on extremely small scale of the size from 1 nanometer to 100 nanometers. In 1959, Richard Feynman first introduced the concept of nanotechnology. The technology is based on two thoughts—one is to miniaturize the functional objects/machines so that they occupy less space and the other is basically an inspiration from living organisms where the molecular interactions taking place at miniature scale are able to produce directed functions (e.g. enzymatic actions). These objects for sheer size are referred to as nanomolecules. Despite the rationality in thought and the widespread interest development encompasses lot of hurdles and technology progress is not a straight path. As with quantum physics that does not follow the laws of particle physics, nanomolecules have unique chemical and physical properties that do not follow the laws of macromolecules/larger objects. Understanding the same is the primary reason for delay and limitation because control of these parameters has produced a new scientific field, experts of which are still evolving. The molecular interactions in human body occur at 4–400 atomic units measured in nanometers. Nanotechnology heralds to reproduce/produce/manipulate such processes on a scale of <100 nm by integration of nanoscopic materials into macro/microscopic systems. In general, two approaches are used for nanoscience evolution, one uses the bottom-up approach where the simpler smaller elements are arranged in the designated patterns (e.g. in 3D printing) to produce complex molecules and expected to have predefined function while the other approach is called the top-down approach where miniaturization comes to work and smaller and smaller objects are developed that can work similar to their larger predecessors. Nanophase describes conventional matter at very small sizes (<100 nm) but preserved atomic structure. At such small sizes the physical properties behave in terms of quantum (in simple terms both wave + particle properties) physics instead of particle physics. The prominent characteristic exploited by biological systems for nanoparticles is its markedly enhanced surface area as we know that with reduction in size the surface area increases. Such large surface area provides for faster and much higher magnitude of reactions/processes to occur. So for orthopedic implants modified by nanotechnology the interaction with bone cells and mesenchymal cells would enhance by multiple times. This is expected to produce better cell adsorption, differentiation, growth and ultimately osseointegration and other desired properties.

Despite the limitations there are potential applications of nanotechnology that may be pertinent to the medical field for the resemblance to molecular mechanisms that occur at same scale. In orthopedics the development of nanomedicine has currently focused on devices and implants for surface characteristics, molecular structure, bonding with bone, etc. while the typical clinical application is still limited to tissue-engineering, diagnostic aspects of musculoskeletal infection and oncology. Therapeutic applications are still far away in orthopedic field. The current application of nanomedicine pertaining to orthopedics in nanoscale surface modification and tissue engineering is vastly expanding opening new horizons. If specific nanotopographical features are developed on implants that resemble biological surfaces, viz. type X collagen initiating endochondral ossification; complications like loosening and implant subsidence may be ameliorated. The major focus of nanotechnology in orthopedics is to reduce the complications associated with operative procedures namely—aseptic loosening and periprosthetic osteolysis, infection, scar tissue formation and management of bone defects; a spillover effect of technology is seen in cartilage regeneration, drug delivery system, etc.

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The specific surface modifications presently studied include: Nanophase ceramics (like nanophase hydroxyapatite), aluminum oxide and titanium dioxide, carbon, selenium, titanium, and nanocrystalline diamond. These are further supplemented by the use of fibronectin and vitronectin in a controlled manner that facilitates osteoblast activation, adhesion, and recruitment to a biomaterial. The currently used polished implants are smooth in nanoterms while the osseous inorganic phase has sizes of 50 nm × 25 nm × 4 nm; interaction of these produces fibrous interface. Nanoscience surface modification aims to roughen the implant surfaces so that bone-implant interface interacts in a productive way to get better integration. Surface modification by conjugation of substances such as bone morphogenetic protein-2 (BMP-2) to chitosan membranes also produced a significantly increased proliferation of osteoblasts, alkaline phosphatase activity, and calcium deposition. Nanocomposites have been created utilizing the above described nanoinorganic phase coupled to nanophase collagen improving osseointegration.

Bone defects: Nanocrystalline hydroxyapatite paste has been found to be efficient filler for bone defects. It has been used for filling distal radius defects and cavity after elevation of tibial plateau. The defects can be bioengineered by 3D printing using the nanohydroxyapatite "ink" and implanted into defects.

Cartilage regeneration and osteochondral defects: The underlying basis is synthesis of 3D mirror scaffolds that precisely control intercellular, cell-matrix and cell-growth factor interactions to provide milieu suitable to hyaline cartilage growth/formation. Additionally, the matrix should adhere to the underlying surface with a pore size larger than diameter of the osteoblasts (10 μm) so that cell penetration and neovascularization can happen. Nanocomposite biological implants can be used as scaffolds to treat the cartilage and osteochondral defects. For the latter a trilayer composite scaffold has been synthesized that comprises a cartilage layer formed from 100% type I collagen and a bone layer composed of nanocrystalline hydroxyapatite (70%) + type I collagen (30%); these are separated by an intermediate transition layer of collagen rich (60%) nanocrystalline hydroxyapatite (40%).

Orthopedic oncology: Nanometric selenium potentiates chemotherapeutic agents and when applied to titanium implants it inhibits the malignant osteoblasts. Similarly, nanocrystalline hydroxyapatite induces the apoptosis of osteosarcoma cells. Biodegradable nanocapsules containing small interfering ribonucleic acid (siRNA) targeting the oncogene inhibited tumor growth in mouse model of Ewing's sarcoma.

Orthopedic infection: Nanophase silver is a powerful bacteriostatic and bactericidal agent that can be specific use in open fractures. Nanophase silver deployed on surface of implants into titanium nanotubes is a strong bactericidal agent and also prevents bacterial adhesion for up to 30 days. This finds special use in revision arthroplasty and implant related infections.

Peripheral nerve injury: Nanophase silver impregnated type I collagen significantly reduces the time to nerve regeneration by increasing the quantity of adsorbed neurotropic proteins that produce thicker myelin sheath and improves nerve conduction.

Drug delivery: Gold has been shown to be an efficient transcutaneous drug delivery system for iontophoresis. Diclofenac administered with 30 nm gold nanopartcicles produced marked anti-inflammatory properties than plain form in transcutaneous system. Nanophase poly-L-lactic acid (PLLA) is also a nanoscopic drug delivery system as has been shown to heal large calvarial bony defects when used as delivery system for BMP-2. Such drug delivery systems (polypeptide nanofilms) when used with total joint prosthesis have shown marked reduction in bacterial load and improved osteoblastic response.

Diagnosis of periprosthetic joint infection (PJI): Apart from the conventional serological markers, current research is ongoing to study the synovial biomarkers like IL-6, IL-8, C-reactive protein (CRP), alpha-2 macroglobulins to rapidly diagnose PJI from samples.

- Alpha-defensin is an emerging and promising marker to this effect. It is an antimicrobial peptide released by neutrophils in the presence of bacteria and has a sensitivity and specificity of 100% and 96% respectively if detected positive. Only deterrent is its high cost. The test is also not influenced by antibiotic treatment.
- Leukocyte esterase is an enzyme secreted by neutrophils at the site of infection and inflammation and is simple and cheap to perform. It is available for diagnosing urinary tract infection as a reagent strip test where neutrophils from the sample get lysed and release the esterase causing color change of the dye.
- Nucleic acid amplification tests like polymerase chain reaction (PCR) amplification (for specific microorganisms like staphylococci, streptococci, anaerobes or a broad battery covering many organisms) and sequencing analysis of 16S

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rRNA (for negative culture of PCR panel), and reverse transcription PCR are newer tools in the armamentarium of detection of infection.

- Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) can rapidly detect staphylococci in patients of PJI with great accuracy.
- Microcalorimetry is another emerging tool that measures the heat intensity produced by proliferating organisms in relation to their metabolism in real time. This can provide a real time microbiological assay of biofilms.

(For further details, kindly refer to Chapter 11 of the book Essential Orthopedics: Principles and Practice, 2nd edition.)

6.2 STEM CELL AND ITS ROLE IN ORTHOPEDICS (Q2–3)

2. What are stem cells? How are stem cells procured for therapeutic use? What are the indications of stem cell therapy in orthopedics? What is the role of stem cell therapy in avascular necrosis (AVN) of head femur?

Ans: Stem cells are unique undifferentiated cells of a multicellular organism, which are capable of giving rise to indefinitely (theoretically at least) more cells of the same type (self-renewal), and from which certain other kinds of cell arise by differentiation in specific physiological or research controlled conditions. Stem cells are uniquely different from other cell types, as they possess three distinctive characteristics:

1. *Nonspecialization:* These cells have no tissue-specific structure or function that they would perform in human body. This repair characteristic is one of the most important distinctions that differentiate living from nonliving.
2. *Self-renewal and theoretical unlimited proliferation:* Stem cells are capable of dividing and renewing themselves for long periods without losing their basic identity and without differentiating.
3. *Ability to differentiate:* Stem cells can produce specialized cells under specific circumstances (chemokine or physical influence through contact from neighboring cells or microenvironment).

There are two broad types of stem cells:

1. Embryonic stem cells
2. *Somatic stem cells or tissue specific stem cells:*
   - iPS cells (induced pluripotent stem cells)
   - SCNT (somatic cell nuclear transfer).

Procuring stem cells:

- Mesenchymal stem cells can be derived from a number of sources but optimization is lacking and we are in process of identifying the best source for them. The commonly used/studied sources of stem cells for orthopedic research use are:
  - *Bone marrow-derived mesenchymal stem cells (BM-MSCs):* MSCs from the bone marrow (BM-MSCs) has been the most popular source of stem cells, although the yield is small and the procedure is painful. For a long time, BM-MSCs have been used as plain aspirate from iliac crest or greater trochanter for treating nonunions/delayed unions. The cells behave as multipotent cells capable of differentiating into trabecular bone, articular cartilage, ligament, and tendon.
  - *Bone marrow concentrate:* This is just a centrifuge of bone marrow aspirate from iliac crest containing a higher percentage of BM-MSCs.
- *Adipose-derived mesenchymal stem cells (AD-MSCs):* AD-MSCs can be easily harvested in good numbers through lipoaspiration and they can resist serum–deprivation-induced apoptosis well.
- *Cortical bone fraction stem cells (CBF-MSCs):* Cortical bone is the more potent than bone marrow as a stromal source for MSCs. Although bone marrow can produce a subset of clonogenic, multilineage cells; they are outnumbered and outperformed by an equivalent harvest of CBF-MSCs.
- Lineage-depleted CBF-MSCs have shown greater than 150-times enrichment of colony forming unit–fibroblasts (CFU-F) per cell incidence compared to bone marrow-derived MSCs.
- *Synovial tissue-derived mesenchymal stem cells (ST-MSCs):* The stem cells are scarce, as their availability is limited and has been used for potential regeneration of cartilage.

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- *Peripheral blood-derived mesenchymal stem cells (PB-MSCs):* The stem cells are obtained by automated cell separator from peripheral blood. The stem cells have also been used for cartilage regeneration.
- Amnion, tendon, and skin have been also studied as source of stem cells but the usage is limited to specific research.

Orthopedic indications:

- *Cartilage synthesis and regeneration:* Newer techniques of using MSCs in natural matrices hence demand exacting engineering to provide optimal milieu (mechanical stability) for ideal differentiation of the implanted cells into hyaline cartilage. This mechanical stability (protecting from axial and shear stress) imparts important cell-matrix interactions (enough porosity to allow nutrient diffusion while maintaining adequate adhesion), so that functional tissue growth can happen. MSC-based constructs use (as described by various authors) poly (vinyl alcohol)/polycaprolactone (PVA/PCL) nanofibers or alginate or collagen gel/powder covered with periosteum or hyaluronic acid membrane, while free injection of MSCs has also been done. Various studies performed utilizing different combinations claim variable success in obtaining hyaline cartilage. Some of the methods include combining BM-MSCs with transwell permeable membrane (Murdoch et al.), BM-MSCs with connective tissue growth factor (Zhu et al.), BM-MSCs with TGF-β (Guo et al.), etc.
- *Nonunions and delayed unions:* MSCs have been used by Libergall et al. [MSC + PRP (platelet rich plasma) + DBM (demineralized bone matrix)] and Giannotti et al. (iliac crest MSC with induction to osteogenic differentiation in culture). The studies showed good bone formation in the treated patients but as a technical challenge critics put forward the challenge to prove that the regenerated bone comes from implanted cells. Hernigou et al. demonstrated correlation between callus volume and number of progenitor cells used thus quality of bone marrow aspirate would also have bearing when using alone.
- *Treating bone defects:* Masquelet technique is favored by and large for management of bone defects as is Ilizarov apparatus, the former relying mostly on MSCs in the second stage. It has been postulated that supplementation of bone graft with MSCs may help in enhancing the healing potential of the cancellous bone.
- *Tendon and ligament repair:* Ideal carrier is unknown and inhomogeneous results restrict its clinical translation. For ligament repair, anterior cruciate ligament (ACL) has been the primary contender, as it is commonly injured and has significant morbidity, if not reconstructed. Studies have been done in animals where partially transected ACL showed good recovery and healing in the knees injected with MSCs as compared to controls. Repair of Achilles tendon has been attempted with the use of BM-MSCs showing some nonstandardized support to its use.
- *Osteonecrosis (or AVN):* Decompression of a structurally maintained femoral head has been commonly practiced and advised, but the results are often variable with decompression alone and it is difficult to arrest collapse. Often the "forage" is combined with fibular grafting or cancellous grafting depending on the experience of surgeon. Hernigou et al. produced the largest case series of autologous bone marrow concentrate in 2002 and 2009 suggesting that results are very good in early stages and the progenitor cells home well in the transplanted bone. The relation is also proportional to the number of progenitor cells with higher the number of cells higher is the chance of cellular homing. The clinical improvement is in terms of reduced pain and slower progression of the disease.

Other less commonly studied indications for use of stem cells are:

- Spinal fusion
- Treating bone cysts and bone defects
- Osteogenesis imperfecta
- Osteoarthritis
- Nerve injury and spinal cord injury.

(For further reading and details, kindly refer to Regenerative Medicine and Stem Cell Research in Orthopedics in the book Essential Orthopedics: Principles and Practice, 2nd edition.)

3. Write the advantages and disadvantages of mesenchymal stem cells in trauma and orthopedics.

Ans:

Advantages:

- They not only differentiate into tissue-specific cell lines (cartilage, bone, fat, fibroblast, etc.) replacing the lost cells but also modulates inflammatory process.

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- They have low immunoreactivity and high immunosuppressive properties.
- They have proven to be anti-inflammatory such as inhibiting maturation of helper T, cytotoxic T, dendritic and B-cells, and having immunosuppressive properties by secretion of transforming growth factor β-1 (TGF-β1), nitric oxide (NO), prostaglandin-E2, human leukocyte antigen G (HLA-G), hepatocyte growth factor (HGF), and interleukin 10 (IL-10).

Disadvantages: These stem cells are found in nearly all tissues but are very few in number and located in remote deep-seated places of the tissue often difficult to access, isolate, and grow in laboratory.

6.3 RECENT ADVANCES (Q4–25)

A. Cup and Stem Designs of Cemented and Uncemented Hips

4. What are the recent advances in cup and stem designs of cemented and uncemented hips?

Ans: As such the designing of acetabular cup (shell) and femoral stem has more-or-less stabilized in total hip prosthesis. Only two areas of active research are rapidly progressing—one is with respect to the bearing surfaces (this is also stabilizing) and the other one is regarding surface treatment of the prosthesis for improving bone integration and averting loosening (gaining attention of nanotechnology also).

Cementless Total Hip Prosthesis

Acetabular cups and press-fit design: Press-fit cups are 1–4 mm larger than reamed bone to impress bone implant bonding by adjusting hoop stresses. We are using third generation cup design where the liner is flush with the shell rim and does not protrude out. The congruity of the liner and acetabular cup has improved to allow placing ceramic, metal and highly cross-linked polyethylene (PE) liners all in single design. The first generation liners used to protrude from the acetabular cups and got easily damaged by impingement causing loss of locking mechanism and liner subluxation. The congruity was also not well maintained with empty area between the cup and liner causing liner failure in case thin poly was used. Ceramic liners were incompatible in this scenario. Second generation liners were also extruded but were much thicker to endure impingement, this however did not make them fail proof. The current contention in acetabular shell design involves improving the surface by specialized treatment to form trabecular tantalum bone or nanotreated surface that induces just enough roughness to stimulate osteogenesis and osteointegration (kindly see the above answer on nanotechnology).

The new introduction has been "dual mobility" head where femoral head articulates within a retentive PE. The PE is free to move in metal-back shell in a nonretentive way (in a bipolar prosthesis there is no movement between the poly liner and the shell and instead the shell is smooth that moves within acetabulum). Both the surfaces are mobile but outer bearing moves only in extremes of movements (nonphysiological ranges). The outer cup is surface modified for osteointegration and acetabular fixation. The main advantage is dual mobility design is reduced dislocation rate as it is the ever-concerning complication of a total hip replacement (THR). One should not be obsessed with dual mobility cups as they are not a substitute for classic hip design and are specifically indicated. The indications of dual mobility cup are typically:

- Situations in which primary hip is more likely to dislocate (elderly, patients with poor muscle mass and build, dementia)
- Revision hip arthroplasty
- Total hip replacement in developmental dysplasia of the hip (DDH), rheumatoid patients, and deformed hips
- Hyperlaxity, neuromuscular disease.

Intraprosthetic dissociation is a unique complication of this design which has to be reduced by open methods. The other disadvantage is inability to visualize acetabular floor during cup impaction as this is a monolithic cup.

Acetabular component is most susceptible to osteolysis, one of the factors for which is stress shielding due to rigid acetabular shells. Few modifications in materials and design have been produced to reduce the stress-shielding as follows:

- *Cambridge cup® (Howmedica, Staines, UK):* This is a horseshoe-shaped all polymer acetabular construct of ultra-high molecular weight polyethylene (UHMWPE) liner and carbon fiber reinforced polybutylene terephthalate shell with hydroxyapatite (HA) coating to fix to acetabulum.
- MITCH PCR cup (Stryker SA, Montreux Switzerland), a second-generation horseshoe-shaped cup made of polyetheretherketone (PEEK)/carbon fiber composite articulating with alumina femoral head.

Cementless femoral stem designs: The stems available are either unibody or bi-body (SROM type). The unibody designs vary with respect to the porous coating (proximal, distal, complete, tantalum, HA coated, etc.). The bi-body designs

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offer advantage as to improved adjustment of anteversion and offset, also it traps the particulate debris that develops at the interface without allowing it to percolate down once integration occurs. Slim anteroposterior designs have been developed but real advantage is unclear. Recently custom designs have been introduced. The custom stem can be prepared intraoperative (time consuming and limits the porous coating that can be provided) or preoperative customization using the radiological templating. Advantages over off-the-shelf stems have yet to come. The first generation cementless femoral stems of the hip arthroplasties include anatomic medullary locking (AML) (DePuy/Johnson & Johnson, Warsaw, IN, USA), the porous-coated anatomic (PCA) femoral stem (Howmedica, Rutherford, JN, USA), and the anatomic femoral stem (Zimmer, Warsaw, IN, USA) suffered from pain in the femur, the stress shielding phenomenon in the distal femur, osteolysis, dissociation, and difficulties in removal during revision. Second generation femoral stems were designed to fit firmly into the femoral proximal area by the concept of the tapered shape design, and maintain the hoop stress continuously to avoid stem subsidence. The tapered design did not match the shape of the femoral endosteum, and thus weight and stress transduction gets focused on special areas leading to formation of distal femoral shelf. Plasma sprayed stem surfaces tend to have less thigh pain than bead sintered stem designs.The most preferred stem design currently incorporates the following features:

- Proximally coated single wedge stems with wide proximal portions
- Collarless stem
- Shortened distal part by approximately 4–5 cm, compared to conventional stems
- The lateral shoulder of the proximal stem is inclined to make a slope to encourage bone preservation
- The neck is designed to minimize collision between liners and acetabular cups
- Reduce elasticity of distal stem by making long grooves on both the anterior and posterior sides of distal parts of stems, parallel to the vertical axis
- The lateral part of stem tips is partially removed to reduce contacts with lateral cortical bone to reduce thigh pain.

Cemented cups and stems: It is the improvements in cementing technique that has produced improvements in cemented hip arthroplasty rather than much changes in stem or cup designs. Only introduction of highly cross-linked poly is a major change in cup. In stem design the introduction of cement-in-cement revision stems has helped in cemented revisions otherwise the contemporary designs have not met major changes.

B. Anterior Cruciate Ligament Reconstruction

5. Discuss recent advances in arthroscopic anterior cruciate ligament (ACL) reconstruction with reference to creation of femoral tunnel and femoral fixation methods.

Ans: The placement of femoral tunnel and fixation methods have been a concern. Over a period of time the current recommendations are:

- Though double bundle technique has been envisaged to provide better rotational control, the clinical differences are yet to be proven. Single bundle technique by using anteromedial portal to create femoral tunnel more anatomically possibly yields similar results.
- Femoral tunnel placement should be at 10:30 position for right knee or 1:30 for left knee.
- The femoral tunnel should embrace the posterior cortex that can be achieved by 7 mm offset drill guide.
- It is better to widen the femoral notch so that it looks like a smooth inverted U "roman arch" rather than a pointed "gothic arch".

The femoral fixation devices have advanced to the following types:

- Compressive fixation (these produce compressive forces to the longitudinal axis of the graft pushing them against the bony tunnel). The commercial devices for such fixation are various interference screws that may be metallic (steel or titanium), bioabsorbable screws (polyglycolic acid, poly-L-lactic acid, poly-D, L-lactic acid, polyglycolic acid with trimethylene carbonate, poly-L-lactic acid with HA and poly-L-lactic acid with tricalcium phosphate). Bioabsorbable screws (available since 1995) instead are more compatible with ligament fixation and get absorbed in the body over a period of time. The PEEK cages have been introduced that provide strong fixation of soft tissue grafts with circumferential aperture compression.

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- Expansive fixation (these devices produce a bulging effect of the graft again compressing it against the bony tunnel). The cross pin (Rigifix®) system has been a popular technique among expansion mechanisms that utilizes two bioabsorbable (poly-L-lactide) cross pins inserted across the graft through two parallel drill holes from the lateral femoral condyle perpendicular to the femoral socket made by a guide. The system has good stability and a high failure load, easier revision surgery and overall lower complication rate. The problem, however, is higher cost and guide misfire after prolonged usage. Expansion bolt is another expansive fixation device.
- Suspension of the graft (suspending the graft into the femoral tunnel). The suspension mechanism may be located within the graft bone interface (as in transfix) or may be located more or less far away from the knee joint. Depending on the type of bone the fixation system latches into, three divisions can be made:
  1. *Cortical:* This system is most common in practices and utilizes buttons (endobutton®, tightrope®, etc.), Swing Bridge, or Ligament Plate as fixation device
  2. *Cortical-cancellous:* These suspension devices consist of cross pin and bone mulch screw
  3. *Cancellous:* Cancellous fixation is very near to or just abutting the graft as is used with Linx-HT, PEEK cage fixation device or tape locking screw (TLS) screw system.

(For further details, kindly refer to chapter on 'Sports medicine: Knee' of the book Essential Orthopedics: Principles and Practice, 2nd edition.)

6. Discuss the role of fixation devices in cruciate ligament reconstruction.

Ans: Femoral fixation devices have been already described above.

Tibial side: Two broad categories of fixation methods are utilized for fixation of graft on tibial side:

1. *Intratunnel fixation:* These are the primary methods of fixation deployed in most reconstructions and mainly comprise interference screw (metallic or bioabsorbable) providing fixation by compression. Evolgate® system utilizes titanium-based components for fixation of graft on tibial side by reinforcing the tunnel wall with a coil while metallic screw provides interference fit and a washer gives stable cortical fixation. Xenogenic spongiosa cylinders have also been used as bone plugs to provide interference fit. Intrafix system (compressive fixation) provides relatively more secure fixation, while cross pins and CentraLoc® has also been used for expansive fixation. Tape locking system (TLS)® system or polyetheretherketone (PEEK) cage fixation suspends the graft within the tunnel.
2. *Extratunnel fixation:* Most surgeons use this as a supplementary fixation method to intratunnel fixation. Common methods are using a cancellous/cortical screw as a post, staples, or ligament washers.

C. Diagnosis of *Mycobacterium (M) Tuberculosis*

7. A. Discuss recent advances in detection of *M. tuberculosis*.
B. Enumerate various newer methods with their sensitivity and specificity.
C. GeneXpert/CB-NAAT and its specific advantages.

Ans: A. To rapidly diagnose tubercular infection, direct diagnostic measures are rapidly advancing that can demonstrate the bacterium in the specimen with high certainty. The gold standard is microscopic demonstration of the organism or formation of "central caseating necrotic granulomas" on histopathological examination (though other uncommon causes forming such granulomas also exist) as evidence of tubercular infection. As an extended application demonstration using nucleic acid amplification tests (NAAT) in the obtained sample from representative lesion should also be acceptable under proper clinical setup. Molecular diagnosis using NAAT is gaining popularity for rapid diagnosis (few hours to less than 1 day), high sensitivity, and specificity. The specimens sent to the laboratory are directly subjected to amplification of specific *M. tuberculosis* DNA sequences using one of the many available techniques such as polymerase chain reaction (PCR), real-time PCR or strand displacement amplification. These are highly sensitive and specific to confirm in acid-fast bacilli (AFB) positive cases and even in AFB negative extra-pulmonary tuberculosis (EPTB) cases DNA-PCR is, however, unable to differentiate between viable and nonviable bacillus and cost is also a prohibiting factor. The mRNA-based reverse transcriptase-PCR (RT-PCR) can differentiate viable from nonviable *M. tuberculosis* and is a rapid diagnostic method for EPTB too. RT-PCR has also been used to monitor drug resistance. Bacterial mRNA has a mean half-life of 3–5 minutes only, thus demonstrating positive mRNA signal would indicate viable organisms.

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B. Newer targets have been studied for differentiation of latent from virulent and active organisms. Alpha crystallin (α-crystallin, *acr*) protein encoded by *acr* gene (also known as *hspX, Rv2031*) is such a marker; this protein is synthesized by mycobacterium under stress (reduced oxygen, immune response or treatment by antibiotics) and is associated with increased bacterial wall thickness. Synthesis of *acr* exponentially increases when bacterium undergoes transition from log phase to stationary mandating that the protein is essential for survival of stationary phase bacteria. Demonstration of *acr* is hence a new tool to identify latent infection, this can be done both in the tissue samples and even in patient serum. In contrast, the early secreted antigenic target-6 (ESAT-6) and culture filtrate 10 protein (CFP-10) act as virulence factors in *M. tuberculosis,* and contribute to pathogenicity. ESAT-6 and CFP-10 are particularly expressed by *M. tuberculosis* but not by Bacillus Calmette–Guérin (BCG) strains so *in vitro* T cell responses to ESAT-6 and CFP-10 appear to be highly sensitive and specific for the detection of infection with *M. tuberculosis* even in those immunized by BCG. Th1 proinflammatory cytokines are expressed at high levels when challenged with CFP-10 and ESAT-6 presentation in patients with active TB. Another method to diagnose active TB due to virulent bacteria expressing CFP-10 and ESAT-6 is to identify the CFP-10/ESAT-6 fusion protein using enzyme-linked immunospot (ELISPOT) assay for diagnosis of active TB either in tissue samples or patient sera.

C. The GeneXpert test (I personally recommend this test for diagnosis of active infection): Under the EXPAND-TB (expanding access to new diagnostics for TB) project a collaboration between WHO, foundation for innovative new diagnostics (FIND), and STOP-TB partnership's global drug facility (GDF) and global laboratory initiative (GLI) the Xpert MTB/ rifampin (RIF) assay was introduced to 6 EXPAND-TB countries (Azerbaijan, Ethiopia, India, Myanmar, Swaziland and Uzbekistan) in 2012 covering 21 countries in 2013. Xpert MTB/RIF is a fully automated diagnostic molecular test (applied on the tissue or sputum sample) using the NAAT. It simultaneously detects TB and rifampicin (R) drug resistance (*rpoB* gene) in less than 2 hours offering treatment opportunity same day. WHO strongly recommends the test to be used as the initial diagnostic test in individuals suspected of multidrug-resistant (MDR)-TB or HIV/TB. Conditionally, it is recommended as a follow on test to microscopy in settings where MDR-TB or HIV is of lesser concern especially in smear negative cases (like OATB). Line probe assay (DNA strip test) for first-line drugs (approved by WHO 2008) is recommended (encouraged) for diagnosis of MDR-TB (resistance to isoniazid (H) and/or (R) and is a good supplement to diagnosis in MDR-TB regions but requires rigorous setup. Still WHO recommends conventional culture methods and drug susceptibility testing (DST) to determine extended drug resistant (XDR) cases in endemic regions. The beacon assay and line probe assay are extended form of the GeneXpert test that can be used for detection of drug-susceptibility/resistance.

[For further details, kindly refer to Chapter 11 Joint Disorders Including Inflammatory and Noninflammatory Arthritis and Infective Arthritides (Including Mycobacterial infection and Prosthetic Joint Infection) of Essential Orthopedics, Principles and Practice, 2nd edition.]

D. Management of Polytrauma Patient

8. Describe recent advances in management of polytrauma patient highlighting the role of various investigative treatment modalities.

Ans: Metabolic imbalances and oxidative stress influence the outcome of critically ill polytrauma patients. Most often just a damage to an organ does not indicate the true decompensation or hemodynamic compensation. The peripheral measures like blood pressure, pulse rate, and central measures like cardiac output and central venous pressure (CVP) are more or less approximations. Such cases are increasingly evaluated by evaluation of the microenvironment and molecular diagnosis. Some of the studied markers are mentioned in **Table 6.3.1**.

TABLE 6.3.1: Serum inflammatory markers.

Acute-phase reactants	LBP, CRP, procalcitonin
Mediator activity	TNF, IL-1, IL-6, IL-10, IL-18
Cellular activity	TNF-RI, TNF-RII, IL-1R-I, IL-1R-II, IL-6-R, mIL-6-R, ICAM 1, E-selectin, CD11b, elastase, HLA-DR class-II

Lipopolysaccharide-binding protein (LBP) is of hepatic origin and has ability to bind bacterial lipopolysaccharide (LPS). LBP level rises during II or III day of trauma or sepsis, systemic inflammatory response syndrome (SIRS), and multiple

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organ dysfunction syndrome (MODS). LBP is significantly high in-patient with MODS with infection and can be used to differentiate SIRS from nonseptic MODS. C-reactive protein (CRP) has no role in polytrauma. Procalcitonin may indicate sepsis following SIRS. Development of SIRS followed by compensatory anti-inflammatory response (CARS) leads to activation of various inflammatory pathways. After CARS the patient may evolve into resolution or MODS depending on balance of pathways. Specifically, the activation of nuclear factor transcription-κB (NF-κB) modulates the activation of specific adhesion molecules, such as vascular cell adhesion molecules-1, intercellular adhesion molecules-1, and E selectin. Moreover, the activity of NF-κB is responsible for the modulation of some proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β). IL-1 (difficult to detect due to short half-life of 6 minutes) appears to be a marker of traumatic insult, with significantly elevated levels occurring within 1–4 hours after trauma, and correlates with the severity of illness. IL-6 helps in identifying patients who are less likely to survive. Increased concentrations of IL-6 associated with a poor outcome in patients with acute respiratory distress syndrome (ARDS). IL-6 is not predictive of septic complications, but rather correlates with the magnitude of the injury. IL-6 seems to be the most reliable marker systemic inflammation while LBP appears to be an accurate and early marker of infection. The use of these two markers together may offer the ability to detect the onset of SIRS and allows early intervention to prevent MODS. In polytrauma patients, the recognition of high levels of inflammatory markers favors the damage control orthopedics (DCO) application, in order to prevent the effects of the "second hit" inflammatory reaction. IL-6 is considered the most specific prognostic indicator (discussed later) and early high levels of IL-6 have been associated with the development of organ failure (measuring IL-6 has become a routine in dedicated trauma centers).

Micro-RNA: As we know that primary and secondary injuries both contribute to reduced survival of polytrauma patients, it becomes imperative at directing the molecular analysis to identify this aspect. Numerous studies have been conducted regarding the identification of expression of micro-RNAs in the different traumas. Significant among studied are 17–92 micro-RNA, micro-RNA-181, micro-RNA-146a, micro-RNA-155, micro-RNA-511, micro-RNA-132, micro-RNA-122, micro-RNA-21, micro-RNA-125b, micro-RNA-187, and micro-RNA-223 that modulate activity of antigen-presenting cells or T cells correlating with increased TNF-α and IL-1 levels. Additionally, expression of micro-RNA-181b is found to be greatly reduced in critically ill polytrauma patients.

(For further details, kindly refer to Chapter 120 "Polytrauma, Mass Casualties and Disaster" of Essential Orthopedics: Principles and Practice, 2nd edition.)

E. Reducing Recurrence of Giant Cell Tumor

9. Describe recent advances in reduction of recurrence of giant cell tumor (GCT) with emphasis on the medical treatment.

Ans: Simple curettage, with or without bone grafting, has a significantly high rate of local recurrence of up to 60%. The intralesional and marginal procedures without adjuvants are associated with higher recurrences (the recurrence is actually "persistence" of original disease) due to inability to completely remove the microscopic disease, and recurrence is not correlated with grade or site of lesion. Modern treatment of GCT with extended curettage (making a wide window, using headlamps or dental mirror, angled curettes and high-speed burrs and pulsatile lavage) and cryosurgery (using liquid nitrogen) to the tumor cavity has achieved a recurrence rate of less than 3%. Routine use of adjuvants is recommended. Cryotherapy with liquid nitrogen popularized by Marcove has various side effects and has been effectively abandoned due to frostbite of soft tissues and bone necrosis. Photoablation with an argon laser is another therapy that can lead to successful tumor necrosis.

Bone cement has a tumor kill effect by exothermic reaction and possible chemical reaction (solvent aerosol is cytotoxic) that produces necrosis of tissue for 1–2 mm from contact area. Some people have used methotrexate and adriamycin in the bone cement to augment cytotoxic effect. Bone cement has the advantage of filling the defect and having tumoricidal effect.

Bisphosphonates especially the newer forms (zoledronic acid and pamidronate) have been proposed to reduce the osteopenia due to osteoclastic effect of giant cells and can be used as adjuvant to extended curettage. Also, they have been shown to have *in vitro* tumoricidal action. With the recognition of osteoclast differentiation factor receptor activator of nuclear factor kappa B (NF-κβ) ligand (RANKL) on tumor cells, targeted therapy against the receptor has been shown to be promising. Denosumab is the first agent licensed to be used for this purpose by Food and Drug Administration (FDA)

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in 2013. Denosumab is indicated in the US for treatment of adults and skeletally mature adolescents with giant-cell tumor of bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity.

The increased expression of several angiogenic growth factors observed in GCT led to the use of interferon alpha (IFN-α) as an anti-angiogenic agent. Pegylated (PEG)-IFN has also been shown to have anti-GCT activity.

(For further details, kindly refer to Chapter 5 "Bone Tumors, Common Soft Tissue Tumors and Heterotopic Ossification" of Essential Orthopedics: Principles and Practice, 2nd edition.)

F. Advances in Biomaterials

10. Discuss recent advances in biomaterials in joint replacement to increase their longevity?

Ans: Kindly see Answers to Questions 1, 3, and 13 for detail.

G. Management of Infected Persistent Wounds

11. Discuss recent advances in the management of infected persistent wounds.

Ans: The following are some of the recent additions in management of chronic persistent wound infections.

Use of sliver and nanoactivated silver topically: Newer forms of delivery aim to increase the efficacy while minimizing side effects. It has a favorable broad-spectrum coverage [Yeast, Fungi, Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE)] even against antibiotic resistant organisms. Nanoactivated silver ions interact readily with negatively charged particles such as proteins, DNA, RNA, and chloride ions inhibiting the respiratory chain at the cytochrome level, interfering with electron transport, denaturing nucleic acids, inhibiting DNA replication, and altering cell membrane permeability. The pathogens are immediately killed upon contact due to this multi-pronged attack. Wound healing is also improved due to inhibition of zinc ions [hence matrix metalloproteinases (MMP)], and it has inhibitory effect on release of proinflammatory cytokines and TNF-α reducing inflammation in wound. Nanocrystalline silver dressings have two layers of high-density PE net sandwiching a layer of rayon/polyester gauze. The outer layer is coated with a nanocrystalline (<20 nm), noncharged form of silver (Ag^+), and the inner layer helps maintain a moist environment for wound healing.

Negative pressure wound therapy (NPWT): Vacuum-assisted closure (VAC) is recommended to be used as a comprehensive treatment plan in indicated acute or chronic wounds especially those that fail (or show delay) to heal normally and are challenging. It incorporates the use of negative pressure to optimize conditions for wound healing and has been found to reduce the need for frequent dressing changes, improve patient comfort, and reduce associated costs. Controlled negative pressure (50–125 mm Hg) is applied by an adjustable vacuum pump which reduces interstitial fluid accumulation and edema formation helping minimize bacterial colonization of the wound and increase proliferation of the granulation tissue by arteriolar dilation in negative pressure. The noted benefits of VAC therapy are:

- Removal of exudate from the wound and reduction in interstitial edema.
- Increased local microvascular flow and improved vascularity (arteriolar dilation).
- Increased controlled production of granulation tissue formation by reduction in the exposure to proteolytic enzymes. Vacuum also puts shear force producing cellular hyperplasia.
- Reduction in the need of antibiotics.

Improvements in dressing materials: Various advanced dressing materials have been introduced to improve wound healing—

- *Hydrocolloids:* These are impermeable to water, bacteria and other contaminants but permeable to water vapor.
- *Alginates:* They act as fillers for undermined and tunneled wounds and promote angiogenesis.
- *Foams:* These are nonadherent, easy to apply and remove, and are meant for highly exuding wounds.
- *Collagen:* It is chemotactic for fibroblasts and macrophages and also provide a temporary scaffold to allow in growth of tissue.
- *Hydrogels:* They are best suited for dry wounds or those with minimal exudates but need additional dressing.
- *Hydrofibers:* They maintain a moist environment and allow autolytic debridement so highly suitable for pressure ulcers.

Skin substitutes: They are available for wound coverage and are of various composite materials depending on type of wound. Bioengineered cellular therapies like Apligraf® (bilayered construct consisting of a bovine collagen matrix seeded

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with living human neonatal fibroblasts and a neonatal keratinocyte neoepidermis) and Dermagraft® [human fibroblast-derived dermal substitute (HFDS) comprising a cryopreserved, absorbable, three-dimensional polyglactin mesh substrate seeded with living neonatal dermal fibroblasts] are available for specific purpose. Human dermal allografts have become increasingly popular in recent years for augmenting tissue regeneration in chronic lower extremity wounds.

Growth factors and biologic wound products: Biological therapies refer to tissue-based treatments (acellular and cellular), autologous platelet-rich plasma (PRP), as well as recombinant human growth factor therapies. These aim to accelerate healing by augmenting or modulating inflammatory mediators viz. prostaglandin E1, cytokines like chemokines, lymphokines, monokines, interleukins, colony-stimulating factors, and interferons. Becaplermin (Regranex) is a combination of recombinant human platelet-derived growth factor (rhPDGF) and recombinant human epidermal growth factor (rhEGF). Topical insulin has been found trophic for wounds and is being increasingly used in combinations.

Wound debridement systems and pressure irrigation: Ultrasonic and powerful jet-based wound debridement systems are available for removing dead and infected material from wound providing clean surface for further intervention. Power-jets of compressed oxygen combined with minimal amount of saline solution produce fast and virtually painless debridement compared to other mechanical debridement methods.

Extracorporeal shock wave therapy (ESWT): Promote a cascade of cytokine and growth factor upregulation leading to enhanced neovascularization, anti-inflammatory response, and tissue regeneration expediting wound repair.

Hyperbaric oxygen and ozone therapy: While ozone is delivered by "bagging" technique locally, hyperbaric oxygen therapy (HBOT) is given in 100% high pressure oxygen tanks for patients to breathe. Ozone therapy is beneficial for diabetic infected wounds. HBOT is beneficial for a wide variety of chronic wounds by increasing tissue oxygen tension, angiogenesis, fibroblast proliferation, collagen deposition, and enhanced bacterial killing.

Stem cell therapy: Mesenchymal stem cells (MSCs) (bone marrow or placental) can directly differentiate into mesenchymal tissues, such as bone, tendon, and cartilage but need paracrine trophic function for cutaneous repair. MSCs produce growth factors, such as TGF-β3, to limit excessive scarring as well as modulate the balance between MMP and tissue inhibitors of metalloproteinases while regulating collagen deposition.

(For further details, kindly refer to chapter on wound healing and principles of wound care of the book Essential Orthopedics: Principles and Practice, 2nd edition.)

H. Management of Prolapsed Intervertebral Disks

12. Discuss recent advances in management of prolapsed intervertebral disks.

Ans: Prolapsed intervertebral disks (PIVD) causing intractable pain can be managed by a number of interventions apart from conventional microscopic or endoscopic diskectomy, fusion and disk replacement as follows:

- *Lumbar epidural steroid injections (transforaminal or caudal):* It is usually indicated after thorough evaluation for acute radicular pain due to irritation or inflammation, symptomatic herniated disk with failed conservative therapy, acute exacerbation of diskogenic pain or pain of spinal stenosis, neoplastic infiltration of roots, epidural fibrosis, chronic LBP with acute radicular symptoms. The drug is deposited in posterior epidural space in a blind procedure similar to giving epidural anesthesia/analgesia.
- *Selective nerve root block:* It is preferred for management of radiculopathy in patients with equivocal neurological finding or discrepancy between clinical and radiological examination. It can also be done in patients with unexplainable or recurrent pain.
- *Epidural adenolysis or percutaneous decompressive neuroplasty:* Epiduroscopy (a fiber-optic scope to visualize epidural space) helps in establishing the diagnosis of adhesions and also site of these adhesions. These adhesions can be managed by adhesiolysis during epiduroscopy under vision.
- *Trigger point (TP) injection:* The iliopsoas and quadratus lumborum are two muscles commonly involved in the origin of low back pain in the lumbar region. Neutralization of TP is the treatment of choice. TP injection with local anesthetic, deposteroid, ozone gas or even dry needling gives pain relief.
- *Botox paraspinal muscle injection:* This relieves the intractable muscle spasm associated with unrelieved low back pain and breaks the cycle of pain → spasm → deformity → neural compression → pain.

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- *Facet joint or pericapsular injection and medial branch block:* Relief from intra-articular local anesthetic injection or medial branch block with 0.5–1.5 mL local anesthetic confirms diagnosis of facet joint as source of pain. Radiofrequency (RF) ablation procedure of medial branch gives good and sustained pain relief. Therapeutic facet joint injection with steroid/RF ablation of medial branch of dorsal rami gives long-term relief.
- *Spine prolotherapy and manipulation:* It is done with normal saline, hypertonic saline with/without hyaluronidase.
- *Gray ramus block:* Gray ramus block (GRB) is effective to relieve low back pain caused by diskogenic pain. This procedure is used when surgery is not an option to relieve pain from disk.
- Percutaneous disk decompression:
  - *Laser diskectomy:* Holmium:yttrium-aluminum-garnet (Ho:YAG) laser is most commonly used. Nucleus pulposus is vaporized, intradiskal pressure decreases, allowing the disk to return to its normal state. Best candidates for laser diskectomy include those with back and leg pain with a confirmed disk herniation.
  - Radiofrequency coblation (plasma diskectomy)
  - *Mechanical disk decompression:* This procedure is usually performed under fluoroscopic guidance using a disposable, self-contained, battery operated handpiece connected to a helical probe (dekompressor®). Percutaneous diskectomy has a reported success rate of 60–87%.
  - *Percutaneous endoscopic diskectomy:* Percutaneous nucleotomy by means of arthroscopy instruments for disk removal for the treatment of posterior or posterolateral lumbar disk herniation under local anesthesia was demonstrated by Hijikata et al. in 1975. This technique is based on arthroscopic visualization of the herniation via the posterolateral approach for diskectomy of contained herniations. Ideal patient for this procedure is one who has paramedian, foraminal, or extraforaminal contained herniation.
- *Annuloplasty:*
  - *Intradiskal electrothermy(IDET):* Intradiskal electrothermy is based on modification of collagen making it thicker and causing it to contract decreasing its ability to revascularize. This in turn also prohibits the reinnervation and inflammation which may be causing root irritation.
  - *Radiofrequency posterior annuloplasty:* This is a minimally invasive method of delivering radiofrequency thermal energy to the disk to treat diskogenic lower back pain. Ideal candidates for this procedure are patients with intervertebral disc disease (IDD) grade 3/4/5 as per CT classification with chronic low back pain.
  - *Biacuplasty:* Intradiskal biacuplasty utilizes a bipolar system that includes two cooled radiofrequency electrodes placed on the posterolateral sides of the intervertebral annulus fibrosus to produce shrinkage.
- *Augmentation of nucleus pulposus and nucleus replacement:* Nucleus replacement arthroplasty aims to replace the intervertebral disk (IVD) nucleus while preserving the annulus and vertebral endplates. This would prevent disk height loss and the associated biomechanical and biochemical changes.
- *Gene therapy and stem cell-based therapies:* These are aimed to improve the intradiskal environment and production of healthy matrix. The gene-vector complex is directly injected into the target tissue producing the requisite growth factor. Various other approaches (cell based) are also under study but have limited success rates.

(For further details, kindly refer to Chapters 86, 87, 88 and 89 of the book Essential Orthopedics: Principles and Practice, 2nd edition.)

13. A. Disc replacement surgery.
B. Navigation in spine surgery.

Ans:

A. In this procedure, the biological injured or degenerated disc material is removed, and an artificial disc is implanted in the spine. Total disc replacement (TDR) technology is not totally new, and first attempts were made in the 1950s using the Fenstrom steel-ball endoprosthesis. The technology has been used for many years in Europe but is still mostly in trial stages in the United States of America, more than 100 designs were developed but only few are in use. More widespread application of TDR followed after the mid-80s developments of a TDR designed at the Charite Hospital in Berlin, Germany. The principle of replacing almost the entire IVD is based on the success of hip and knee replacements. Proponents of TDR view, it as a technology to treat back pain while attempting to decrease adjacent segment disease. The initial excitement with TDR got tampered by the realization that specific cause of LBP is still not known, so complete relief in all patients is far-fetched expectation and the fact that mechanical failure of devices were quickly reported.

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Aims of Total Disc Replacement

- Restore the physiological kinematics of the IVD
- Relieve pain
- Improve stability and resist wear
- Protecting the adjacent discs and facet joints from undue degeneration.

Indications: The classic indication for TDR includes failure of aggressive conservative treatment with disabling LBP attributed to the lower lumbar spine affecting no more than two discs. Other indications are like those of fusion.

Prerequisite:

- Demonstrable disc degeneration as the cause of pain
- Intact facet joints posteriorly and no other pain generators demonstrated

Contraindications:

- Lumbar spinal stenosis
- Facet disease
- Old fractures
- Previous laminectomy
- Instability as seen in spondylolisthesis
- Osteoporosis
- Pars fracture
- Infection

Relative contraindication—patients with a steep lumbosacral angle at the intended TDR level. It is difficult to implant disc in such situation.

Total Disc Repair Designs

The materials that have been used for TDR are similar to those that have been employed in other major joint arthroplasties (e.g. polyethylene, chrome cobalt, titanium). And to this effect, the replacement designs are also available in varying conformities:

- Unconstrained
- Semi-constrained
- Constrained

The surgical approach is like the one used to obtain an anterior lumbar interbody fusion and carries similar rates of vascular complications.

Outcome of implantation: The reports have been encouraging and, in most cases, have not been found to be inferior to fusion surgery. The long-term complications and benefits of TDR are yet to be realized, especially in terms of preventing adjacent level disc degeneration.

Complications:

- Osteolysis
- Implant fracture or wear
- Vertebral body fracture
- Failure of ingrowth
- Instability with dislocation

The revision surgery is technically difficult as there is prominent anterior fibrosis after the procedure increasing the chances of vascular injury and other complications.

B. Navigation in spine surgery

Safety and efficiency during spine surgery is of paramount importance due to the sensitive nature of the neurovascular structures involved. The complexity of the three-dimensional anatomy of the spine innovative and modern techniques that improve 3D orientation and guidance during surgery have gained popularity. Intraoperative computer-aided navigation (CAN) during spine surgery has been classically used for pedicle screw placement that gets smoothly incorporated into minimally invasive spinal surgery procedures to reduce intraoperative radiation exposure and enhance surgical

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accuracy. To combat the relative inaccuracy of traditional methods of pedicle screw placement and involved high stakes (neurovascular injury), CAN was introduced as a means to improve accuracy. Now the computer-based navigation systems guide surgeons while placing instrumentation and also for noninstrumented cases. CAN uses novel computer-based technologies, including stereotaxy, navigated surgery and robotics.

Basic Components of Navigation System

- *Image acquisition and processing unit:* High-resolution images are obtained either preoperatively or intraoperatively. Due to the anatomical changes between image acquisition (usually supine position) and actual operative procedure (prone position), re-registration of landmarks intraoperatively is essential. Intraoperative images are acquired using fluoroscopy, CT scan or MRI.
- *Referencing system:* The intraoperative landmarks are referenced to the image/navigation database using referencing system. This consists of:
  - *Dynamic reference frame/array (DRA):* DRA is attached to fixed landmark (spinous process/iliac crest) which should remain undisturbed throughout surgery. Preoperative image is taken along with the fixed DRA to synchronize between the virtual navigated images and anatomical landmarks.
  - *Light emitting diodes (LED):* Emit (positive array-like DRA) or reflect light (passive array—instruments), which is tracked by an electro-optical camera and are known as active arrays to provide a real-time tracking of the exact location of these devices over the surgical field.
  - *Tracking system:* Optical (more accurate), mechanical, acoustic or electromagnetic systems calculate the location and provide real-time 3D positional data of the handheld surgical instruments in relation to the surgical field.

Registration process: This synchronizes virtual images to real anatomy. *Three types:*

1. Paired point registration
2. Surface matching
3. Automatic registration

Generations of CAN system:

a. First generation—image acquisition using thin-slice CT scan, manual point-matching referencing (long and tedious).
b. Second generation—intraoperative reconstruction images of the spinal anatomy using 2D and 3D (isocentricity based concept) fluoroscopy. Improved versions used cone-based CT that have better image quality, larger vertebral span and automatic registration.
c. Third generation—intraoperative CT scan with subsequent automatic registration, screening whole spine, total navigated spine surgery and complete support to minimally invasive techniques are some of its salient features.

Clinical applications:

- Cervical spine pedicle screw and lateral mass screw placement, Hangman fracture osteosynthesis and occipitocervical surgeries in congenital defects.
- Minimally invasive surgery—the accuracy and safety of pedicle screw placement is highly improved over free-hand technique.
- Correction of spinal deformity (osteotomy) and fixation (pedicle screw placement in dysmorphic pedicles).
- Spinal tumor surgery—better localization of tumor and clearer- defined margin for resection + safety of displaced sensitive neurovascular structures.
- Complex lumbosacral trauma osteosynthesis—placement of S1, S2, alar and iliac screws.

Advantages of navigation-assisted spine surgery:

- Accuracy and improved safety
- Reduced surgeon fatigue
- Reduced operative time (depends on familiarity with system however)
- Minimal radiation exposure

Disadvantages (areas of improvement):

- Wobbling and motion-related artefacts
- Altered accuracy due to distance from reference array.

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I. Diagnosis and Management of Rheumatoid Arthritis

14. Elaborate recent advances in diagnosis and management of rheumatoid arthritis.

Ans: Specific diagnostic tests do not exist for definitive diagnosis of rheumatoid arthritis (RA). The diagnosis is mainly clinical but to speed up the diagnosis few tests act as supportive measures as follows:

- *Anti-cyclic citrullinated peptide (CCP) antibody:* The second generation anti-CCP assay is recommended as a routine work-up of patients clinically diagnosed as (RA).
- *Anti-mutated citrullinated vimentin (MCV) antibody:* These are associated with more severe RA. The assay may prove to be of high specificity for the diagnosis of RA and is likely to be useful in clinical practice due to its simplicity.
- Ultrasonography and MRI scan are being increasingly used to determine synovitis and joint erosion to implement specific therapy.

European League Against Rheumatism (EULAR) new criteria (2010) for clinical diagnosis ***(Table 6.3.2)****:*

TABLE 6.3.2: European League Against Rheumatism criteria (2010) for clinical diagnosis.

Joint involvement (0–5)	
1 medium-large joint	0
2–10 medium-large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least one small joint)	5
Serology (0–3)	
Negative rheumatoid factor and negative anti-citrullinated protein antibodies	0
Low positive rheumatoid factor or low positive anti-citrullinated protein antibodies	2
High positive rheumatoid factor or high positive anti-citrullinated protein antibodies	3
Acute phase reactants	
Normal C reactive protein and normal erythrocyte sedimentation rate	0
Abnormal C reactive protein or abnormal erythrocyte sedimentation rate	1
Duration of symptoms	
<6 weeks	0
≥6 weeks	1

These criteria are intended for patients with at least 1 joint with definite clinical synovitis (swelling, not just tenderness), and in whom the synovitis is not explained by another disease such as psoriasis, systemic lupus erythematosus, or gout. Patients are considered to have RA if they have a score of at least 6.

Management aspect: Biologic agents refer to complex protein molecules produced by using molecular biology methods in prokaryotic or eukaryotic cell cultures. It is now well validated that biologic therapies have changed the way RA is managed. These directed therapies act either on the cytokines or their receptors.

Anti-TNF agents: These improve symptoms while reducing radiographic progression of joint erosions and are the most commonly deployed biological agents for management of RA. A number of them (etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol) are available and others being actively developed for improvement in specific activity. There is a demonstrable benefit of early treatment with TNF inhibitors and methotrexate, suggesting that early intervention may have lasting benefits to patients with regards to disease progression.

Interleukin-1 (IL-1) antagonist (Anakinra) has demonstrated improvement in symptoms but is not commonly used due to its comparatively low efficacy as against anti-TNF agents.

Inhibitors of T-cell costimulation: Abatacept blocks T-cell activation through inhibition of CD28-B7 mediated costimulation of the T-cell and has been effective in patients not responding to anti-TNF agents.

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IL-6 receptors antagonist (Tocilizumab): This agent is approved for management of moderate to severe RA showing inadequate response to anti-TNF agents.

Anti-B-cell agent (Rituximab): This is also approved for patients failing on anti-TNF agents. These are not associated with risk of tuberculosis reactivation and are not contraindicated in previous history of cancer.

Kinase inhibitors: These are under development novel agents that are different from conventional biological agents in that they target intracellular molecules that are involved in signal transduction instead of cytokines or receptors. In particular, janus kinases (JAKs), spleen tyrosine kinase (SyK), and p38 mitogen-activated protein kinases (MAPKs) as targets are under study.

Apart from above lots of molecules are under developments that target various integrated and intermediary pathways like IL-15, IL-17, IL-32, lymphotoxins, and B-lymphocyte stimulator (BLyS).

[A detailed description on the use of biological agents and diagnostics is provided in the chapter on Joint Disorders Including Inflammatory and Noninflammatory Arthritis and Infective Arthritides (Including Mycobacterial Infection and Prosthetic Joint Infection) of the book Essential Orthopedics: Principles and Practice, 2nd edition.]

J. Total Hip Arthroplasty

15. Discuss recent advances in total hip arthroplasty.

Ans: Total hip replacement has established itself as a successful orthopedic intervention for management of specific hip disorders beyond doubt. Attempts have been and are being made to improve the outcomes still further. The recent advances have been made specifically in bearing surfaces, improving longevity, stem and cup designing (limited), cementing techniques and resolving controversies for hip exposure technique. Methods to ameliorate infection are applicable to all joint arthroplasties and osteosynthesis in general.

Bearing surfaces: Currently this has moved in a circle with various advances not proving significantly advantageous in general over standard metal-on-poly (MOP) articulation. Some alternative bearing surfaces do have indications in specific situations.

Ceramic (alumina or zirconia) on poly: When envisaged this was considered a superior counterpart of MOP bearing, but this has not been consistently proven. Oxidized zirconium (Oxinium®, Smith and Nephew) has been specifically produced for this articulation but wear properties are not very impressive (compared to available materials). The oxinium improves the wear characteristics of zirconium while simultaneously utilizing the hardness and its fracture resistance. This has also allowed the use of large heads as the volumetric wear would be less ultimately while increasing stability. Alumina seems to have outpaced zirconia in the race against wear as it has reduced wear rates than the latter. The inconsistent reports of sometimes increased and at other times reduced wear would be explained by presence of third-body wear. This also explains the imperative need of hardened poly as a safety measure to be used against harder femoral head bearings (hence preferring highly cross-linked poly). The newer highly cross-linked PE show annual linear wear at 45% of conventional UHMPE in prosthesis implanted for 5 years. This indicates that osteolysis may not possibly occur at all.

Ceramic-on-ceramic (COC) bearings: While alumina remains the most widely used ceramic and is preferred for COC bearings, zirconia is utilized as a replacement for alumina femoral heads for COP bearings (UHMWPE acetabular liner). This is reasoned on the fact that zirconia is stronger than alumina and therefore it can resist higher degrees of stress. The advantages conferred by zirconia include superior mechanical strength posing a reduction in bearing fracture risk. The advantages on COC bearings are minimal wear and virtually no osteolysis due to inert nature of alumina wear particles, alumina ceramics are highly oxidized so they cannot be further oxidized and are biologically inert and resistance to surface damage.

Ceramic-on-metal (COM) bearings: The wear for alumina COM articulations is very favorable, but the articulation should be ceramic femoral heads 28 mm in diameter articulating against acetabular cups manufactured from medical-grade, high carbon-wrought cobalt-chromium alloy. In addition, this bearing also appears to produce less stripe wear with edge loading than metal-on-metal (MOM) or COC implants. The potential advantage of this novel COM bearing is thus lower wear and the production of significantly reduced metal particles quantitatively.

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Metal-on-metal (MoM) bearing: MOM bearing has been withdrawn world over since around 2010 for concerns of ill-effects of metal ions and untoward biological response including cancer risk.

Silicon nitride bearing surfaces: Si_3N_4 shows good fracture toughness, high-flexural strength, and resistance to hydrothermal degradation (like alumina). Si_3N_4 is currently used in aerospace bearings and in high-temperature places like in diesel engines. When studied for THA, the Si_3N_4 cups have been shown to highly reduce the wear rates when used against Co-Cr or Si_3N_4 femoral heads. The Si_3N_4-Si_3N_4 bearings have very low friction coefficient of 0.001 even when compared COC alumina bearing of 0.08.

Carbon-fiber polymeric composites and PEEK bearings are under study and would need substantial time for clinical development and acceptability.

Recent advances in cup and stem designs of cemented and uncemented hips—see Question 3 above for details. *Improvements in surface finish and design to improve implant longevity* is discussed in Answer to Question 1 above.

Recent advances in cementing technique and bone cements: Apart from the standard hand mixing and pressurization of bone cement advancements have been made to provide a composite cement mantle devoid of deficiencies and having uniformity. The third-generation cementing technique involves:

- Use of vacuum-centrifugation for cement preparation to reduce porosity
- Pulsatile lavage irrigation of femoral canal and packing with adrenaline soaked swabs
- Insertion of the cement in a retrograde fashion and cement pressurization using proximal pressurizers
- Adrenaline-soaked sponges for femoral canal
- Prosthesis is inserted using distal and proximal centralizers to ensure optimal position and even cement mantle.

Cartridge mixing and delivery is a further improvement using a universal power mixer that quickly mixes and then injects nearly all types of bone cement. It has the advantage of reduced mixing times and consistency of the mixture. Also, the operating room personnel are spared of toxic fumes.

Composite cements are being produced for improving bone cement interface characteristics. Polymer fibers are added to poly (methyl methacrylate) (PMMA) for improving fracture toughness and fatigue strength. The following are currently studied additives:

- Carbon fibers as multiwalled carbon nanotubes
- Glass fibers
- Kevlar (used in F1 racing car's petrol tanks)
- Oriented PMMA
- Rubber impregnated PMMA
- Ultra-high-molecular-weight polyethylene
- Polyethylene terephthalate
- Aramid
- Graphite
- Nano-sized titanium fibers
- Embedded continuous stainless steel coils
- Zirconia fibers with and without acrylic coating.

For improving cement integration into bone mixing the 40% w/w calcium phosphate (Brushite) into two-solution pseudoplastic system (non-Newtonian material where the viscosity decreases as the shear rate increases) to yield highly viscous, injectable, bioactive cement with high compressive strength and has shown encouraging results *in vitro*. Osteoconduction can also be improved by addition of bioactive ceramics.

Heat generation in bone cement can be reduced by adding 1-dodecyl mercaptan, ammonium nitrate, zeolytes or N-acetyl cysteine as appropriate.

Recent advances in diagnosing periprosthetic joint infections are discussed in Answer to Question 1.

Advances in preventing and managing the DVT after arthroplasty is discussed in Chapter 1 elaborately.

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Advances in surgical exposure of hip: Direct anterior approach and minimally invasive surgery (MIS) are new contenders for surgical exposure of hip joint. The anterior approach has been proposed to avoid damage to abductor function (lateral approach) and also reduce dislocation rates after THA (posterior approach). The MIS anterior approach has been found to have longer operative time, higher blood loss, four intraoperative conversions to posterolateral, more complications and the same length of stay in hospital with no functional difference. Currently no systematically performed study demonstrates superiority of any approach and possibly the approach in which the surgeon is most comfortable and trained should be used.

(Details on various advances discussed can be read from Chapters 58, 60 and 61 of the book Essential Orthopedics: Principles and Practice, 2nd edition.)

K. Articular Tissue Engineering

16. Discuss advances in articular cartilage tissue engineering.

Ans: Articular cartilage tissue engineering requires the integration of stem-cell therapy, 3D printing and surgical modifications to come together. Principle is culturing chondrocytes in an implantable biological matrix with ideal properties—biocompatible, biodegradable and bioactive while preserving the phenotypic characteristics, thus favoring the cellular proliferation and synthesis of the extracellular matrix (ECM), which is permeable, easy to use and inexpensive. The matrix is bioengineered using 3D printing technology. Innovative approach is to use a combination of structures that use "force dissipation pattern" utilizing stem cells or chondroblasts that can be influenced by the mechanical stimuli. "Smart scaffold designs" are created by combining different biomaterials that influence deposition of extracellular matrix by influencing cellular alignment. These constructs have to be, however, grown in a controlled environment in a bioreactor into functional tissue that then matures in the body. The process has been taken a step further by trying to incorporate the functions of tissue into synthesized construct itself. Construct such as cell-laden heterogeneous hydrogel can be produced with 3D printing to be potentially used as osteochondral grafts. Decellularized extracellular matrix (dECM) has been bioprinted that can provide microenvironment to chondrons for induction of cartilage tissue growth by providing crucial signals for cell engraftment, survival, and future functions. To mimic the zonal (three zones of native hyaline cartilage) construct of cartilage combination of polymers have been used like polyethylene glycol (PEG), hyaluronic acid, chondroitin sulfate, and metalloprotease-sensitive peptides that encapsulate single lineage of MSCs.

Mesenchymal stem cells are the work-horse for providing the source cells that could regenerate into cartilage but it is easier said than done. Newer techniques of using MSCs in natural matrices demand exacting engineering to provide optimal milieu (mechanical stability) for ideal differentiation of the implanted cells into hyaline cartilage. This mechanical stability (protecting from axial and shear stress) imparts important cell-matrix interactions (enough porosity to allow nutrient diffusion while maintaining adequate adhesion), so that functional tissue growth can happen. MSC-based constructs use (as described by various authors) poly (vinyl alcohol)/polycaprolactone (PVA/PCL) nanofibers or alginate or collagen gel/powder covered with periosteum or hyaluronic acid membrane, while free injection of MSCs has also been done.

(For further details, kindly refer to Chapters 10, 130 and 131 of the book Essential Orthopedics: Principles and Practice, 2nd edition.)

L. Management of Periarticular Fractures

17. Discuss the advances in management of periarticular fractures.

Ans: The periarticular fractures are managed on primary principle of accurate joint line restoration and alignment. If intra-articular extension is seen, then anatomic reduction and absolute stability needs to be added. The most important concern is the articular surface depression and compaction into the subchondral cancellous bone in associated intra-articular extension and common finding of comminution at the metadiaphyseal interface. So the goals of osteosynthesis are:

- Joint line alignment in anatomical position (with respect to the mechanical/anatomical axis)
- Joint surface (articular surface) restoration
- Adequate stability to allow early joint mobility to prevent stiffness.

To achieve all three goals usually the joint surface is to be lifted that leaves a void in the supporting cancellous area. Also, the implant construct need to provide good stability over a prolonged period to support rehabilitation. The following are the advances in current practice supporting this end:

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Filling of cancellous bone defect: Apart from the conventional autogenous and allogenic bone graft synthetic materials have been introduced to act as bone fillers. Most of the current available synthetic bone graft substitutes can be grouped into HA products, soluble calcium-based blocks and granules, or injectable cements. Injectable calcium phosphate cement may leak through intra-articular defects and harden in the articular surface causing arthrosis of joint so injectable resorbable calcium sulfate cement is favorable. The biodegradable calcium sulfate cement has been designed to harden with the defect and provide intraoperative stabilization. It can be drilled through and receive self-tapping screws after hardening without hindering material strength or integrity properties.

Use of 3D-printed blocks as bone defect spacers: 3D printed biocompatible porous 3D matrix scaffolds allow conducive environment for cell attachment, migration, incorporation of growth factors, and encouraging vascular ingrowth. These scaffolds apart from above properties should be sufficiently mechanically stable providing requisite strength at the site of usage. For cellular growth, it has been found that in a hydrogel model (alginate scaffold) addition of peptide like arginine-glycine-aspartic acid increases bone formation. PEG hydrogel as also demonstrated promising results in terms of its properties for supporting cellular growth. 3D printing controls the precise form, architecture, and disposition of scaffold producing clinically optimal combinations.

Arthroscopic assisted-reduction and fixation: The arthroscopically-assisted reduction and internal fixation (ARIF) techniques has advantages of accurate diagnosis of the fracture and associated soft tissue involvement, the potential for concomitant treatments (removal of loose fragments/ligament reconstruction), anatomical reduction and minimal invasiveness. This is especially useful in minimally invasive plate osteosynthesis (MIPO) technique where accurate reduction can be effected by intra-articular manipulation of the displaced fragments to align them anatomically. The "PART" and "dry technique" are further advancements where complex fractures can also be addressed.

Use of hybrid fixators: In high energy trauma where skin condition is unfavorable hybrid fixation with wire frame combined to regular fixator may serve the purpose. The reduction can be improved by arthroscopic techniques.

Use of locked plate constructs: Anatomical locked plates with fixed angle screws have drastically improved the stability of periarticular osteosynthesis. The plates have further gone advancements like variable locked screw plate constructs where the screw can be locked in different positions as needed by surgeon and design improvements for matching the anatomy.

Use of allograft-plate construct: This is rarely used in cases with bone loss but repairable tissues where osteoarticular allograft is first fixed to the locked plate and the composite can be used for osteosynthesis.

Custom printed implants: This is a new frontier opened by the 3D-printed technique where patient specific implants can be printed using data from CT scans preoperatively, facilitating application and osteosynthesis.

18. Recent advances in various imaging modalities in orthopedics?

Ans: This would need a complied answer [the reader is encouraged to read the positron emission tomography *(PET) scan, magnetic resonance imaging (MRI), and ultrasonography* from chapters—123, 125, and 126, respectively of the book *Essential Orthopedics—Principles and Practice*]. There have been subtle changes only in advances of imaging such as zero-ECHO MRI. Some additional details are written below:

- *Magnification radiography:* Magnification radiography is occasionally used to enhance bony details not well appreciated on the standard radiographic projections. This technique may help is detecting early arthritic changes and some metabolic disorders. Very rarely it may be useful in demonstrating subtle fracture lines otherwise not seen on routine projections.
- *Digital radiography:* Digital (computed) radiography (DR) is the name given to the process of digital image acquisition using an X-ray detector comprising a photostimulable phosphor imaging plate and an image reader-writer that processes the latent image information for subsequent brightness scaling and laser printing on film.
- *Tomography:* Tomography is a body-section radiography that permits more accurate visualization of lesions too small to be noted on conventional radiographs or demonstrates anatomic detail obscured by overlying structures. Newly developed tomographic units can localize the image more precisely and have aided greatly in the ability to detect lesions as small as approximately 1 mm.
  - *Computed tomography (CT):* The newest advances in sophisticated software-enabled 3D reconstruction, which is helpful in analyzing regions with complex anatomy, such as the face, pelvis, vertebral column, foot, ankle, and wrist. New computer systems now permit the creation of plastic models (3D printing) of the area of interest based

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on 3D images. These models facilitate operative planning and allow rehearsal surgery of complex reconstructive procedures. High-resolution flat-panel volume CT (fpVCT) uses digital flat-panel detectors and provides volumetric coverage as well as ultra-high spatial resolution in two-dimensional (2D) and 3D projections. It reduces metal and beam hardening artifacts and fpVCT also allows dynamic imaging of time-varying processes. 3D CT-angiography is effectively used to determine the presence or absence of injury to the vessels near the fractured bones.

19. Discuss various considerations, pros and cons and future perspective of day care surgery in orthopedics.

Ans: The Royal College of Surgeons' definition for day care surgery is when the surgical day case patient is admitted for investigation or operation on a planned nonresident basis and who nonetheless requires facilities for recovery. It is a part of ambulatory surgery but is different from outpatient surgery in that some degree of postoperative specialized nursing care/observation is needed during postoperative recovery. The definition also includes 'extended' (23 hours 59 minutes admission) stay surgeries based on individual patient needs. Commonly performed orthopedic surgeries include Dupuytren's release, carpal tunnel release, ganglion excision, arthroscopy, bunion surgery, implant removal, etc.

Considerations:

- Patient selection
  - For GA, patients must preferably be American Society of Anesthesiologists (ASA) classes I or II. ASA class III and IV are only taken up in a well-established experienced Day Care Surgical Centre.
  - Psychologically stable patients are preferred who understand the pros and cons and are not just monetarily inclined.
  - Obese, elderly and frail are generally better managed on an inpatient basis.
  - Operations should be so chosen that have minimal blood loss and produce mild to moderate (bearable) postoperative pain.
  - Operations should preferably be of <1 hour duration.
- *Contraindications:*
  - Unstable cardiovascular patients—Angina, recent MI, on blood thinners, uncontrolled hypertension, and cardiac failure
  - Pulmonary complications—acute respiratory infection, COAD/ILD like emphysema, chronic bronchitis, and asthma.
  - BMI > 35
  - IDDM
  - Psychologically unstable on medications, anxious patient
  - Patient living far from the center who may not return fast enough should any complication arise.

Advantages (Pros)

- *To patient:*
  - Less likely to be cancelled due to prebooking and minimal impact of emergency surgeries due to dedicated facility.
  - Shorter waiting lists
  - Minimal disruption of patient's personal life and easier domestic arrangements
  - Earlier mobilization
  - Earlier return to normalcy and work (job)
  - Reduced risk of cross-infection
  - Less psychological disturbances in children
- *To hospital:*
  - Economic savings
    - Less staff and facilities needed.
    - Minimal/no need of night staff
    - Lass capital intensive than a regular hospital bed
    - Reduces the number of in-patient beds need of hospital
  - Happy staff due to less shift work

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Disadvantages (cons):

- There is additional need for a responsible/understanding person at home to oversee the patient for first 24–48 hours.
- The day case surgery needs experienced senior staff due to high turnover where junior staff may keep fumbling on trivial logistical arrangements.
- Extra work for the medical officer in the postoperative period
- Cost-effectiveness of the unit is reduced if less complex cases (that may be managed in outpatient surgical care) are dealt with on a day-care basis.

Future perspective: Considering the advantage to the patients and reduction in economic burden, the list of day care surgeries is increasing. This is also in-line with the much pushed affordable health care in developing countries where hospitals struggle to cope-up with the expenditures they have to make compared to the limited returns from government schemes. Now the scope of day-care surgeries is being extended in orthopedics to all surgeries that can be done under regional anesthesia like fixation of peripheral uncomplicated fractures, arthroscopies, simple deformity corrections, etc.

20. Discuss the current concepts in treatment of osteomyelitis.

Ans: The recent advances in osteomyelitis deal with pathogenic mechanisms and novel therapeutic strategies. The latter especially deal with novel local delivery materials with appropriate mechanical properties, lower exothermicity, and controlled release of antibiotics, and absorbable scaffolding for bone regeneration is progressing rapidly. Emerging strategies for prevention, early diagnosis of low-grade infections, and innovative treatments of osteomyelitis such as biofilm disruptors and immunotherapy are also described.

Pathogenic mechanisms of bone infection (novel descriptions): The description describes the development of chronic osteomyelitis from acute osteomyelitis involving three distinct mechanisms:

1. Staphylococcal abscess communities in the local soft tissue and bone marrow
2. Glycocalyx formation on implant hardware and necrotic tissue
3. Colonization of the osteocyte-lacunocanalicular network (OLCN) of cortical bone

In contrast, *Staphylococcus aureus* intracellular persistence in bone cells has not been substantiated *in vivo*, which challenges this mode of chronic osteomyelitis.

Management of osteomyelitis (recent trends):

Diagnostics:

- Direct measurement of bacterial burdens from infected specimens is increasingly possible due to advances in protocols for bone homogenization.
- Micro-computed tomography (microCT) is a high-resolution, 3D imaging modality frequently used in the field of bone biology because of its ability to calculate bone density and volume. MicroCT is used to quantify pathogen-induced changes in bone remodeling during osteomyelitis, including both bone destruction and aberrant new bone formation.
- Blood-serum-based *S. aureus*-specific antibodies as diagnostic marker:
  - Antibody responses against iron-sensing determinant proteins (IsdA, IsdB, IsdH) could be predictors of infection outcomes in patients with *S. aureus* prosthetic joint infection (PJI), and that higher serum anti-IsdA and anti-IsdB IgG levels in patients are associated with increased mortality.
  - IgG levels in serum against a cell division protein called autolysin (Atl) was protective against *S. aureus* infections in patients undergoing orthopedic surgeries.
  - Pathogen-specific B-cells stimulated in germinal centers of lymph nodes proliferate, secrete their antibodies and enter the circulation. These plasmablasts, often called antibody-secreting cells (ASCs), emerge early in an infection and are circulating in the blood as long as the infecting pathogen remains active.
  - Media enriched for newly synthesized antibodies (MENSA) represent a measurable and accessible way to detect acute immune responses to ongoing infections. MENSA levels are direct indicators of ongoing infections as they develop and as the infections wane under the attack of the host's immune responses. MENSA evaluation could be used as a prognostic tool to guide clinical decisions in orthopedic infections.

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Some of the current treatment methods are:

- *Immunotherapies* may be effective adjuvants with antibiotics for combating hard-to-treat osteomyelitis. Passive immunization involving monoclonal antibodies (mAbs) is an evolving method to treat *S. aureus* osteomyelitis. A benefit of passive immunization with mAbs is their high antigen-neutralizing specificity. Some examples include mAbs that target fibrinogen-binding cell surface protein (ClfA), cell wall components [lipoteichoic acid (LTA), poly-N-acetylated glucosamine (PNAG)] and secreted toxin, such as α-hemolysin. The second generation of immunotherapy target multiple antigens with essential functions for *S. aureus* immunoevasion, colonization, intracellular growth, and persistence within the host cells. Examples of these include mAbs that target the B-cell antigen staphylococcal protein A, the immunodominant surface protein IsaA, 170 and the immune-stimulatory staphylococcal superantigen SEB.
- *Antibiotic-coated implants and nanotechnology surface-modified implants to kill pathogens and disrupt the biofilms:* Intramedullary nail-coated nanoparticles with antibiotic and its growth factor.
- *Formulation and development of composite biodegradable scaffolds as antibiotic delivery system and also a regenerative device for bone:* The major focus is developing a combined 3D system that induces bone regeneration + a drug delivery system (3D-DDs). The 3D-DDs can be taken as injectable or moldable, which composed of a biocompatible, biodegradable polymer, with a combination of decellularized bone matrix [bovine bone substitute (BBs)] and with the antibiotic drug (aminoglycoside/vancomycin microparticles). The moldable 3D scaffold is formulated in such a way that it can be separated by cutting into desirable length, hydrated, and can be remodeled by a surgeon according to their specification, for fitting and curing the bone defect. The injectable composite scaffold is obtained with the method of lyophilization and also results in high porosity, and the obtained spongy structure of lyophilized scaffolds allows fast hydration of scaffold in blood or any physiological fluids of the body, without any change in the physical structure. Certain advantages of 3D-DDS are: it is ready to be used at any time, administration can be done through cannula or can be administered into the defected part through surgical procedures, easy to insert into irregular body spaces or cavities caused due to the disease or caused due to fracture and perfectly fit in the defected site of the bone, keeping the physical integrity stable throughout.
- *Bioactive hydrogels for bone regeneration:* Bioactive hydrogels are polymer scaffolds with several advantages for repairing bone defects. Hydrogels are the formation of 3D hydrophilic polymer chains, which are having high mechanical strength and provides nutrient environments suitable for the growth of endogenous cells.
- *Formulation and development of vancomycin-incorporated chitosan/gelatin coatings coupled with the TiO_2–SrHAP surface-modified Cp-titanium for the osteomyelitis treatment:* This method improves the implant material providing a biointeractive surface that will restrict or obstruct the growth site bacterial agents and increase the biological activity.

There are two layers: In the first layer, there is a combination of TiO_2 metal oxide and SrHAP ceramic oxide (increases electrochemical resistance). The second layer is a formation of the drug, i.e. vancomycin, which is encapsulated with chitosan/gelatin coating.

- *Single-stage treatment of diabetic calcaneal osteomyelitis with an absorbable gentamicin-loaded calcium sulfate/hydroxyapatite biocomposite: The Silo Technique*—in recent studies, it has been seen that using of calcium sulfate (CAS), combining with hydroxyapatite (HA) in a synthetic and injectable mixture has become "the new era bone substitute" that can be fortified with antibiotics.
- *Biodegradable polyurethane (PUR) scaffolds* have shown promise for dual delivery of both an antibiotic and bone regenerating small molecule during experimental osteomyelitis. PUR scaffolds have also been shown to promote biofilm dispersal and resolution of infection when loaded with D-amino acids.
- *Newer home-based antibiotic medications (currently unavailable in India):* Telavancin has shown good antimicrobial activity against methicillin-resistant *S. aureus* (MRSA) and its biofilm as compared to vancomycin. It also inhibits formation of biofilms at concentrations below each isolate's respective maximum inhibitory concentration (MIC). Telavancin is a semisynthetic derivative of vancomycin, exhibits concentration-dependent bactericidal activity via a dual mechanism of action involving inhibition of bacterial cell wall synthesis as well as disruption of cell membranes. It has broad anti-staphylococcal activity, including activity against isolates with methicillin resistance, and intermediate vancomycin susceptibility. Dose for therapy is 10 mg/kg/day for 30 days. Dose adjustments are needed as per renal function. Adverse effects are nausea, anemia of chronic disease, vomiting, metallic taste, diarrhea, infusion reaction,

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pruritus, red man syndrome, aspartate transaminase (AST) or alanine (transaminase) ALT greater than 3 times upper limit of normal, serum creatinine increase of 2 times baseline or estimated glomerular filtration rate (eGFR) decrease of 50%. Oritavancin is a long-acting semisynthetic second-generation lipoglycopeptide approved by the Food and Drug Administration (FDA) in treatment. Pharmacokinetic/pharmacodynamic data shows single 1200 mg dose as intravenous (IV) infusion per week for 2–3 weeks is safe, well tolerated and optimizes concentration-dependent killing against several gram-positive organisms. It demonstrated potent *in vitro* activity against *Staphylococcus, Streptococcus,* and *Enterococcus* species.

21. What is the effect of COVID-19 pandemic on orthopedic surgery? Describe the various precautions which you will take in avoiding complications during surgery in such cases?

Ans: Presently, I would say that there is no effect of COVID-19 pandemic on orthopedic surgeries barring possibly elective surgeries in COVID-19 positive patients. There was an initial panic phase during the pandemic onset and progression, where it became extremely difficult to formulate guidelines, and hence all surgeries especially generating aerosols were prohibited. Only the emergencies and nondeferrable conditions were allowed by various agencies and organizations in their interim recommendations. Pathologies considered nondeferrable electives were septic arthritis, malignant tumor, risk of impeding pathological fractures, neurological symptoms, traumatic tendon injury, dislocations and aseptic loosening of total joint replacement, and loose bodies/joint locking. It was generally considered that orthopedic surgeries should be very rare for COVID-19 patients. As a result many fractures went on to develop mal- or nonunion and joint stiffness. Now the effect of COVID-19 disease is limited to seropositive symptomatic patients undergoing surgery. If elective surgery, then it is postponed till patient becomes sero-negative while for emergency surgeries assessment is based on disease severity and taking universal precautions while operation procedure. The following precautions are legible:

- Both patients and providers should be educated and follow hand hygiene.
- Wearing a mask and social distancing should be the norm.
- Waiting rooms should be avoided.
- High contact surfaces cleaned regularly.
- Visitors should have restricted access, and be updated by phone.
- Patients should be housed in single rooms.

22. Musculoskeletal symptoms associated with SARS-CoV-19 virus infection and their management.

Ans: The following are the commonly reported symptoms in patients with SARS-CoV-19:

- Myalgia
- Fatigue
- Arthralgia
- Rarely arthritis

Management: The management is on standard procedures for symptom control and prevention of aggravation using NSAIDs, short-term low-dose steroids, if former fail and supplementation with vitamin D. Ice packs for arthralgias and arthritis helps. Arthritis per se from the disease has not been promptly reported and mostly represents aggravation of symptoms of underlying joint disease.

23. Discuss current advancements in the treatment of chronic lateral ankle instability.

Ans: *Conservative management:* Due to prolonged peroneal reaction times in these patients structured rehabilitation program for improving proprioception and coordination of peronei improves patients with dynamic instability component (nearly half of the patients).

Operative management: This is done in patients with mechanical instability and failed conservative management.

- *Anatomical:* Brostrom repair augmented by Gould (inferior retinaculum pull-up) modification—Gold standard still.
  - Suture-tape extracapsular augmentation of the Brostrom repair {Internal Brace® or LARS (ligament advanced reconstruction system)}

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- Autograft/allograft ligamentous reconstructions—in cases of revision surgery or long-standing instability where no ligaments are available for repair using anchor sutures.
- Using artificial ligament (Leeds-Keio ligament) for reconstruction
- Nonanatomical procedures—fallen out of favor
- *Minimally invasive—low-quality evidence:*
  - Arthroscopic repairs and reconstructions:
    1. Arthroscopically assisted—repair/reconstruction
    2. All-inside repair
    3. Inside-out repair
  - Percutaneous reconstructions only

24. Discuss recent advances in management of osteochondritis dissecans in knee joint.

Ans: Apart from the conventional techniques like microfracture, loose fragment fixation, mosaicplasty, OATS, allograft implantation various new techniques have emerged that are being increasingly used for reconstruction of the defect of osteochondritis dissecans.

Autologous chondrocyte implantation: Autologous chondrocyte implantation (ACI) is a first- generation cell-based therapy that involves transplantation of autogenous chondrocytes/chondrospheres into articular cartilage defects. The specific advantage is that it promises to provide complete hyaline repair tissues for articular cartilage repair.

The main drawbacks of ACI are:

- Need for large open arthrotomy
- The two-stage procedure (one for cell harvesting and the other for implantation)
- The prolonged period of time required to expand sufficient numbers of chondrocytes *in vitro*
- High cost of cell culture system

Collagen-covered autologous chondrocyte implantation: The collagen membrane has a compact layer to prevent diffusion of the cells out of the pouch and an inner porous layer to encourage cell invasion and attachment. This adaptation avoids the second incision needed in the classic ACI technique.

Matrix-assisted chondrocyte implantation: This is an advancement over the use of membranes. It is logical to use a scaffold for cells to colonize and develop into tissue rather than just using the membranes. The technique uses adaptation from tissue engineering. MACI is a second-generation approach for articular cartilage reconstruction where chondrocytes are combined to a three-dimensional scaffold (matrix) replicating the defect.

Third-generation chondrocyte grafting: This is still under evaluation and basically involves chondrocyte and matrix culture system. Principle is culturing chondrocytes in an implantable biological matrix with ideal properties—biocompatible, biodegradable, and bioactive while preserving the phenotypic characteristics, thus favoring the cellular proliferation and synthesis of the ECM, which is permeable, easy to use, and inexpensive.

Gene therapy: Gene transfer delivers a therapeutic protein to a target cell or tissue that after incorporation starts acting as a local source of the particular growth factor. This provides a constant and regular source for the desired growth factor. Most commonly a plasmid DNA containing a specific reporter gene that can stimulate a desired gene expression (to synthesize a growth factor) is used for incorporation through a virus vector.

(Each technique has specific details that can be read from Chapter 8 of the Essential Orthopedics: Principles and Practice, 3rd edition. Also, students should mention role of scaffolds in third generation chondrocyte grafting and gene therapy)

25. A. What is industry 5.0 technology?

B. Discuss role of 5.0 technology capabilities in trauma and orthopedics.

Ans: (A) *Industry 5.0: The Human-Centric Industrial Revolution:*

Core concept: Industry 5.0 advances beyond Industry 4.0's automation focus by integrating human expertise, sustainability, and collaborative technologies to create resilient, value-driven ecosystems.

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Key Pillars:

- Human-machine collaboration
  - *Cobots:* Enhance productivity by handling repetitive tasks while humans focus on creativity and problem-solving.
  - *Artificial intelligence (AI)/machine learning* (ML): Supports decision-making with predictive analytics and real-time process optimization.
  - *Augmented reality (AR)/virtual reality (VR):* Enables immersive training and remote assistance, improving safety and efficiency.
- Sustainability
  - Circular economy principles, energy-efficient processes, and waste reduction are central to production.
- Workforce empowerment
  - Prioritizes upskilling, well-being, and ethical labor practices to harness human ingenuity alongside automation.

Challenges:

- Workforce adaptation, ethical AI use, and cybersecurity risks in interconnected systems.

Impact: Drives competitive advantage through innovation, employee engagement, and eco-conscious operations, ensuring long-term industrial resilience.

(B) The Role of Industry 5.0 Technology Industry 5.0 in Trauma and Orthopedics:

- Robotic-assisted surgery
  - *Precision:* AI-guided robotic systems enhance accuracy in complex procedures (e.g. joint replacements, fracture fixation).
  - *Haptic feedback:* Provides tactile sensitivity during minimally invasive surgeries, reducing complications.
- AR/VR for surgical planning and training
  - *Preoperative visualization:* 3D reconstructions from CT/MRI enable virtual rehearsals of surgeries.
  - *Intraoperative navigation:* AR overlays anatomical markers in real time for safer execution.
  - *Education:* Immersive simulations train surgeons without risk to patients.
- AI and predictive analytics
  - *Personalized care:* Machine learning analyzes patient data (imaging, genetics) to optimize surgical plans.
  - *Risk prediction:* Identifies high-risk patients for complications (e.g. infections, delayed healing).
  - *Postoperative monitoring:* AI tracks recovery trends and flags deviations (e.g. implant failure).
- Smart rehabilitation
  - *Wearables:* Sensors monitor mobility, gait, and muscle activity, tailoring rehab protocols.
  - *AI-driven adjustments:* Adapts exercises in real time based on recovery progress.
- Ethical and security challenges
  - *Data privacy*: Secure handling of sensitive health records [General Data Protection Regulation (GDPR)/Health Insurance Portability and Accountability Act (HIPAA) compliance].
  - *Human oversight*: Ensures AI supports—not replaces—clinical judgment.
  - *Impact*: Faster recovery, fewer complications, and patient-centric care through human-machine collaboration.

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