Chronic Osteomyelitis of Long Bones in Children: Overview and Challenges in Management

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The management of chronic osteomyelitis of long bones in children continues to remain a major challenge facing the third world orthopaedic surgeon. Delayed diagnosis, and lack of, or maltreatment of, acute osteomyelitis or open injuries is the predominant cause. Obtaining an etiological diagnosis using bone specimens is important to target antibiotic therapy to the specific cause, most commonly staphylococcus aureus. Plain radiographs can demonstrate sequestrate, involucrum, pathological fractures or deformity in different combinations and where available, advanced imaging can be useful adjuncts to plan management. Surgical debridement remains the mainstay of treatment but the timing and extent of debridement is debated. The involucrum should be allowed to incorporate or mature before sequestrestomy is performed. Small bone gaps can be managed with local grafting whereas larger gaps require large grafts, bypass grafts or bone transport by distraction osteogenesis. Use of the Ilizarov type fixator allows simultaneous correction of co-existent deformity or limb length inequality. Pathological fractures are common and have a propensity to non-unite. Rarely, longstanding cases can develop malignant changes, most often a squamous cell carcinoma. Wound coverage is of paramount importance to achieve and maintain bone healing. Joint contractures can develop due to disuse and remain problematic inspite of physical therapy and/or traction. The over-riding priority remains to urgently diagnose and treat an acute osteomyelitis or open injuries. This alone can reduce the burden of this difficult and indolent condition that is very demanding on the treating surgeon as well on resources available.

Keywords: children, chronic osteomyelitis, long bones, management.

Chronic osteomyelitis continues to remain a major challenge in developing countries. It is a common problem in our country, and chronic osteomyelitis involving the extremities is a common cause of disability in Nepal.[1,2,3]

The over-riding concern remains late diagnosis or inadequate/ inappropriate management of acute osteomyelitis and open fractures.

Persistence of an acute hematogenous osteomyelitis resulting in chronic osteomyelitis is thought to occur in about 4.4% of children.[4] A 15% chronicity of the acute episode was reported by Waldvogel et al. in 1970.[5] Although the management of osteomyelitis is aimed at "curing" the illness, this elusive disease is known to remain quiescent for long periods of time following treatment, only to reappear without any apparent cause, and reappearance after decades, even as long as after 80 years of the original episode have been reported.[6,7,8,9]

Natural History and Pathogenesis

The infection in osteomyelitis starts in the metaphysis, facilitated by the sluggish flow through the hair-pin like arrangement of vessels in this region. Transphyhseal vessels, which obliterate at around 2 years, facilitate spread of infection to the joint before 2 years of age.[10] After two years, the physis acts as a barrier to spread of infection but bones with intra-articular

Figure 1: A) AP and lateral views of the right tibia of a 13-year-old girl who was discharged without any treatment from a rural hospital where she presented with pain in her right leg and fever, B) Presentation at our center 1 year later with exposed right tibial diaphyseal sequestrum, C) X-rays at presentation to our center showing mottling of the mid to lower third of the right tibial diaphysis; a tubular sequestrum is evident, D) A sequestrectomy and stage one Huntingtons transfer was done E) Clinical pictures at 6.5 years follow-up showing a fully healed skin and good function. A limb length discrepancy of 2 centimeters was well compensated. F) X-rays at 6.5 years showing tibialized fibula and a fused proximal tiobiofibular joint. Note the distal tibiofibular and ankle joints have undergone spontaneous fusion.

metaphysis (proximal femur, proximal humerus, distal radius) are still at risk of septic arthritis following osteomyelitis. Following infection of the bone, the resultant inflammation produces pus that follows the path of least resistance, usually coming out as a sinus on the overlying skin. The infected bone dies forming a sequestrum, around which efforts at subperiosteal new bone formation (involucrum) takes place. Sequestrae harbor micro-organisms, so act as a persistent infective nidus. The fate of the sequestrum is one of resorption, incorporation into the involucrum[11,12] discharge through sinuses, or iatrogenic removal **(Figure 6)**. Long bones are usually affected and the tibia and femur are the most common sites. Constitutional symptoms like fever, malaise, anorexia may be present and local tenderness, discharging sinus and even exposed bone is not uncommon **(Figure 1, 2)**. The erythrocyte sedimentation rate and C-reactive protein are usually elevated and are useful in monitoring disease activity and response to treatment. Trauma or surgery, producing dead and devitalized bone fragments, renders bone susceptible to infection.[13,14,15] Bacteria like staphylococci adhere to bone matrix (or implants) via receptors to fibronectin or other proteins and trigger a cascade that results in release of cytokines from polymorphonuclear cells leading to eventual osteolysis. Trauma leads to activation of cytokines which can have a deleterious effect on the host response to infection.[16] The difficulty in eradicating infection in chronic osteomyelitis is attributed to the micro-organisms ability to develop a "slimy layer" or "biofilm" that helps escape phagocytosis and/ or their ability to acquire a very low metabolic rate, making them less ready targets for antibiotics.[17,18,19] These events coupled with the inevitable presence of ischaemia in dead and diseased bones, makes bone penetration by antibiotics and disease eradication very challenging.[17] The Cierney-Mader classification takes into account both disease and host factors and highlights the importance of improving the host response to the infective process by improving nutrition, treating any anemia and coexisting infections.[20]

Growth disturbances can result from either extreme virulence of the organism or improper surgical choice and technique causing irreversible damage to the growth plate.[21] Angular deformities can result from such physeal damage or from the malunion or nonunion of pathological fractures. Limb shortening due to damage to physis or lengthening due to overstimulation of the physis in response to the infection can occur, causing limb length inequality.

Microbiology

Microbiology Staphylococcus aureus is implicated almost two-thirds of the time followed by pseudomonas and enterobacteriace.[22,23,24] In newborns and children, organisms common for that age group (e.coli, hemophilus etc.) must be entertained. Osteomyelitis associated with in-situ implants and pin tracks are mostly attributed to coagulase-negative staphylococci like staphylococcus epidermidis[25,26] Cultures are positive in only 50% of patients[22] and this is less where antibiotic use is indiscriminate.

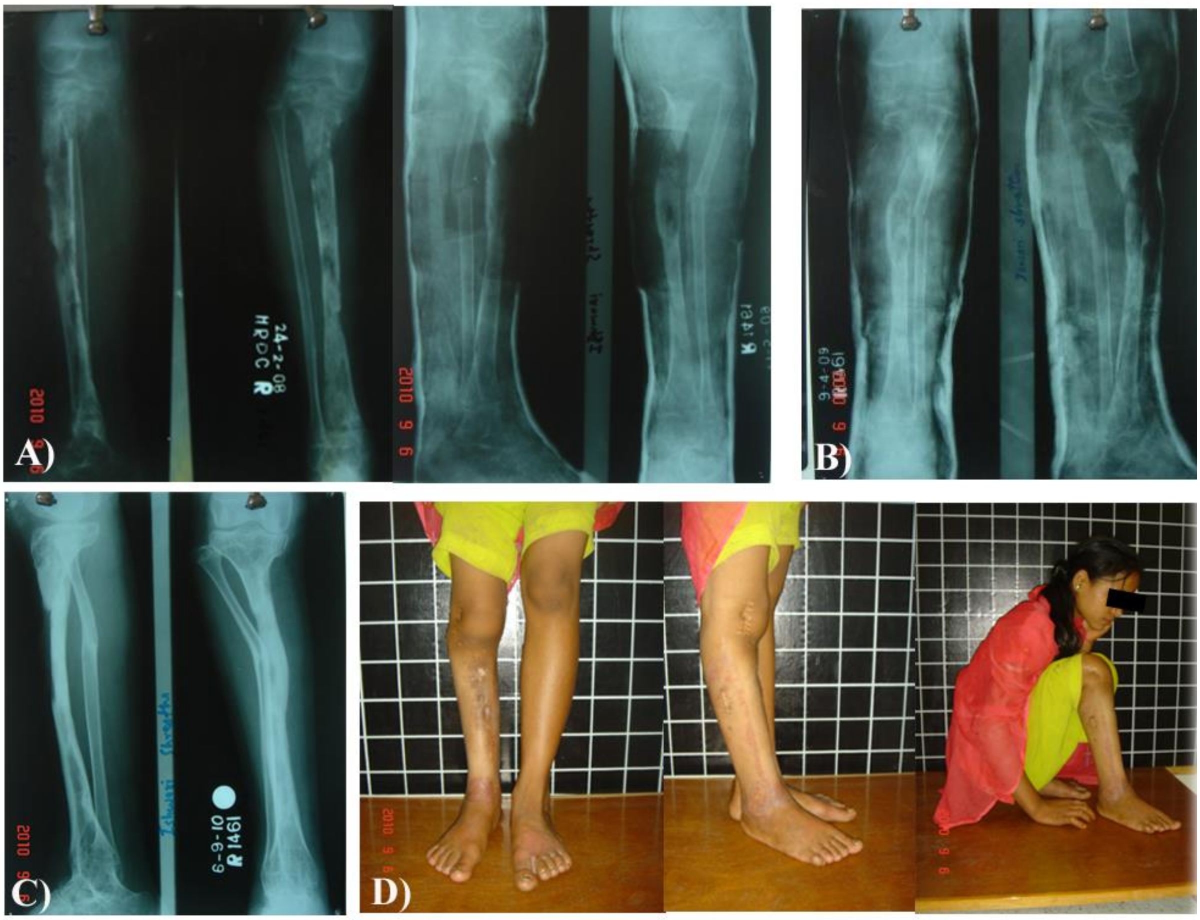

Figure 2: A) Incorporation of a complete diaphyseal tubular sequestrum 2B) AP and lateral x-rays of a 10 year old girl showing complete diaphyseal sequestrum of her right tibia 2C) Treatment in a cast with gradual protected weight bearing 2D) Complete incorporation of the sequestrum at 3 years follow-up, Clinical picture at 3 years follow-up showing healed sinuses and a fully functional patient

A review of 33 cases of osteomyelitis presenting to our center[27] showed culture positivity in 63% and no growth in 27% when bone specimens were examined. Positive culture cases revealed staphylococcus aureus in 53%, tuberculosis in 9%, pseudomonas in 6% and proteus and E.coli in 2.5% cases each.

It is important to target antibiotic therapy based on microbiology and combine this with adequate debridement because dead and devitalized tissues are poorly penetrated by antibiotics.[28] Bone cultures are the gold standard for the etiologic diagnosis of chronic osteomyelitis. Zuluaga et al. [29] found that bone cultures allowed agent identification in 94% of cases, including anaerobic bacteria in 14% and emphasized that the diagnosis of chronic osteomyelitis requires bone cultures and that non-bone cultures were invalid for this purpose. The timing and duration of antibiotics use is a subject of debate and some authors have reported good results without the use of any antibiotics emphasizing the fact that it is the eradication of the dead and devitalized tissue that alone will contain the disease.[30,31]

Matzkin et al.[32] in their retrospective review of 55 hospitalized children with chronic osteomyelitis found that staphylococcus aureus was cultured in 64% of the cases with 43% of those being methicillin resistant S. aureus, the average antibiotic treatment was 135 days (28 days intravenous, 107 days oral) and included clindamycin, cefazolin and ciprofloxacin in most cases, an average of 1.3 irrigations/debridements was required per case and 45% required a sequestrectomy. Mader et al.[33] pointed out that treatment failure in chronic osteomyelitis is due to inadequate debridement and antibiotic therapy of more than 4 to 6 weeks duration is unlikely to be effective and will only contribute to resistance. We follow a regime[34] where empiric antibiotics, usually a combination of cloxacillin, fusudic acid or clindamycin, is started and modified as per culture and sensitivity report, usually for duration of six weeks (intravenous for up to 3 weeks) depending on the clinical response and the erythrocyte sedimentation rate, with emphasis on building the nutritional status and treating any coexisting infections while local debridement continues as necessary.

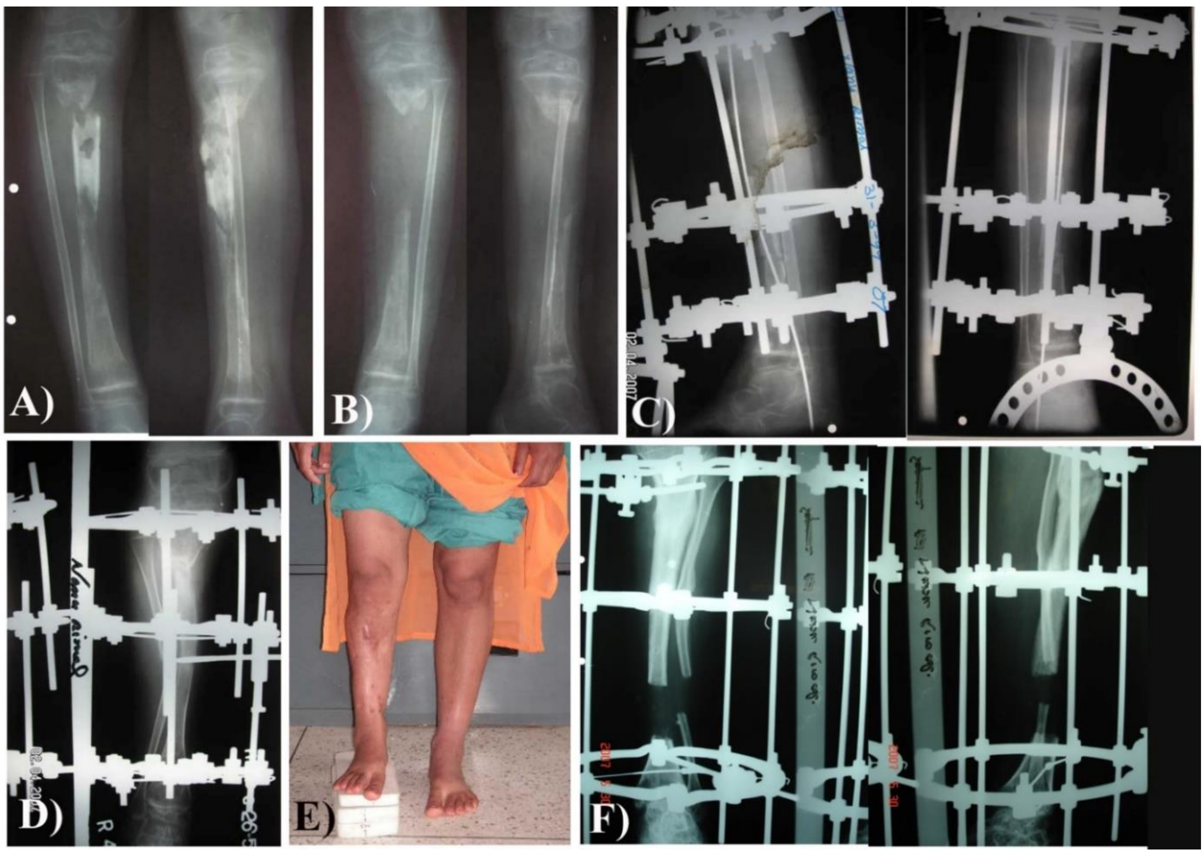

Figure 3: Ring fixator and distraction osteogenesis 3A) AP and lateral views of the right tibia of a 14 years old girl showing a proximal tibial diaphyseal sequestrum with pathological fracture 3B) A sequestrectomy was done and 3 C) distraction osteogenesis using a ring fixator was carried out through a distal tibial osteotomy over an intramedullary rush pin to 3D) achieve union 3E) The affected leg was 7 centimeters short so 3F) the ring fixator was reapplied and distraction done through another distal osteotomy to achieve the limb length

Figure 4: A) Two and half years follow-up showing a residual limb length inequality of 2 cms, healed sinuses and a fully functional patient 4B) AP and lateral x-rays at two and half years follow-up showing well consolidated regenerate

Imaging

Acute osteomyelitis is a clinical diagnosis and the earliest x-ray changes take at least 7 to 14 days to appear and include a periosteal reaction and subperiosteal bone formation, which can be exuberant at times, and confused with other benign or malignant conditions which can radiologically mimic such a presentation. Radiographs are much more useful in chronic osteomyelitis to demostrate sequestrate, pathological fractures, bone gaps, deformities or reparative involucrum in various combinations.

Al-Sheikh et al[35] found that bone radiography had a sensitivity of 60% and a specificity of 67% in diagnosing subacute and chronic bone infection. In their study, bone scintigraphy was superior to radiography and showed similar sensitivity and specificity for Indium and Gallium. Technitium scintigraphy was found to be very sensitive (100%) but with low specificity (25%) to rule out the presence of bone infection. Other modalities like MRI (sensitivity 84%, specificity 60%) have also been used to diagnose bone infection with variable success but the most reliable modality, where available, seem to be a flurodeoxyglucose positron emission tomography (PET) scan followed by bone scintigraphy, either alone or combined with leukocyte scintigraphy.[36] In our type of setup where the available imaging modality is limited to plain radiographs, a meticulous effort to corroborate clinical and radiological findings, and proper culture and biopsy techniques to ensure the maximum possibility of obtaining an etiological diagnosis, is indispensable.

Surgical debridement: The mainstay of treatment

While there is little debate that surgical debridement gives the patient the best chance of successful treatment, the timing and extent of such a debridement is debated.

Some authors advocate early aggressive debridement with or without reconstruction[37] whereas others adopt a more conservative approach, allowing the body to form new bone (involucrum) around the infective nidus (sequestrum) or incorporation of the sequestrum into the involucrum, while attempting to contain the infection with limited debridement and antibiotics.[11,12]

The removal of large sequestrate, resulting in bone gaps, has to be weighed between early removal to facilitate healing[38,39] and late removal after a solid involucrum is established, usually 3 to 6 months.[31,34,40] Some authors feel that a sequestrectomy should only be undertaken when there is no evidence of decrease in its size in serial radiographs or no increase in size of the involucrum and any early removal will deny the chances of such sequestrate being completely incorporated into the growing involucrum[11,12] (see algorithm). Simpson et al.[41] prospectively studied the relationship between the extent of debridement and infection-free survival and found that there was no recurrence in patients who had wide resection (clearance margin 5mm or more), 28% recurrence in patients who had clearance margin less than 5mm and 100% recurrence in patients who had intralesional debulking alone at one year follow up. In a study of 90 children with chronic osteomyelitis of long bones conducted at our center over a 3 year period, 69% children had a debridement procedure alone (sequestrectomy in 59% and saucerization in 10%) whereas 31% had some additional procedure out of which the Ilizarov fixator treatment was the most common (13.4%).[42]

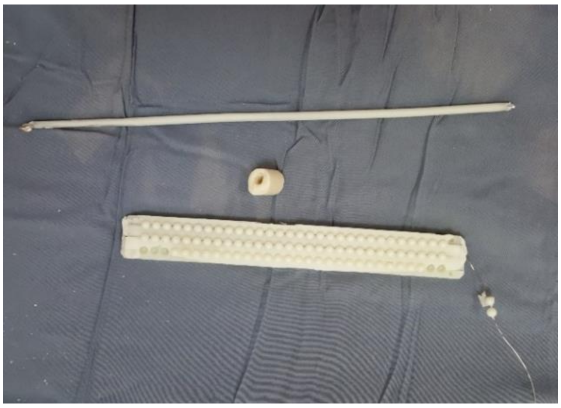

Figure 5: Antibiotic impregnated bone cement can be used as beads, spacers or rods to achieve infection control in chronic osteomyelitis

Sequestrectomy is a major surgical undertaking; especially the potential to profuse bleeding intra- and post-operatively, so should be meticulously planned and executed. A tourniquet should be used where possible and blood should be cross-matched. Sinograms are useful to localize the site of active involvement. An extraperiosteal exposure is utilized to preserve as much subperiosteal circulation as possible, excising sinuses and cloacae to reach the affected segment. An oval window or a longitudinal partial diaphysectomy is done to reach the medullary cavity until puntate bleeding (paprika sign) is visible.[43] The defect in bone is covered with bone graft[44] or a muscle flap as suitable.[45] Gentamycin impregnated PMMA beads or fillers have been used to fill the bone defect and are reported to achieve higher local antibiotic permeation.[46] A cast is used when more than 70% of the cortex is intact; otherwise an external fixator is advised.[34] The wound is closed over a drain to facilitate residual drainage and a low threshold for repeat debridement is recommended.

Intramedullary reaming in chronic osteomyelitis was first described in 1980.[47] Reaming allows for intramedullary debridement, restoration of medullary canal and, eventually, better intramedullary circulation and hence better antibiotic penetration.

A setup including an image intensifier, rigid and flexible reamers is required. Reaming for chronic osteomyelitis is not the same as reaming for a fresh fracture and caution is warranted. Proper patient selection is very important as deformed bones and obliterated canal secondary to chronic infection can lead to complications like pathological fractures or excessive bleeding.[48] Obviously, in children, areas of growth have to be preserved while introducing the reamers.

Management of Bone Loss

Bone loss in COM can be focal or segmental and can result from the natural history of the disease itself or from iatrogenic removal of a large sequestrum. Management of focal bone loss (loss of equal or less than 2 centimeters) depends on the degree of loss. Segmental bone gaps of greater than 2 centimeters are difficult to manage with autogenous bone grafts alone, the amount of graft available for harvest being a major limiting factor.[38,49]

Focal bone loss can be managed by observation and protection, especially in young children, and the entire tibia is known to have reformed around a tubular sequestrum[50] **(Figure 2)**. Where skin coverage is possible, adequate debridement followed by conventional bone grafting after an adequate granulation bed has formed, usually at six weeks, is an excellent option.[38,51] For more extensive focal loss, the Papineau staged technique[52] or its variations[53,54,55] are recommended. The underlying principles are similar and involve 1) thorough debridement (single or at weekly intervals) with regular dressing (usually antibiotic soaked) **(Figure 5)** to stimulate a healthy granulation bed 2) Open cancellous iliac crest bone grafting to fill the bed thus formed and 3) Coverage by granulation tissue growth, skin graft or local flaps.

Segmental bone loss poses a daunting challenge and the implications of prolonged treatment and the importance of patient compliance for successful outcome should be clearly outlined to the patient and his/her family. Where the necessary expertise is available, the Ilizarov or a similar type fixator device can be a versatile tool for simultaneous correction of bone loss, angular deformities and leg length discrepancy[56] **(Figure 3, 4)**.

Eralp et al.[57] combined external fixator with an intramedullary nail to reconstruct segmental bone defects in 13 patients aged 18 to 60 years and reported excellent results at a mean follow up of 47.3 months. This system may have an added advantage of the intramedullary device maintaining alignment of the regenerate bone should there be any problems with the ring fixator. Bone transport starts with thorough debridement and the application of an external fixator (usually a ring fixator). A corticotomy is performed which may be unifocal or bifocal depending on the degree of bone loss. Distraction is at the rate of 1 mm/day. Bone graft may be necessary at the docking site to prevent or treat a nonunion. Pin-track infections are common and may be problematic where compliance to regular care at home may be poor. Other complications include loss of fixation, which may be due to poor surgical technique or non-compliance to post-operative instructions, delayed or nonunion at docking site, fracture or premature consolidation of the regenerate, and subluxation, dislocation or stiffness of the adjacent joints. Callus distraction to fill bone defects or treat non-unions has also been successfully used in the humerus.[58] Some authors have reported similar results comparing conventional bone grafting with Ilizarov and bone transport and consider resources and expertise available to be important determinants in the form of treatment chosen.[56, 59]

Segmental bone defects in the tibia and forearm can be managed by bypass grafting.[40, 60,61,62] In case of tibia, this can be a native fibular strut graft slotted in proximal and distal tibial troughs, or a fibular cross union (Huntington procedure). The latter is accomplished by cross-uniting the native fibula with first the proximal and then the distal portions of the native tibia in a multi-staged procedure. This results in the hypertrophy of the cross-united fibula under physiological loading, thus assuming the function of the tibia. The hypertrophied fibula can then be subjected to distraction osteogenesis or corrective procedures to manage any accompanying leg length discrepancy or deformities respectively **(Figure 1)**. Complications include peroneal neuropathy, delayed or nonunion at the cross-union sites (usually the proximal and distal tibiofibular joints) and valgus deformity of the ankle which can be prevented by fusing the distal tibiofibular joint.

Zahiri et al.[63] reported excellent results in 9 children with chronic osteomyelitis involving the entire tibial shaft by removal of the tibial sequestrum and transfer of the native fibula into that space keeping the middle third musculature and blood supply intact. At 18 months, all fibulae hypertrophied to assume the role of the removed tibiae and all the children could carry out all their activities of daily living. Similarly, bone gaps in the forearm can be managed by creating a single bone forearm provided the wrist and elbow joints are normal.[61,64] In the “induced-membrane technique” of bridging large bone gaps, an antibiotic-laden spacer (usually bone cement) is used for 6 to 8 weeks followed by removal of the spacer and bone grafting of the defect.[65]

A classification based on the location, type and extent of bony involvement in chronic osteomyelitis is described by Penny, and is useful in selecting and planning treatment.[66]

Pathological fractures & Nonunions

The risk of pathological fractures in COM is greatest before the involucrum has formed, or following sequestrectomy in the presence of an inadequate involucrum.

Very low energy trauma can result in fractures that have a propensity to non-unite. Such fractures should be protected in a cast or external fixation. Internal fixation and/or bone grafting may be necessary once the infection has dried out. The Ilizarov ring fixator is versatile and allows compression to achieve union and simultaneous correction of deformity and limb length discrepancy by callus distraction in such situations.

Malignancy in COM

The risk of malignancy in COM is thought to be less than 1% and develops in cases where the infection has persisted for decades. A high index of suspicion is warranted especially when a pre-existing sinus demonstrates increasing pain, foul-smelling discharge or hemorrhage (Rowland's triad). The most common transformation is into a squamous cell carcinoma.[67,68] In their series of 53 patients (44 males, 9 females) treated at the Mayo clinic, McGrory et al.[67] found 50 squamous cell carcinomas, one fibrosarcoma, one myeloma and one lymphoma, 44 of whom underwent an amputation. The authors advocated amputation as the most reliable method of addressing these tumors despite a majority being low-grade neoplasms. Other tumors like malignant fibrous histiocytoma[69] and malignant hemangioendothelioma[70] arising in pre-existing chronic osteomyelitis have also been reported. Amputation is also reserved for cases where other modalities of treatment have failed to control the infection and its sequelae or when such treatment is not feasible (eg. severe leg length discrepancy) **(Figure 7)**.

Wounds, sinuses and joint contractures

Early wound closure, either primarily, by secondary healing, or by the use of grafts and flaps, facilitates bone coverage and thus healing. Sinuses, when present, should be excised along the surgical wound used for debridement.[34] For associated joint contractures, we have used skeletal traction alongside regular wound debridement to attain a functional position, reduce skin tension and aid wound healing, though the resultant joint function continues to remain poor in our experience.

Chronic sclerosing osteomyelitis and recurrent multifocal osteomyelitis are variants that run protracted courses with periods of exacerbation, may cause growth disturbances and may require surgical intervention if symptomatic.[71]

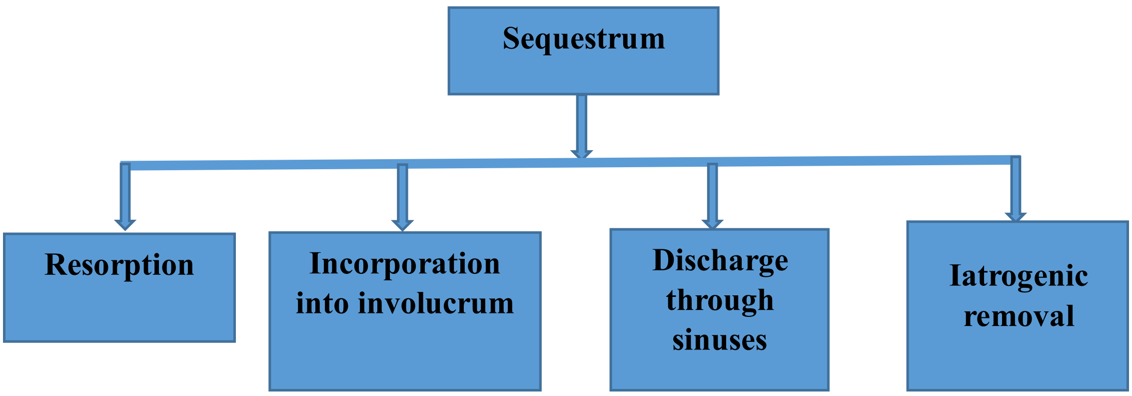

Figure 6: The possible fates of a sequestrum in chronic osteomyelitis

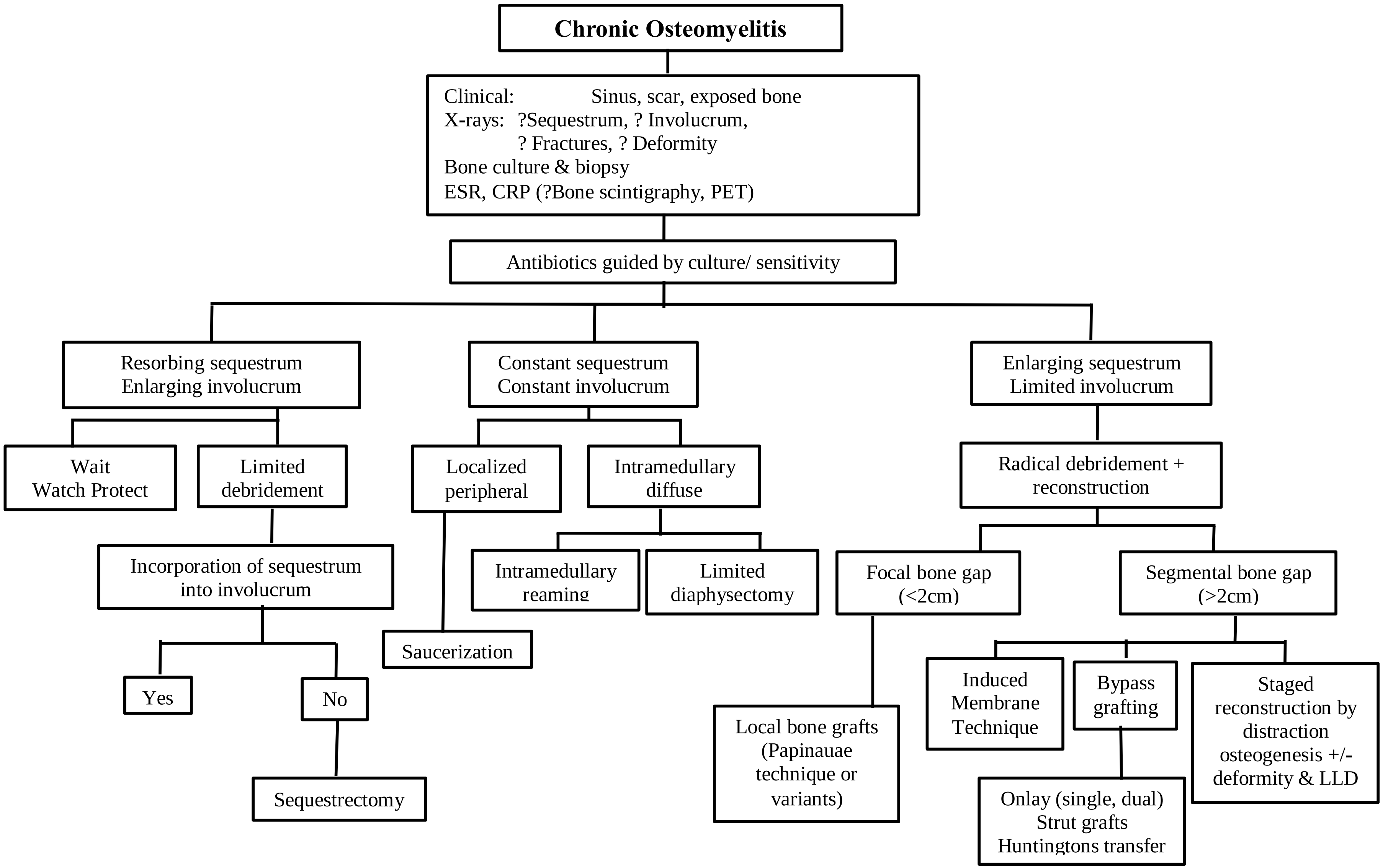

Figure 7: An approach to management of sequestrum in chronic osteomyelitis: The HRDC algorithm

Conclusion

Since chronic osteomyelitis often affects children from socioeconomically deprived backgrounds who have very limited access to healthcare facilities, treatment of acute osteomyelitis at the outset is the most effective means to reducing its burden. We feel that there is a great need to prime rural healthcare personnel and the population at large, to identify and treat, or refer, acute osteomyelitis urgently. Whether such people, who form the first point of contact with these patients, should be guided to treat any child presenting with fever and bone pain with a course of empirical antibiotics and maybe even be taught simple techniques to puncture and decompress the bone before urgent referral is made to a higher center, is an issue that needs to be debated in resource-poor settings like ours where universal access to healthcare is still a far cry. Thus, timely identification and treatment of acute osteomyelitis and open bony injuries cannot be overemphasized as the resultant chronicity results in a very challenging clinical scenario that faces the treating surgeon.

Key Message

The course and management of chronic osteomyelitis is often protracted, placing considerable burden on resources available, especially in a socioeconomically constrained environment, where, unfortunately, it is mostly encountered. The overwhelming priority lies in identifying and treating acute osteomyelitis and open injuries opportunely so that this difficult problem can be prevented.

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