Optimizing Management of Open Fractures in Children

Abstract
Open fractures in children differ from adults owing to their better healing potential. Management strategies for open fracture in children are changing with improvement in our understanding of soft-tissue reconstruction and fracture fixation. A literature review was performed for articles covering management of open fractures in children. The cornerstones of management include prevention of infection, debridement, and skeletal stabilization with soft-tissue coverage. The injury should be categorized according to the established trauma classification systems. Timely administration of appropriate antibiotics is important for preventing infections. Soft-tissue management includes copious irrigation and debridement of the wound. Fractures can be stabilized by a variety of nonoperative and operative means, taking into consideration the special needs of the growing skeleton and the role of a thick and active periosteum in the healing of fractures. The soft-tissue coverage required depends on the grade of injury.

Keywords: Antibiotics, children, debridement, open fracture
MeSH terms: Pediatrics, open fractures, debridement, antibiotics

Introduction
Open fractures in children are associated with considerable morbidity, with an increased risk of complications. There is still considerable debate on the strategies of infection control, soft-tissue management, and principles of fixation. The principles associated with the management of open fractures in adults may not hold true for pediatric open injuries. A comprehensive literature review of articles published in PubMed was performed covering open fractures in children and management of open fractures. Other literatures reviewed included evidence-based guidelines on open fracture management. The keywords included were open fracture, injury, paediatric, children, and management. The aim of this review was to understand the current concepts and guidelines for the management of open fractures in children.

Incidence
The epidemiology of open pediatric fractures is still not completely understood. The incidence varies from center to center, but most authors agree that they comprise 2%–9% of all pediatric fractures, while estimates vary from 0.7% to 25%.1–4 In the Indian setting, Tandon et al. have reported an incidence of 2.8% of open injuries in 500 pediatric fractures.5 The incidence is almost 10% in a child with multiple injuries.5,6 Injuries in other regions of the body are found to be as high as 25%–50% in children presenting with open fractures.6 Open fractures are more common in boys, probably owing to increased outdoor activities. The lower incidence of open fractures in children younger than school age can be attributed to less body mass with increased body fat.7

Most cases of pediatric open fractures are a result of high-velocity trauma, including motor vehicle accidents and fall from heights. Low-velocity injuries such as falls or sports injuries also lead to open fractures, usually Type I injuries.8 Athletic injuries in adolescents also result in open fractures in <5% of cases.7 Gunshot and firearm injuries also contribute to open fractures, almost 50% of gunshot injuries to extremities producing significant fractures.8

Most open fractures have been reported involving the forearm and tibia. In a retrospective multicentric analysis of pediatric fractures, Skaggs et al. have reported 34% of open fractures involving the tibia/fibula and 32% in the forearm followed by hand (10%), femur (6.7%), humerus (6.5%), foot (4.3%), elbow (2.5%), and ankle (2.3%). Other sites including patella, pelvis, and clavicle accounted for 3% to 4% of all fractures.9

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for 1% of the open injuries analyzed.\textsuperscript{10} Out of 40 Type I open fractures reported by Iobst \textit{et al.}, 32 fractures (80%) involved diaphyseal both bones or distal ends of the radius and ulna\textsuperscript{11} [Figure 1].

\textbf{Initial Assessment and Management}

Considering the frequent association of open fractures with other potentially life-threatening injuries in children, stabilizing the patient’s condition is the first priority. Manuals of pediatric advanced life support\textsuperscript{12} and advanced trauma life support\textsuperscript{13} provide the recommended guidelines to be followed for initial resuscitation and management of the injured child. The amount of hemorrhage needs to be assessed and suitably replaced. Large-bore intravenous lines are secured and intravenous fluid resuscitation is begun promptly. In case of difficulty in intravenous access, intraosseous infusions using large-bore bone marrow needle have been found to be an effective and safe route of fluid administration in children in the emergency setting.\textsuperscript{8}

Orthopedic evaluation and management should follow after immediate life-threatening conditions of the patient are stabilized. Information about the nature and mechanism of injury is essential for the trauma surgeon to assess the injuries with respect to severity, other associated injuries, and extent of environmental contamination [Table 1].

All physical findings should be meticulously noted, and the nature of injury and treatment required, along with any neurological or vascular issues, must be communicated to the parents.

Antitetanus prophylaxis should be given in the emergency room. A single dose of tetanus toxoid is administered in patients who have not had a tetanus dose in the past 5 years or whose immunization status is unknown.\textsuperscript{7} An assumption of complete immunization for age may be fraught with grave consequences. Human tetanus immunoglobulin is considered to provide immediate protection, but indications in children are not clear.

\textbf{Classification of Injury}

The commonly used systems for grading and classifying open injuries are as follows:

\textbf{Mangled Extremity Severity score}

Mangled Extremity Severity Score (MESS) [Table 2] helps to identify patients likely to benefit from primary amputation. A score of 7 or more is predictive of amputation. Although specific, it suffers from the drawback of low sensitivity and is better suited for limbs with vascular injury.\textsuperscript{14}

\textbf{Modified Gustillo and Anderson classification}

It is one of the most commonly used grading systems for both adults and children [Table 3].\textsuperscript{15} Since the true extent of soft-tissue injury may not become evident initially, the grading is best done at the time of surgery after wound exploration and debridement. The grading may itself change with each debridement. This system has been under criticism for lack of interobserver concurrence.

\textbf{AO/ASIF system}

It allows a complete description of the injury complex and is considered easier for computerization, audit, and research with better interobserver concurrence [Table 4].\textsuperscript{16} The AO/ASIF classification of fractures is used to classify skeletal injury. Its use is limited by the complexity of the system.

\textbf{Ganga Hospital Open Injury Severity Score}

Realizing the heavy bias of most of the available scoring systems toward vascular injury and efforts to derive an “amputation score,” Ganga Hospital Open Injury Severity Score was developed [Table 5].\textsuperscript{17} It includes the role of comorbid conditions and was designed to help the surgeon identify the reconstruction requiring postdebridement. A cutaneous score of 3 or more predicts a complex soft-tissue reconstruction, while score of 17 or higher is predictive of amputation [Figure 2].

Other classification and scoring systems include the following:

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\hline
\textbf{Classification of Injury} &
\hline
\textbf{Mangled Extremity Severity score} &
\textbf{Modified Gustillo and Anderson classification} &
\textbf{AO/ASIF system} &
\textbf{Ganga Hospital Open Injury Severity Score} &
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Table 1: Orthopedic evaluation of open injuries in children

| Define injury   | Location | Dimension | Soft-tissue involvement | Extent of muscle damage | Loss of soft tissue and/or bone | Contamination |
|-----------------|----------|-----------|-------------------------|-----------------------|-------------------------------|---------------|
| Emergency setting | Removal of gross contaminants | Photographic recording | Wound sealing with moist dressing | Avoid digital exploration | Cautious gross alignment and splinting |
| Neurovascular examination | Color of skin, digits, and nail beds | Capillary refill | Temperature | Distal pulses compared with contralateral limb | Doppler sonography – severe injury or feeble/absent pulses |
| Motor and sensory examination of all major nerves in injured and uninjured limbs | Spontaneous movements and response to sensory stimuli in uncooperative/young children |
| Compartment syndrome | High index of suspicion | Cause of pain (fracture/compartment pressure) may be difficult to distinguish | Open injury does not exclude compartment syndrome |
| Pallor, pulselessness, and paresthesia late to develop and unreliable |

- NISSSA is an acronym for Nerve injury, Ischemia, Soft tissue injury, Skeletal Injury, Shock, and Age; it has a total score of 16. It is found to be more sensitive and specific than MESS. The effect of plantar sensation on the overall result was overemphasized.
- Limb Salvage Index proposed by Russell et al. evaluated seven variables in the injury, namely arterial, nerve, skeletal, skin, muscle, deep venous system, and warm ischemia time. A score of 6 or higher was regarded as the criterion for amputation. The index did not enjoy widespread acceptability.
- Byrd and Spicer classification system grades injuries into four types based on the endosteal and periosteal vascularity and status of the surrounding soft tissues and suggests flap coverage for Type III and Type IV injuries. Large interobserver variability limits its practical application.
- Hannover Fracture Scale combines description of fractures with assessment of skin, deep soft tissues, amputation, ischemia or compartment syndrome, nerves, contamination, bacteriological smear, and onset of treatment. Heavy bias toward the presence of vascular injury and reliance on bacteriological samples limit its use.

We used Gustillo–Anderson system to grade open injuries in our practice.
Table 4: AO/ASIF open injury classification system

| AO-ASIF soft-tissue injury classification | Score |
|-------------------------------------------|-------|
| 1: Normal (except open fractures)         | 0-2   |
| 2-4: Increasing severity of lesion        | 4     |
| 5: A special situation                    | 5     |

Skin lesion (closed fractures)

| IC 1: No skin lesion                      | 1     |
| IC 2: No skin laceration, but contusion   | 2     |
| IC 3: Circumferential degloving           | 3     |
| IC 4: Extensive, closed degloving         | 4     |
| IC 5: Necrosis from contusion             | 5     |

Skin lesions (open fractures)

| IO 1: Skin breakage from inside out        | 1     |
| IO 2: Skin breakage <5 cm, edges contused | 2     |
| IO 3: Skin breakage >5 cm, devitalized edges | 3     |
| IO 4: Full-thickness contusion, avulsion, soft-tissue defect, muscle tendon unit injury | 4 |

Muscle tendon unit injury

| MT 1: No muscle injury                     | 1     |
| MT 2: Circumferential injury, one compartment only | 2     |
| MT 3: Considerable injury, two compartments | 3     |
| MT 4: Muscle defect, tendon laceration, extensive contusion | 4 |
| MT 5: Compartment syndrome/crush injury    | 5     |

Neurovascular injury

| NV 1: No neurovascular injury              | 1     |
| NV 2: Isolated nerve injury                | 2     |
| NV 3: Localized vascular injury            | 3     |
| NV 4: Extensive segmental vascular injury  | 4     |
| NV 5: Combined neurovascular injury including subtotal or complete amputation | 5 |

Principles of Management

Prevention of infection and antibiotic prophylaxis

Infection prevention forms one of the main aims of open fracture management. It includes antibiotic coverage, surgical debridement, soft-tissue coverage, and fracture stabilization [Table 6].

Timely and appropriate antibiotic administration has been clearly proved to be pivotal in infection management. The current literature recommends prompt antibiotic administration within 3 h of injury. A delay of more than 3 h has been shown to increase infection rates.

The duration of antibiotic therapy is debatable, as no studies have shown the influence of duration on infection rates. In fact, no difference in infection rates has been noted when therapy was instituted for 1 day or 5 days.

However, most authors recommend antibiotic therapy lasting for 24–48 h for Gustillo Type I and II fractures and 72 h of antibiotic therapy for Type III injury, which can be reduced to 24 h following definitive soft-tissue coverage. Ideally, an antibiotic cover against both Gram-positive and Gram-negative organism should be provided. Most authors recommend first-generation cephalosporins (Cefazolin) for patients with Type I or Type II fractures. In severe Type II and Type III injuries, gentamicin is added. Anticlostridial drugs may be added in case of farm injuries or ischemic injuries where anaerobic growth may occur due to low oxygen tension. The use of antibiotic-impregnated polymethyl-methacrylate beads has been shown to reduce infection rates in open tibial fractures in adults. The bead pouch technique consists of placement of antibiotic bead chains in the open wound, covered and sealed by an adhesive porous polyethylene wound film,
changed every 2–3 days. It prevents further contamination while maintaining an aerobic wound environment. The role of local antibiotic therapy, however, has not been studied adequately in children. The authors recommend prompt administration of intravenous first-generation cephalosporins/co-amoxiclav alone for Type I injuries for 24 h. Clindamycin is used in case of penicillin allergy. Gentamicin is added for Type II and Type III injuries. Antibiotic prophylaxis for Type II injuries is continued for 24 h, while for Type III injuries, 72 h of prophylaxis is given. Metronidazole is added for injuries associated with agricultural or vegetative contamination. No conclusive guidelines for oral antibiotics are available and are given beyond 72 h on an individualized basis.

**Timing of Surgery**

It has been a part of traditional teaching to advocate the wound debridement within 6 h of injury. Only few clinical studies have supported this concept. Current recommendations suggest wound excision in open fractures within 24 h of injury. Immediate exploration of the wound is indicated only in the presence of gross wound contamination, compartment syndrome, devascularized limb, or in a multiply injured child. In our practice, open injuries are dealt with on an urgent basis within 24 h.

**Management of Soft Tissues**

Soft-tissue management is essential to maintain an environment conducive to fracture healing and prevent infection. The concept of “Orthoplastic Approach” is an integrated approach to address both fracture fixation and soft-tissue management. Irrigation acts adjunctively to reduce microbial load of the wound. High-pressure pulsatile lavage may be useful for removing large particulate debris and foreign matter, but it remains a matter of debate with regard to concerns of damage to viable soft tissues, driving foreign material into the wound, and a paradoxical rebound in the bacterial counts. Routine use of low-pressure systems is advised, while high-pressure systems should limit pressure to 50 psi. Anglen had recommended 3 L solution for irrigating Grade 1 fractures, 6 L for Grade 2 fractures, and 9 L for Grade 3 fractures. The use of high volumes in small wounds may lead to deleterious increase in compartment pressures. The use of bulb syringe and/or elevated fluid bag and a giving set is therefore preferable. Controversies still exist regarding the ideal irrigation solution. The use of soap, bacitracin, and benzalkonium chloride was shown to reduce initial counts, but demonstrated a rebound increase to 89%–120% when compared to that of normal saline. Antiseptics (e.g., povidone-iodine) are known to have a negative effect on fibroblast function, microvascular flow, and endothelial integrity. 1% solution of povidone-iodine is preferable to 5% povidone-iodine solution. The pharmacokinetic and pharmacodynamic properties of antibiotics limit their use as irrigation solutions, along with high cost and risk of anaphylaxis. Crowley et al. have recommended the use of normal saline.
without additives and antibiotics. The authors recommend the use of low-pressure and high-volume irrigation with saline for irrigation.

Debridement aims to provide a wound and fracture environment as close as possible to conditions found in closed fracture surgery. The concept of “Zone of injury” must be kept in mind, which stresses the need to reassess tissues which may look apparently healthy and the use of wound extensions for deeper tissues.

1. A tourniquet must be used to ensure a bloodless field in the absence of vascular injury
2. Assessment of tissues, superficial to deep, must be carried out
3. Removal of all foreign matter and tissues with compromised viability including muscle, bone, and skin edges must be done. Fracture ends must be delivered and cleaned
4. Extension of wounds along fasciotomy lines to preserve perforator vessels and evaluation of tissues from periphery to center is advised. Incisions along watershed areas should be avoided.

The muscle tissues are debrided based on color (pink), contractility (on pinch), consistency (tearing on forceps during retraction), and capillary bleeding (on incision). Medullary bleeding from bone should not be considered a sign of viability. All loose fragments and fragments with avascular soft-tissue attachment must be removed. It may be advised to preserve bone fragments containing large areas of articular cartilage. Acceptable coverage should be possible after one or two debridements, if adequate wound excision has been performed. Stewart et al. have advised retention of tissues and devitalized bone of doubtful viability at first debridement, relying on the good healing potential of children, in cases where a second debridement is planned.

Most low-grade injuries can be satisfactorily treated with a single procedure; it is however advisable to plan a second-look debridement procedure in Grade II and Grade III injuries. It is beneficial to have a multidisciplinary plan of action for severe type III injuries.

While formal surgical debridement is the rule for open fractures, some studies have shown good results with nonoperative management of Type I fractures. The protocol usually recommended comprises early antibiotics, debridement with saline, dressing, reduction, and cast application, with admission for 24 h. Iobst et al. treated forty pediatric Type I open fractures and reported an infection rate of 2.5%. Bazzi et al. found no infection in forty patients after nonoperative treatment. In the absence of any Level I evidence supporting such protocols, formal surgical irrigation and debridement should be undertaken in all open fractures.

It is important to remember that an open fracture does not signify an open compartment. An aggressive prophylactic approach with a low threshold for fasciotomy must be undertaken. In cases with vascular injury and severe crush injury, a prophylactic fasciotomy should be performed.

Soft-tissue coverage for open fractures needs to be planned and difficulties should be anticipated, before fixation. Cullen et al. advocated that in the absence of gross contamination or extensive damage, Type I or II open fractures may be closed over drains. Zalavras et al., however, advised against primary closure of open fractures, to minimize the risk of gas gangrene, and proposed returning to the operating room in 24–48 h for reassessment. One can also consider the primary closure of wound extensions, while leaving the wound itself open.

The timing of closure remains a controversial issue. Most authors agree that rates of infection increase if coverage is delayed beyond 7 days, but report no difference if coverage is undertaken <3 days or between 3 and 7 days. The concept of “fix and flap” with immediate definitive vascularized muscle flap with a split-thickness graft by Gopal et al. has shown good results. If closure is delayed, various methods such as antibiotic bead pouche technique, vacuum-assisted closure, and porcine allograft can be used as temporary dressings to prevent contamination.

Split-thickness skin grafts can be used in a majority of open wounds. Large open wounds with exposed bone require local or free flap coverage. Muscle-free flaps are said to provide excellent coverage owing to the plastic property, elimination of dead space, increased vascularity, and prevention of infection. Fasciocutaneous flaps provide simple, versatile options for coverage and prevent muscle sacrifice. Current guidelines advocate fasciocutaneous flaps for metaphyseal areas.

The peculiar complication of around 0.5–2 cm overgrowth observed following femoral or tibial fractures in a young child may also allow an initial shortening of almost 1 cm to reduce soft-tissue tension and size of defect.

**Fracture Stabilization**

Fixation in open fractures should be aimed at providing stable fixation of fractures and facilitating wound care, apart from decreasing pain; preventing further soft-tissue damage from fracture fragments; restoring length, alignment, and rotation; and supporting a robust host response against microbes despite the presence of metallic implants. Fracture stabilization in children is also influenced by the physiological differences between adults and children. The presence of an open physius must be kept in mind before planning fixation, as iatrogenic growth disruption must be avoided at all costs. In children, rigid fixation is not always as essential as it is in adults. It must however be remembered that with increasing age of the child, the healing ability approaches that of the adult, and requirement for more rigid fixation increases, as compared to a young child. The surviving periosteum also shows remarkable potential to
regenerate bone, even in the setting of considerable bone loss, and bone grafting is seldom required.

A variety of implants and fixation constructs are at the surgeon’s disposal, the decision itself should be governed by the bone(s) involved, the location within the bone, the extent of damage and contamination of the soft tissues, and the physiological status of the patient. Also important considerations are the amount of bone loss; logistical factor; and the need for transfer to higher center, vascular injury, and planned soft-tissue coverage.

Traction or plaster casts do not provide adequate fixation, and their use is generally debated. External fixators can be used both for provisional and definitive fixation. External fixators form an integral tool in damage control orthopedics, for temporary stabilization, wound care, and improved nursing care. The shorter operative time and lower blood loss have proven to be distinctive advantages in borderline patients.\(^{34}\) Other indications for use of external fixators include extensive soft-tissue damage with contamination; severe comminution and bone loss, in medically unfit patients; fractures with burns; and vascular injury needing repair [Figure 3]. Ring and monolateral fixators can also be used primarily when bone transport is anticipated. The complications of external fixation include pin-tract

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**Figure 3:** Radiographs of distal thigh with knee joint showing the use of external fixation with K-wires in the treatment of an open fracture of the distal femur for soft-tissue loss

**Figure 4:** X-ray distal arm with proximal forearm and elbow joint anteroposterior view showing radial neck fracture with fracture ulna and was treated using elastic stable intramedullary nailing (b) X-ray of forearm with wrist and ulna showing radial neck fracture and ulna was treated using elastic stable intramedullary nailing to provide stable fixation while allowing soft-tissue healing and early mobilization.
infection, malalignment, and delayed healing, while others arise due to conversion to other forms of fixation.

The use of percutaneous Kirschner wires has been shown to provide adequate fixation in most cases of distal radial fractures,\textsuperscript{35} distal ulna,\textsuperscript{36} supracondylar fractures,\textsuperscript{37} distal tibial fractures, etc. The advantage of smooth Kirschner wires crossing the physis without causing growth abnormalities makes it a suitable implant for epiphyseal injuries as well.\textsuperscript{38} The use of flexible intramedullary nails in forearm fractures\textsuperscript{39} [Figure 4] and diaphyseal and noncomminuted metadiaphyseal fractures of femur and tibia provides superior soft-tissue access, cosmesis, and early rehabilitation.\textsuperscript{40,41} The use of plates and screws for internal fixation in open fractures has been reported in some studies for femur and forearm fractures.\textsuperscript{42,43}

**Specific fractures**

**Humerus**

Proximal humeral injuries can be managed by percutaneous Kirschner wire fixation or retrograde elastic nailing with good results.\textsuperscript{8} Open diaphyseal humeral fractures (Grade III A and III B) treated with intramedullary nailing were shown to have a good outcome by Garg et al.\textsuperscript{44} Irrigation, debridement, reduction, and pinning for supracondylar fractures are recommended\textsuperscript{8} [Figure 5].

**Femur**

Treatment options for open femoral fractures include traction and hip spica cast, external fixator, intramedullary nailing, and open reduction and internal fixation. Most studies show good results with traction and hip spica casting in young patients. The general consensus seems to be favoring the use of spica cast in children <6 years of age, if soft-tissue condition permits.\textsuperscript{45} Elastic intramedullary nails have become the preferred method of treatment for diaphyseal femur fractures. The indications include patients <13 years, weight <55 kg, and stable fractures.\textsuperscript{46} Rigid interlocking nails can be used thereafter. The use of external fixator is advisable only for fractures with severe soft-tissue damage or factors precluding nailing, owing to high refracture rate, scarring, and delayed unions associated with external fixator.\textsuperscript{45,47} Submuscular bridge plating is another option for open fractures with comminution or complex patterns, but is rarely the treatment of choice.\textsuperscript{48}

**Tibia**

Options for stabilization of open tibial fractures include casting, pin and plaster, external fixation, elastic intramedullary nails, plates and screws, or a combination. Casting has been commonly used for the treatment of tibial fractures, and recent trends have shown an increasing tendency to use casting for Type I and Type II injuries, with early antibiotic administration and wound debridement.\textsuperscript{11,49}

External fixation has been the preferred choice for surgical stabilization of open tibial fractures, with indications, as previously discussed. Hull and Bell also advocated the use of external fixator for unstable fractures of distal tibia.\textsuperscript{50} In addition, external fixators can be used to span joints in cases of periarticular fractures and to maintain plantigrade foot in injuries around the foot and ankle.

Elastic nailing has been successfully used in open tibial fractures. Many authors have reported shorter healing times and superior functional outcomes with their use in tibial diaphyseal fractures.\textsuperscript{8,49,51} The use of supracutaneous locking plates for treatment of open tibial fractures was reported by Radhakrishna and Madhuri with no incidence of nonunion/malunion in 29 open tibial fractures. According to the authors, supracutaneous locked plates combine the advantages of angular stability, unicortical screws for oblique/partial fractures especially in cases of juxtaphyseal fractures, and reduced infection rates.\textsuperscript{52}

The outcome of open tibial fractures depends on a number of factors. The authors have reported superior results in younger children, especially under 6–8 years of age.\textsuperscript{53} Other factors

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**Figure 5:** (a) Clinical photograph showing supracondylar Supracondylar fracture with laceration in the cubital fossa treated with debridement, open reduction, and crossed pinning (b) X-ray of elbow joint showing supracondylar fracture with laceration in the cubital fossa treated with debridement, open reduction, and crossed pinning
include severity of soft-tissue injury, fracture configuration, and infection. The most dreaded complication of open fractures remains infection, the strategies of which have been discussed. Problems in fracture healing, although less frequent than in adults, can be avoided by effective infection control, early soft-tissue coverage, and stable fixation. Stiffness and other complications are also less frequent in children.

Injuries Common in Indian Circumstances
A few injuries are commonplace in India on account of agrarian lifestyle in most rural areas. These include fodder and chaff cutters, threshers, hand tools such as spade and sickle, tractors, and cycles. More than 40% of patients injured with chaff cutters were 5–15 year olds, with majority being hand/finger injuries or amputations. Thresher and fodder cutting machine injuries included 45% of patients aged 0–14 years resulting in crush injuries or amputations of the hand. In a retrospective analysis, Huda and Wasim reported approximately 30% of fractures in 146 children with agriculture-related injuries. Agarwal and Pruthi reported an incidence of 19% of open fractures related to bicycle and cycle rickshaw injuries, attributed to either cycle spokes or rear sprocket and chain. There is still a great lacuna in literature describing the characteristics and problems related with such injuries.

Overview
The healing potential of tissues in children along with the active role of periosteum in bone formation helps in healing of open fractures. The role of timely antibiotic administration and adequate debridement cannot be overemphasized. Stable fixation of fractures and robust soft-tissue coverage also contribute to the reduction of infection [Figure 6].

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There are no conflicts of interest.

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