Musculoskeletal injuries are the most common reason for operative procedures in severely injured patients and are major determinants of functional outcomes. In this paper, we summarise advances and future directions for management of multiply injured patients with major musculoskeletal trauma. Improved understanding of fracture healing has created new possibilities for management of particularly challenging problems, such as delayed union and non-union of fractures and large bone defects. Optimum timing of major orthopaedic interventions is guided by increased knowledge about the immune response after injury. Individual treatment should be guided by trading off the benefits of early definitive skeletal stabilisation, and the potentially life-threatening risks of systemic complications such as fat embolism, acute lung injury, and multiple organ failure. New methods for measurement of fracture healing and function and quality of life outcomes pave the way for landmark trials that will guide the future management of musculoskeletal injuries.

Introduction

Musculoskeletal injuries are the most common reason for surgery in severely injured patients after blunt trauma. More than 70% of all patients with major trauma need at least one orthopaedic surgical procedure. Survivors with orthopaedic injuries, particularly injuries of the lower limb, have poor functional outcomes and quality of life. A population-based registry for major trauma in Victoria, Australia, showed that even without other major injury, 83% of patients with fractures of the pelvis or lower limb had not returned to pre-injury function 2 years after injury, 35% had not returned to work, and 30% still had moderate to severe persistent pain.

Despite much progress in the science of fracture healing and substantial investment in implant and device development, research-based advances that improve outcomes for patients with major orthopaedic injuries have been constrained by two important factors. First is an over-reliance on clinical examination and radiographic endpoints and insufficient attention to patient-centred outcomes. Despite the apparent objectivity of radiographic fracture union, the radiographic appearance seems to correlate poorly with important clinical outcomes, such as pain, function, and need for further surgery. Second is the paucity of high-quality studies. Fewer than 10% of clinical studies published in the top orthopaedic surgery journals were randomised trials.

Key messages

- Orthopaedic injuries are major determinants of resource use and long-term outcomes in multiply injured patients
- Traumatic and surgical tissue injury drives the inflammatory response through endogenous danger molecules, even without haemorrhagic shock or infection
- Individually tailored timing of major fracture fixation can maximise the benefits of timely skeletal stabilisation and minimise the risks of systemic complications
- Increased understanding of the effects of systemic inflammation on fracture healing is needed
- Biological enhancements of fracture healing that are in development could be of particular benefit for large bone defects
- The evolving definition of fracture healing will provide better endpoints for future trials
- Patient-centred outcome measures show that patients have substantial long-term disability after major orthopaedic injury, and such measures should be included in clinical trials
- Comparative effectiveness research is needed to define the benefits of modern implants on patient outcomes
these trials, more than 80% were methodologically limited by small sample sizes, insufficient blinding, scarcity of allocation concealment, and no independent assessment of outcomes. Randomised trials of fracture surgery have included on average 80 patients and many have been underpowered to detect potential real differences between treatment groups. The small size and low quality of many studies of fracture management has restricted the translation of preclinical studies to patient care and left many areas unresolved.

In this paper we address advances, present challenges, and future directions in management of musculoskeletal injuries in multiply injured patients.

**Systemic inflammation, fracture healing, and timing of surgery**

Major transfer of mechanical energy to the body stimulates the immune system (figure 1). Haemorrhage and resuscitation, cell death, bacterial invasion, and pain can release proinflammatory elements with local and systemic effects. However, even without shock, substantial soft-tissue injury leads to cellular release of danger-associated molecular patterns (DAMPs) into the circulation, which activate innate immunity and result in systemic inflammatory response syndrome. Mitochondria are the main source of DAMPs. Because mitochondria are derived phylogenically from bacteria, the DNA and peptides released from the cytoplasm of injured cells can activate polymorphonuclear leucocytes through receptor-ligand bindings, which result in intracellular calcium flux, phosphorylation of protein kinases, and degranulation. Via this mechanism, which is absent in normal post-injury apoptosis, circulating mitochondrial DAMPs can cause widespread inflammation and secondary organ injury.

Fractures cause release of lipid particles and inflammatory cytokines into the circulation. Highly acidic lipid emboli lodge in vital organs, stimulating inflammation and causing fat embolism syndrome. The marrow of fractured long bones is also a potent source of proinflammatory cytokines. Concentrations of interleukin-6 in the marrow of fractured femora are 1000-times higher than those in the femora of patients undergoing major elective surgery. Concentrations in the medullary canal of patients with femoral fractures are 40-times higher than those in their corresponding serum, independent of fracture complexity and overall injury severity; the intramedullary concentration of interleukin-6 increases further during intramedullary nailing.

The effects of intense and often excessive local and systemic inflammation on fracture healing are poorly understood; however, findings from animal studies of fractures with concomitant chest injury showed an
inhibitory effect of systemic inflammation in the early phase of fracture healing. This phase is itself an inflammatory process that has many cellular and humoral components of both systemic and local inflammation. Local and margined macrophages are pivotal to creation of a stimulating humoral environment and derivation of osteoblasts and osteoclasts. Early innate immune responses (mediated through polymorphonuclear leucocytes) and early adaptive immune responses (mediated through T and B lymphocytes) are inhibitory to bone healing. Animal models have shown that depletion of polymorphonuclear leucocytes and a scarcity of lymphocytes (knockout models) facilitate bony union, but the clinical significance of these findings is unknown for human beings.

Better understood is remote end-organ injury, which is mediated through trauma-associated systemic inflammation and exacerbated by resuscitation and surgical intervention. Incidence of acute lung injury, sepsis, and multiple organ failure has been reported to be up to 15% in patients with polytrauma managed by reamed intramedullary nailing. A patient’s susceptibility to secondary organ damage is dependent on patient factors, injury characteristics, and resuscitation and treatment after injury.

Optimisation of outcomes and avoidance of systemic complications is partly dependent on timing of procedures to when patients are least vulnerable to the consequences of accentuated inflammation (panel). The most important concerns for timing of acute surgical intervention are fixation of long bone fractures, pelvic and spinal stabilisation, and management of open fractures. The importance of timing became evident after Bone and colleagues’ 1989 trial showed that early fixation of femoral fractures within 24 h in multiply injured patients led to fewer pulmonary complications and shorter stays in intensive care and hospital than did delayed fixation. In the early 1990s, severely injured patients were often resuscitated with large volumes of crystalloid and colloid fluids, and very early fixation in patients who were physiologically compromised compounded inflammatory complications caused by injury, resuscitation, and surgical stress, which led to excessive rates of acute lung injury, adult respiratory distress syndrome, and multiple organ failure. Since then, timing of fracture fixation has been affected by improved understanding of how orthopaedic injury and surgical repair affect patients with multiple injuries.

Resuscitation and timing of definitive fracture fixation cannot be addressed separately. Temporary fracture stabilisation with splints, traction, or external fixation provides pain relief and minimises blood loss, fat emboli, and further tissue damage. When tolerated, timely definitive stabilisation of fractures can reduce hospital stay, facilitate recovery, prevent joint stiffness, and enable early mobilisation, which indirectly decreases the chances of deep vein thrombosis and promotes fracture healing through potential physiological loading of the injured limbs.

The concept of damage-control orthopaedics promotes initial rapid skeletal stabilisation with external fixation, followed by intramedullary nailing after the systemic inflammatory response has subsided. To aid surgical decision-making, Pape and colleagues categorised patients with femoral fractures as stable, borderline, unstable, and in extremis on the basis of the pattern and physiology of their injury. Early total care was recommended for stable patients and damage-control orthopaedics for those who were unstable or in extremis. A prospective randomised controlled trial of borderline patients showed that early total care led to a higher incidence of transient acute lung injury than did damage control, with no increase in incidence of clinically significant adverse outcomes, such as adult respiratory distress syndrome, multiple organ failure, or death. These findings are reinforced by the experience of centres that routinely provide early total care to patients with borderline physiology, and whose patients have fewer days on a ventilator, earlier discharge from intensive care, and less infectious complications than did those enrolled in the trial.

Because major fractures of the pelvic ring are high-energy injuries that are frequently associated with haemodynamic instability, neurological deficit, and urogenital or rectal injuries, timing of skeletal stabilisation is dependent on the patient’s overall physiological state and the local soft-tissue environment. Non-invasive pelvic binding—which can be provided by clamped bed sheets or proprietary devices—is widely accepted during transport and imaging. In patients with shock, control of extrapelvic and intrapelvic haemorrhage takes priority, with staged fracture management consisting...
of external fixation and subsequent definitive internal fixation.\textsuperscript{39} However, patients with fracture patterns amenable to minimally invasive internal fixation can safely undergo definitive skeletal stabilisation, alongside haemostatic resuscitation and rewarming, within hours of admission.\textsuperscript{35} Furthermore, early stabilisation of unstable thoracolumbar spine injuries in multiply injured patients is associated with reduced ventilator and intensive-care needs, shorter hospital stay, and less respiratory morbidity than late stabilisation, irrespective of neurological deficit.\textsuperscript{36}

Timing of surgery in open fractures has always been regarded as important to minimise the risk of infection, with most orthopaedic surgeons trained to aim for debridement and surgical stabilisation within 6 h of injury. However, findings from studies\textsuperscript{29} of patients with isolated fractures have not shown an association between precise timing of initial surgical debridement and incidence of deep infection, or delayed union or non-union, provided surgery occurs within 24 h and antibiotic coverage is adequate. Little relevant data exists for polytrauma patients with open fractures, but initial debridement should be done as soon as the patient is taken to the operating room for other injuries.

Overall, research supports basing of the timing of acute long bone fixation on patient physiology and injury pattern, rather than on arbitrary timeframes. Pape and colleagues\textsuperscript{27} physiological categories should be regarded as severity scores in which the score for any patient can be affected by clinical interventions. Modern resuscitation strategies that restrict fluid administration before haemorrhage control and simultaneously administer balanced blood and clotting factors help to reverse physiological deterioration in borderline patients. This approach leads to safe early total care in most major trauma patients with long bone fractures. Early does not necessarily mean immediate, it means as early as the patient’s resuscitation makes total care possible, usually in 4–24 h. Frequent reassessment of the patient’s physiology, including blood gases and coagulation status, is an essential part of physiological optimisation.

**Biological enhancement of fracture healing and major bone defects**

Biological enhancements of fracture healing are potentially useful in major musculoskeletal trauma in which high-energy transfer and soft-tissue injuries can result in large segments of exposed or devascularised bone. These fractures are at high risk for delayed union, non-union, and infection. Critical bone defects, defined as those that will not heal spontaneously, often need secondary interventions and subsequent surgery. According to Giannoudis' diamond concept,\textsuperscript{38} the core components of bone regeneration have four pillars: osteogenic cells, growth factors, osteoconductive scaffolds, and the mechanical environment. Figure 2 shows the molecular physiology of fracture healing.

Although growth factors or cell-based approaches in isolation could be used to manage small bone defects, large defects need the structural integrity that osteoconductive scaffolds provide. An ideal osteoconductive scaffold should have surface properties that optimise attachment, have a highly porous interconnected network in three dimensions that facilitates nutrient and metabolite transport and cellular proliferation and differentiation, have sufficient strength to achieve stable biomechanical conditions and vascularisation, and permit continuous tissue remodelling. Furthermore, to prevent failure, osteoconductive scaffolds should be biocompatible and biodegradable at rates that correspond to the formation, remodelling, and maturation of new tissue.\textsuperscript{39}

Prominent options for tissue engineering options for bone regeneration are emerging. The osteoconductive scaffolds can be adapted with osteoinductive properties by addition of cells, such as mesenchymal stem cells, periosteal cells, and osteoblasts, or with growth factors, such as bone morphogenetic proteins. Mesenchymal stem cells are multipotent progenitor cells that can be isolated from mesenchymal tissues—eg, bone marrow, periosteum, and fat. These cells can expand in vitro and differentiate into various musculoskeletal tissues using defined growth factors or cytokines and specific culture conditions.\textsuperscript{40,41} Mesenchymal stem cells from the bone marrow are fairly easy to harvest by aspiration and have high osteogenic potential. Although these cells have been investigated extensively in vitro and in vivo in preclinical studies for their osteogenic capacity and potential for treatment of critical bone defects, this assessment has yet to be done in human beings. The bone morphogenetic protein family of growth factors have high osteogenic potency and are already used to stimulate bone healing in small defects. Genetic treatments can be used to deliver growth factors with techniques that have reached clinical trials of arthritis management,\textsuperscript{42} but have not yet reached such trials of fracture healing. Bone formation can be induced by a recombinant adenovirus vector carrying complementary DNA that encodes the full amino acid sequence of human bone morphogenic protein-1. Autologous cells with large amounts of complementary DNA that encodes human bone morphogenic protein-2 were successfully used to reliably and rapidly heal a femoral segmental defect in rats.\textsuperscript{43} However, with clinical applications come potential risks of cancer stimulation and ectopic bone formation.\textsuperscript{44}

Because no in-vivo animal models are similar to human beings, investigations are underway with different species, various anatomical locations, bone enriched with growth factors, biomaterials, applied cells, and bioactive agents (eg, bone morphogenetic proteins, platelet-rich plasma, and bone marrow).\textsuperscript{45,46} Although preclinical studies have increased understanding of cell biology and biomaterials for bone regeneration, the preclinical models still have to be optimised and piloted.
in human beings before the results can be broadly applied in patients with large bone defects.

Other new laboratory-based approaches to fracture healing might have application for large bone defects (table). Several pharmacological drugs target cell signalling cascades. Intermittent parathyroid hormone stimulates bone formation, but so far, no improvement in union rates have been noted in a murine model of

Figure 2: Fracture healing and present interventions

The course of fracture healing consists of overlapping stages of interplay between tissue formation and resorption and other progresses, including initial haematoma and inflammation, subsequent repair processes, intramembranous and endochondral bone formation, and remodelling (left side, top to bottom). The initial proinflammatory response of the haematoma is characterised by hypoxia and low pH and involves several inflammatory cell types at the fracture site. During the subsequent repair process mesenchymal stem cells are recruited to the fracture site by growth factors and cytokines. These cells mainly derive from the periosteum, but are likewise recruited systemically and derive from surrounding tissues (eg, muscle). Beginning ingrowth of a vascular network is important for proper vascularisation of the fracture gap. Mesenchymal stem cells start proliferating and differentiating into osteoblast lineage, which build woven bone (collagen type 1), and chondroblast lineages, which build cartilage (collagen type 2). The final stage of remodelling is characterised by a balance of hard callus resorption by osteoclasts and lamellar bone deposition by osteoblasts. The right side of the figure lists available clinical interventions, which target distinct mechanisms during bone repair, disturbed bone healing, and management of critical bone defects.

Key:
- Vascular network
- Pre-osteoblast
- Platelets
- Mature osteoblast
- Macrophage
- Osteoclast
- T cells
- Mesenchymal stem cells
- B cells
- Lining cell
- Polymorphonuclear cells
- Chondrocytes

Interventions to facilitate healing
- Skeletal stabilisation
  - Fracture fixation
  - Fracture stability
  - —Reduction of fragments
  - —Reduction of gap size
  - —Interfragmental strain and movement

Interventions in cases of delayed union or bone defect
- Autologous bone grafts containing cells with osteogenic potential
- Delivery of growth factors (rhBMP2/7) and hormones (rhPTH/rhGH)
- Osteoconductive scaffolds
- Change of mechanical environment in cases of hypertrophic non-union
- Low intensity pulsed ultrasound (LIPUS)
- Extracorporeal shockwave therapies (ECSW)
- High intensity focused ultrasound (HIFUS)
open fracture. Teriparatide—a synthetic small-fragment recombinant human parathyroid hormone—has been used for fragility fractures in human beings, and low doses seem to shorten healing time compared with placebo, but this effect has not been noticed at higher doses. Other potential therapeutic targets are components of the Wnt signalling pathway, such as sclerostin or Dickkopf-1, which inhibit progression of osteoblast lineage and thus bone formation. Antiscerostin and anti-Dickkopf-1 antibodies have been developed and shown to promote callus mineralisation and improve mechanical properties, but more work is needed to confirm the biology and safety of these experimental treatments. Control of motion during bone healing might likewise affect healing efficiency. Findings from studies of advanced imaging technologies have shown that in a large bone-defect model, rigid bone fixation is preferable to early mechanical loading because early motion is associated with inhibited vascular invasion into the defect and reduced bone formation. The effects of low-intensity ultrasound, high-intensity focused ultrasound, and extracorporeal shockwave treatments on fracture healing have been assessed in 12 small and clinically heterogeneous trials that to date provide insufficient evidence for the routine use of vibrational treatments.

Adjuvant anabolic strategies might have a role in osteoporotic fractures, which are becoming increasingly common because the average age of major trauma patients is 10 years older than it was 30 years ago. In osteoporotic bone, fixation is less reliable, stiffness mismatch between the implant and bone greater, and patients have less capacity for specific treatment (eg, partial weight bearing) than do patients with normal bone density. Comminution in osteoporotic bone is particularly challenging, especially in elderly patients and in regions of decreased vascularity, which take longer to heal than do well-vascularised regions. For comminuted periarticular fractures in osteoporotic bone (especially around the elbow and knee), which can be impossible to reconstruct, prosthetic replacement might better facilitate functional recovery.

<table>
<thead>
<tr>
<th>Class</th>
<th>Postulated key effects</th>
<th>Clinical applications</th>
<th>Advanced clinical methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia&lt;sup&gt;48&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular endothelial growth factor Polypeptide</td>
<td>Angiogenesis</td>
<td>Potential</td>
<td>Delivery strategies for vascular endothelial growth factor need optimisation</td>
</tr>
<tr>
<td>Hormones&lt;sup&gt;49&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Parathyroid hormone Polypeptide</td>
<td>Osteoblast differentiation (on intermittent administration), mesenchymal stem cell proliferation (on intermittent administration), chondrocyte differentiation, proliferation, cartilage formation (on intermittent administration)</td>
<td>Yes</td>
<td>Teriparatide: recombinant human parathyroid hormone fragment (1–34)</td>
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<td>Growth hormone Polypeptide</td>
<td>Growth hormone or insulin-like growth factor axis: mature osteoblast function, chondrocyte differentiation, osteoclastogenesis</td>
<td>Yes</td>
<td>Recombinant human growth hormone</td>
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<tr>
<td>Cytokines&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Interleukins 1, 5, 6, 11, and 18; tumour necrosis factor-α Polypeptide</td>
<td>Mesenchymal stem-cell migration, proliferation and differentiation, osteoblast differentiation, osteoclast differentiation</td>
<td>Potential</td>
<td>Impending</td>
</tr>
<tr>
<td>Growth factors&lt;sup&gt;50&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone morphogenetic proteins Polypeptide</td>
<td>Mesenchymal stem cell migration, osteoblast differentiation, chondrocyte differentiation, angiogenesis</td>
<td>Yes</td>
<td>Recombinant human bone morphogenetic proteins 2 and 7 are commercially available and in routine clinical use</td>
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<tr>
<td>Fibroblast-like growth factors Polypeptide</td>
<td>Mesenchymal cell proliferation and differentiation, angiogenesis</td>
<td>Trial</td>
<td>Anticipated</td>
</tr>
<tr>
<td>Platelet-derived growth factors Polypeptide</td>
<td>Mesenchymal stem-cell migration and proliferation, osteoblast migration and proliferation</td>
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<td>Impending</td>
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<tr>
<td>Insulin-like growth factors Polypeptide</td>
<td>Mature osteoblast function, chondrocyte differentiation, osteoclastogenesis</td>
<td>Potential</td>
<td>Impending</td>
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<tr>
<td>Transforming growth factor-β Polypeptide</td>
<td>Mesenchymal stem-cell migration and proliferation, osteoblast proliferation, chondrocyte proliferation and differentiation</td>
<td>Potential</td>
<td>Potentially broad biological effects need consideration</td>
</tr>
<tr>
<td>Wnt proteins Polypeptide</td>
<td>Osteoblast differentiation and proliferation</td>
<td>Anticipated</td>
<td>Antibodies for depletion of Wnt signalling inhibitors sclerostin and Dickkopf-1 are in development</td>
</tr>
<tr>
<td>Tissue stability&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant technologies Biomechanical</td>
<td>Interfragmentary movement and stability</td>
<td>Yes</td>
<td>Plates with locking screws for angle-stable fixation and anatomically contoured fragment-specific plates are in routine clinical use</td>
</tr>
<tr>
<td>Tissue vibration&lt;sup&gt;16&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound technologies Biomechanical</td>
<td>Probably flow-induced shear stress and strain</td>
<td>Yes</td>
<td>Low-intensity pulsed ultrasound, high-intensity focused ultrasound, extracorporeal shockwave treatments</td>
</tr>
</tbody>
</table>

Table: Clinical applications of factors affecting bone repair
Improvements to the evidence base for clinical research of orthopaedic trauma

Limitations in clinical research of orthopaedic trauma have not prevented innovation and uptake of new techniques and devices. For example, plates with locking screws that provide angle-stable fixation and stabilised fracture fragments have fundamentally changed strategies for surgical treatment in the past decade. An increasing inventory of anatomically contoured, low-profile, fragment-specific plates is available to aid minimally invasive techniques of insertion through incisions away from the fracture, and anatomical restoration of the joint surface in complex periarticular fractures with optimum reconstruction of the length, axis, and rotation of the joint block.64–65

Although modern plates, locking screws, and percutaneous insertion techniques are popular, few randomised trials have investigated their effectiveness compared with alternative techniques. Published trials have not shown statistically significant or clinically important benefits or harms from locking plates compared with intramedullary nailing of the femur66 and tibia,67–69 or compared with other approaches, including closed reduction and casting of distal radius fractures.68 The remaining published literature does not show a clear benefit of locked plates compared with alternative methods of fixation.

As implants continue to evolve and new products emerge, comparative effectiveness research will be needed to define which treatment works best, for whom, and in what circumstances. In the USA, substantial investment in such research is based on the need for decisions about costly or potentially harmful interventions to be informed by evidence about benefits and harms compared with existing alternatives. The research should include pragmatic and well-powered trials in diverse practice settings, better post-market monitoring of intended and adverse outcomes than exists presently, and a focus on clinically meaningful endpoints.

Endpoints of fracture healing

Some patients need reoperation for delayed fracture union or non-union, especially in cases of severe open fracture or large bone defects with postoperative fracture gap;70 however, definitions of delayed union and non-union have varied greatly.73 Determination of fracture union is most commonly based on serial clinical and radiographic assessments, and healing is often appraised by assessment of orthogonal radiographic views for bridging by fracture callus, absence of fracture lines, and cortical continuity across the fracture ends.74 Radiographic fracture healing is often defined as the presence of bridging callus on at least three of the four cortices (anterior, posterior, medial, and lateral).75

How good plain radiography is at showing actual bone healing is dependent on the correlation between radiographic findings and other meaningful measurements. Experimental data suggests that the number of cortices bridged by callus is a strong predictor of union strength at maximum torque (correlation coefficient r 0·80), and that moderate correlation exists between radiographic healing and stiffness at the fracture site (r 0·59).75 Reliability of radiographic assessment—ie, the ability of independent clinicians reviewing the same radiographs to agree on the level of healing of a fracture—has improved with standardised scales, such as the Radiographic Union Scale for Tibial Fractures (RUST),76 which assesses the anteroposterior and lateral views of the fracture. The extent of callus bridging and visibility of the fracture line is scored for each of the four cortices, with total scores ranging from four points (no healing) to 12 points (complete healing). RUST has shown high interobserver and intraobserver agreement (intraclass correlation coefficient r 0·86 and 0·88, respectively) at several different stages of fracture healing.

Fracture micromotion is a useful indicator of healing, but is largely undetectable with plain radiography. Radiostereometric analysis, also known as roentgen stereophotogrammetric analysis, improves the precision of radiographic assessments with highly accurate three-dimensional measurements in vivo over time with sequential radiographs.77 Micromotion varies on average between 1·5 mm and 3·2 mm during the healing of distal radius fractures and tibial osteotomies, and between 6 mm and 12 mm during that of trochanteric fractures.77 Widespread use of fracture micromotion to assess healing is limited by present scarcity of the necessary technology.

Although radiographic approaches, whether conventional or radiostereometric analysis, are the usual basis for assessments of fracture healing, they are insufficient without supportive clinical correlates. Clinical assessment of fracture healing is largely subjective with no gold standard, and is an amalgam of radiographic and clinical impression. In a review78 of 77 clinical studies that used clinical criteria to define fracture union, the three most common criteria were absence of pain or tenderness when weight bearing, or on palpation or examination, and the ability to bear weight. Weight bearing could be an objective measure of healing of tibial fractures that are treated by external fixation because weight-bearing ability increases with time after fracture and correlates well with bone stiffness.79

The Functional Index in Trauma (FIX-IT) score80 provides a simple standardised approach to assess weight bearing and pain in lower-limb fractures. FIX-IT is a 12-point functional score (minimum zero, maximum 12 points) with two primary domains: weight bearing status (six points) and pain at the fracture site (six points). Early assessment of this score by five content experts showed high face and content validity, and high overall inter-rater reliability (0·88, 95% CI 0·83–0·92). FIX-IT correlates well with validated measures of physical function, such as the 36-item Short Form Health Survey (SF-36) physical component summary score (r 0·68–0·77).
Patient-centred outcomes
Declining mortality after major trauma, recognition of the need to measure quality of survival, and poor correlation between clinical or radiographic findings and patient-reported outcomes, such as pain, have resulted in a recent shift to definition and measurement of patient-centred outcomes—ie, outcomes that are most important to patients. WHO’s International Classification of Functioning, Disability and Health (ICF)8 and the List of All Deficits (LOAD) framework82 describe individual, social, and societal effects that are relevant to major trauma patients with orthopaedic injuries, and provide guidance about domains that are important to measure.

Many patient-reported outcomes that are specific to body region and relate to items of the ICF and LOAD frameworks are available for orthopaedic injury, but interpretation of these outcomes in patients with multiple injuries is challenging. Such outcomes—eg, shoulder and wrist scores—usually have some items that are related to activities of daily living, pain, work, and social and leisure activities, but are designed to contain items that are relevant to only disease or region. The key advantage of this specificity is sensitivity to even small changes, and therefore, an increased ability to detect any differences between treatment groups. However, use of specific outcomes is complicated in patients with multiple trauma for whom measured disability might be partly caused by injuries to other body regions.101 To distinguish the effect of specific orthopaedic injuries from other orthopaedic and non-orthopaedic injuries (eg, head injury) with measures of disease-specific or region-specific outcomes might not be possible.

General health-related quality of life or health-status measures, such as SF-36 or SF-12, WHO’s Disability Assessment Schedule II (WHODAS II), and the EuroQol Group’s EQ-5D, are less specific than outcome measures related to disease or region, but might be overall more relevant to patients with multiple trauma because they are designed to be generic methods and include items related to social, mental, and role functioning. These methods capture patients’ experiences and expectations of their injuries, and broad aspects of health and wellbeing. Because the measures should be collected from the patient themselves, they are of restricted use in patients with pre-existing or injury-related cognitive and communication deficits.9 Nevertheless, their widespread use for different disorders allows for the comparison of outcomes and cost-effectiveness of interventions between many types of injury or disease.

When best to measure patient-reported outcomes is dependent on the time course of recovery to the point of return to pre-injury function or plateau. Little consensus exists about the timing of follow-up of patients with multiple injuries. Some studies80 have reported no improvement in major trauma outcomes at 12-months after injury and others80 have shown that major trauma patients with orthopaedic injuries continue to improve beyond 12 months. Whereas orthopaedic injuries have been associated with poor outcomes 10 years after major trauma,9 the time at which outcomes stabilise cannot be ascertained in studies that measure outcomes at one time point alone. Little evidence exists for the need to follow-up patients with orthopaedic trauma beyond the short to medium term (1–2 years after injury), and in research, investigators should consider the effect of long-term follow-up on follow-up rates, responder bias, and resources.

Several studies5,8,86 have emphasised the prolonged effect of spinal column and lower-limb injuries on function and health-related quality of life, particularly up to 10 years after injury. Emerging data from the population-based Victorian State Trauma Registry2 showed that the presence of any orthopaedic injury reduced the odds of functional recovery 1 year after injury. In patients with head injuries, the odds of any functional improvement in the first year were reduced by 30% if orthopaedic injuries were present.1 In patients with no head injury who had sustained lower-limb injuries, with or without spinal column injury, the age-adjusted and sex-adjusted physical health scores on SF-12 were well below than the population norms and only marginally better than for spinal cord injury (figure 3).

Standardised outcome measures and routine collection of patient-reported outcomes are needed to monitor and assess present and new treatment approaches and to support clinical trials and evidence-based care. Collection should continue throughout recovery to increase understanding of when outcomes stabilise, and to inform trial and study design.

The future of research in polytrauma patients with orthopaedic injuries
Patients with multiple injuries present substantial challenges for coordination of clinical care. Orthopaedic
injuries are important determinants of short-term and long-term patient outcomes, as are treatment decisions made by the orthopaedic surgeon. Modern orthopaedic and trauma care entails each patient receiving the best treatment at the right time. As the range of potential treatment options expands, surgeons will be increasingly dependent on research that addresses important questions, is sufficiently powered to answer them, and uses meaningful primary outcome measures.

The benefits of more individualised approaches to the timing of surgery and adjuvant treatments might soon become apparent, taking into account injury patterns, specific aspects of physiological compromise, the immune response, and genetic polymorphism. For example, clinical decision-making has not routinely incorporated information about the immune response with inflammatory markers that are associated with injury severity, the magnitude of surgical interventions, and clinical outcomes. Collaborative research networks, and further research about fracture healing, immune monitoring, genetic mapping, DAMPs, and shock resuscitation will be central to such advances.

Furthermore, the novel innovations and laboratory-based experimental treatments discussed in this paper will only become available for routine clinical use via the sorts of robust trials that have already transformed specialty areas, such as cardiovascular medicine, osteoporosis, and critical-care medicine. Dedicated surgeon-scientists, development of global networks and coordinating centres for trauma and fracture trials, improved availability of centres for coordinating trauma trials, and improved funding sources are setting new benchmarks in surgical research. Large trials of fracture management, such as the Study to Prospectively evaluate Reamed Intramedullary Nails in Tibial fractures (SPRINT), which analysed 1226 patients, and the study of Fluid Lavage of Open Wounds (FLOW), which aims to analyse 2280 patients, are challenging the dogma that surgical trials are inevitably small single-centre initiatives. Innovative studies of novel systemically-administered biological agents are underway to optimise outcomes in fracture healing, function, and quality of life. These and other important trials will transform the care of trauma patients with musculoskeletal injuries in the next decade by informing practice with sound actionable evidence.

Contributors
ZJB planned the review, selected topics, interpreted evidence, and drafted the abstract and key messages, sections relating to inflammation, fracture healing and timing of surgery, the panel on secondary organ injury, and figure 1. MKR performed search and selection of citations, co-ordinated referencing, and drafted sections relating to biology of fracture healing and figure 2. RLG planned and coordinated the review and the evidence searches, drafted sections relating to introduction and future directions, and led content editing. FMR drafted sections on new laboratory-based approaches to fracture healing and table 2. IAH drafted sections on implants, surgical techniques and timing of surgery in open fractures, MAS drafted sections on major bone defects and osteoporotic bone fractures. BJG drafted sections on patient centred outcomes and figure 3. MB drafted sections on fracture healing endpoints, fracture trials and challenges in orthopaedic trauma research. All authors revised and edited all sections of the manuscript.

Conflicts of interest
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