Crush-related acute kidney injury (acute renal failure)

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INTRODUCTION — Following rhabdomyolysis, several pathogenetic mechanisms can cause heme pigment-associated acute tubular necrosis (ATN), which results in an abrupt rise in serum creatinine, or acute kidney injury (AKI) [1-4]. (See "Definition and staging criteria of acute kidney injury in adults".)

Rhabdomyolysis may be due to either traumatic or nontraumatic muscle injury. Much of our knowledge on rhabdomyolysis-associated ATN derives from observations of traumatic rhabdomyolysis that forms the basis for development of the crush syndrome resulting from large-scale, natural or manmade disasters [5].

Treatment of both acute and chronic kidney diseases after disasters deserves special mention because it almost always requires complex technology and equipment. Crush syndrome-related AKI is the most frequent acute kidney problem after mass disasters [6].

The clinical features and prevention of AKI due to traumatic rhabdomyolysis will be reviewed here. ATN due to nontraumatic rhabdomyolysis and hemolysis and general overviews of rhabdomyolysis, hemolysis, and drug-induced myopathies are discussed in detail separately. (See "Clinical features and diagnosis of heme pigment-induced acute kidney injury" and "Clinical manifestations and diagnosis of rhabdomyolysis" and "Diagnosis of hemolytic anemia in the adult" and "Drug-induced myopathies".)

DEFINITIONS AND EPIDEMIOLOGY — Systemic manifestations that are induced by crush injury are often referred to as crush syndrome. Crush syndrome develops in 30 to 50 percent of cases of traumatic rhabdomyolysis and is frequently seen after catastrophic earthquakes. According to some estimates, the incidence of crush syndrome ranges between 2 and 5 percent of all injured victims of catastrophic earthquakes [7-10]. All disaster victims, irrespective of whether they are mildly or severely injured, should be considered at increased risk.

The incidence of AKI and the frequency with which dialysis is required in these cases have varied widely in different studies. The following reports have analyzed these aspects as part of crush injury following catastrophic earthquakes.

In a report from Bam, Iran, dialysis was required in 6.5 percent of 1975 patients admitted to the hospital [11]. The majority of victims were rescued in less than four hours. In contrast to other reports [12], the authors detected a direct correlation between time under the rubble and outcome. The short

time under the rubble might thus explain, at least in part, the lower rate of requiring dialysis in Bam compared with other reports, although this is not entirely certain.

Much higher rates of dialysis requirement were noted in two other catastrophic earthquakes: 54 percent in the Kobe earthquake and 75 percent in the Marmara earthquake [10,13]. In the Kobe earthquake, the need for hemodialysis correlated directly with increased serum creatine kinase (CK) levels as dialysis was required in 84 and 39 percent of patients with a CK level greater or less than 75,000 units/L, respectively [10].

In the Kobe and Marmara earthquakes, the time under the rubble correlated inversely with both serum CK and the frequency of requiring dialysis. A possible explanation for these counterintuitive findings is that victims with more extensive muscle injury and higher CK levels died before they were extricated and transported to the hospital.

Although not many other natural disasters cause traumatic rhabdomyolysis, a number of manmade disasters may do so (such as terrorist attacks, mining accidents, wars, and torture) [14-16].

CLINICAL MANIFESTATIONS

Compartment syndrome — The most typical local finding of traumatic rhabdomyolysis is compartment syndrome due to swollen muscles. Patients suffer from severe pain, weakness, paresthesia, paresis or paralysis, and pallor in the affected extremities. Distal pulses may be absent when intracompartmental pressure is very high, although increased intracompartmental pressure may be present, even when distal pulses are palpable. In traumatic rhabdomyolysis, signs of penetrating or, more frequently, blunt trauma may also be present. (See "Severe extremity injury in the adult patient", section on 'Extremity evaluation'.)

Hypovolemia — Some patients with rhabdomyolysis have been immobile or comatose for significant periods of time. As a result, hypovolemia due to absence of fluid intake plus ongoing losses may be observed. This is particularly important among patients with rhabdomyolysis due to crush injury since they may have been immobilized for hours to days. In addition, third spacing at the site of muscle injury (compartment syndrome) among such patients significantly worsens hypovolemia. The latter phenomenon typically starts only after decompression due to reperfusion of the traumatized muscle.

Dark urine — The characteristic manifestation of heme pigment-induced acute tubular necrosis (ATN) is discolored urine. Marked release of myoglobin leads to red or brown (or even black) urine, unless pigment excretion is limited, because of a low glomerular filtration rate (GFR), extreme dilution of the urine due to preventive fluid administration, or clearance of myoglobin from the plasma by the reticuloendothelial system [17]. Urinalysis also reveals pigmented granular casts.

The plasma is typically normal in color with myoglobinuria. This is in contrast to conditions resulting in hemoglobinuria-induced ATN, such as massive hemolysis, which are characterized by red-tinted plasma (see "Clinical features and diagnosis of heme pigment-induced acute kidney injury"). The reason for normal-colored plasma may be that massive rhabdomyolysis is required for a color change. However, such extensive rhabdomyolysis is almost always associated with fatal hyperkalemia; thus, these patients die before admitting to hospitals.

Renal insufficiency — The severity of renal insufficiency ranges widely from a mild elevation in the serum creatinine concentration to oliguric AKI requiring immediate hemodialysis. This variability is due to differences in severity of injury to muscle and presence or absence of volume depletion and/or underlying, additional comorbid conditions, particularly sepsis [18,19]. AKI resulting from heme pigment-induced ATN is usually characterized by an initial oliguric period, followed by polyuria, which usually starts within one to three weeks after the primary event. Some cases may present with a nonoliguric course.

Other clinical problems — Other systemic manifestations of crush syndrome may include, but are not limited to, sepsis, acute respiratory distress syndrome, disseminated intravascular coagulation, bleeding diathesis, cardiac failure, arrhythmias, and psychological trauma [20]. (See "Severe extremity injury in the adult patient".)

BIOCHEMICAL ABNORMALITIES — The biochemical abnormalities that characterize rhabdomyolysis-associated AKI include hyperkalemia that may be life threatening, hyperphosphatemia, hypocalcemia (which is occasionally followed by hypercalcemia during the recovery stage), a high creatine kinase (CK), and a low fractional excretion of sodium. These are discussed elsewhere (see "Clinical features and diagnosis of heme pigment-induced acute kidney injury"). High serum levels of myoglobin are very rarely detected because of the short half-life of myoglobin. In addition, myoglobin is cleared very quickly from the plasma.

DIAGNOSIS — Patients with rhabdomyolysis-induced acute tubular necrosis (ATN) typically present with a red to brown color of the urine without presence of erythrocytes at microscopic examination, pigmented granular casts in the urinary sediment, varying severity of kidney dysfunction, and a marked elevation in the plasma creatine kinase (CK) level. (See "Clinical manifestations and diagnosis of rhabdomyolysis".)

DIFFERENTIAL DIAGNOSIS — The intermittent excretion of red to brown urine can be seen in a variety of clinical settings, including heme pigment-induced acute tubular necrosis (ATN). The approach to this issue is discussed separately. (See "Urinalysis in the diagnosis of kidney disease", section on 'Red to brown urine'.)

AKI can also be caused by other conditions or abnormalities commonly observed in patients with traumatic rhabdomyolysis. These include drug-induced AKI (such as aminoglycosides and nonsteroidal anti-inflammatory drugs), sepsis, severe hypotension due to marked hypovolemia, and others. This is also discussed elsewhere. (See "Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute kidney injury in adults".)

PREVENTION — The general goals for preventive therapy in all cases of heme pigment-induced AKI are to both enhance renal perfusion (thereby minimizing ischemic injury) and increase the urine flow rate to wash out obstructing casts. Volume resuscitation should be initiated before the crush is relieved or as soon as possible thereafter, before heme pigment and other intracellular elements have been released into the circulation and before third spacing at the site of muscle injury worsens hypovolemia [2,21-23]. In the case of disaster, preventive measures should be applied to crush victims already at the disaster field, in the field hospitals, during transportation to the hospitals, and after admission to regular hospitals.

The most important preventive measure at the disaster field is the correction of volume depletion. During volume resuscitation, the timing and rate of fluid administration, volume of fluids, and also types of fluid are important elements to consider.

The approach to prevention of AKI also may vary based upon the location of the patient and ability to closely monitor the victim or not.

Before and during extrication — Aggressive fluid repletion should be started before the extrication of entrapped subjects prone to develop the crush syndrome, if possible. Third spacing at the site of muscle injury worsens hypovolemia. Thus, patients with rhabdomyolysis may require massive amounts of fluid (even up to 20 liters) to initiate and maintain a vigorous diuresis [21].

Evidence — The rationale of early and generous volume resuscitation is based upon the observations that early adequate fluid resuscitation is very important to help prevent AKI in patients with rhabdomyolysis due to crush injury.

Practically all of the published experience with volume resuscitation in patients with heme pigment-induced acute tubular necrosis (ATN) has come from retrospective reports of rhabdomyolysis in subjects with crush injury [2-4,21,23,24]. The following studies serve as examples of the importance of early fluid repletion in this setting [21,23]:

- Seven patients with crush syndrome who were trapped under rubble (all with creatine kinase [CK] concentrations >30,000 units/L) were treated with alkaline diuresis immediately after extrication; none developed renal failure [23]. One patient who did not receive prophylactic volume repletion developed AKI and required hemodialysis [25].
- Sixteen earthquake victims trapped for a mean of 10 hours (12 had CK concentrations >20,000 units/L) were treated initially with isotonic saline at 1 L/hour, then with an alkaline-mannitol solution [21]. The four patients who required dialysis were treated approximately nine hours after extrication and received significantly less fluids compared with 12 patients who did not require dialysis and who were treated four hours after extrication with more massive quantities of fluid.
- In other reports of earthquake-related crush injury, AKI occurred in over 50 percent of patients for whom therapy was instituted much later [24,26].

However, in the aftermath of the Marmara earthquake, more extensive fluid administration was unexpectedly associated with a more frequent need for dialysis. This seemingly contradictory finding may be explained by the fact that many victims had already established AKI when they were admitted to hospitals [9]. In such cases, delayed fluid resuscitation might result in hypervolemia and a subsequent higher need for dialysis. Therefore, this finding does not indicate that disaster victims should receive less fluid in order to avoid dialysis, but underscores that, once AKI is established, the risk of volume overload is substantial. (See 'Treatment of established acute kidney injury' below.)

The optimal type and rate of fluid repletion are unclear. No studies have directly compared the efficacy and safety of different types and rates of fluid administration in this setting.

Prior to and during extrication, we agree with the Renal Disaster Relief Task Force (RDRTF) of the International Society of Nephrology (ISN) that isotonic saline, rather than isotonic bicarbonate, be

administered because saline solutions are more readily available in disasters and have a well-described efficacy for volume replacement [27]. If available, isotonic saline plus 5 percent dextrose may be used since it provides the advantage of supplying calories and attenuating hyperkalemia.

Isotonic saline should initially be given at a rate of 1 L/hour (10 to 15 mL/kg of body weight per hour) while the victim is still under the rubble (algorithm 1). After 2 liters are given, the rate of administration should be decreased to 500 mL/hour to avoid volume overload. However, this volume should be individualized. Factors to consider are age (fluid administration should be performed more carefully in older adults); body mass index (more fluids are needed for the victims with larger body volume); trauma pattern (more fluid is needed in patients with more serious trauma); and amount of presumed fluid losses (more fluids are needed in hot climates and in victims who produce urine or have ongoing blood losses).

There is a potential role for isotonic bicarbonate therapy after extrication (see 'Use of bicarbonate' below), but this application is hampered in the aftermath of mass disasters for practical reasons (eg, availability).

Severe hyperkalemia is relatively frequent among patients with crush injuries. As a result, intravenous solutions containing potassium, such as Ringer's lactate, are contraindicated in such patients.

After extrication — Extricated victims should be evacuated as quickly as possible from the site of structural collapse. Vital signs should be checked and a primary survey performed to define the extent and type of medical and surgical interventions needed. Victims with a low potential for survival should be triaged to determine who should receive priority for treatment. Afterwards, an initial systematic assessment of the injured patient should be performed to identify any life-threatening injuries and to prioritize urgent therapeutic needs. Hydration status of victims should be evaluated to determine the volume of fluids required. If no intravenous fluid was given prior to extraction, intravenous isotonic saline at a rate of 1 L/hour for adults should be initiated as soon as possible after rescue. The victim should be evaluated regularly, and urinary output should be monitored at least six hours while administering 3 to 6 L of fluid (algorithm 1) [27].

Use of bicarbonate — After urine output has been documented and overt alkalosis has been excluded, we agree with the RDRTF that an alkaline solution that is approximately isotonic may be used where feasible (such as in small-scale disasters) in an attempt to achieve a forced alkaline diuresis [27]. However, the use of complex solutions such as bicarbonate-containing solutions may be limited by logistic circumstances in mass disasters. The preparation of such solutions is time consuming and carries the risk of contamination and error in preparation.

The rationale for this approach is that raising the urine pH above 6.5 may prevent heme-protein precipitation with Tamm-Horsfall protein, intratubular pigment cast formation, and uric acid precipitation; correct metabolic acidosis; and reduce hyperkalemia [1,3,28]. Alkalinization may also decrease the release of free iron from myoglobin and the formation of F2-isoprostanes, which may enhance renal vasoconstriction. Administration of isotonic bicarbonate instead of NaCl may also prevent chloride accumulation and subsequent hyperchloremic acidosis. (See "Prevention and treatment of heme pigment-induced acute kidney injury".)

Despite these potential benefits, there is no clear clinical evidence that an alkaline diuresis is more effective than a saline diuresis in preventing AKI as no direct comparative trial has been performed. The best data in support of an alkaline diuresis are derived from uncontrolled case series. In a study cited above, for example, renal failure did not develop in seven patients with crush syndrome who were trapped under rubble and were treated with alkaline diuresis immediately after extrication [23]. By comparison, one patient who did not receive prophylactic volume developed AKI and required hemodialysis [25].

The optimal regimen and rate of administration of bicarbonate are unknown. We generally administer one of the following two fluid regimens after extrication:

- One liter of isotonic saline alternating with 1 liter of half-isotonic saline plus 50 mEq of sodium bicarbonate.
- Isotonic saline for the first two liters, followed by 1 liter of half-isotonic saline plus 50 mEq of sodium bicarbonate. This sequence is then repeated, as indicated.

The choice between these two regimens depends in part upon the general clinical and biochemical condition of the patient and the blood pH. As an example, if measured laboratory values reflect only a mild acidosis, more liters of isotonic saline and fewer liters of bicarbonate-containing solution are given.

The rate of fluid administration with either regimen is based upon the ability to attain urinary output goals and assessment of volume status. In general, we administer the intravenous solution at 500 mL/hour for the first 24 hours, as long as there is no evidence of fluid overload and the patient can be closely monitored. (See 'Urine output goal' below.)

The rate of fluid administration is decreased after the first 24 hours but is still maintained at a rate that is greater than the urine output, as long as there is no evidence of fluid overload. Generally, a total of 200 to 300 mEq of bicarbonate is given on the first day, as long as the patient is not alkalemic. The exact rate and regimen are altered based upon ongoing clinical assessment and laboratory values. (See 'Urine output goal' below.)

Potential risks associated with alkalinization of the plasma include promoting calcium phosphate deposition and inducing or worsening the manifestations of hypocalcemia by both a direct membrane effect and a reduction in ionized calcium levels [3]. Manifestations of severe ionized hypocalcemia include tetany, seizures, and arrhythmias. To minimize the risk of these complications, the arterial pH should not exceed 7.5. (See "Clinical manifestations of hypocalcemia".)

Alkalinization can also reduce the plasma potassium concentration secondary to intracellular shift. This is often a beneficial effect since the combination of tissue breakdown and renal failure often leads to hyperkalemia. (See "Causes of hypokalemia in adults", section on 'Increased entry into cells'.)

Because of the potential risks with bicarbonate therapy, we recommend close monitoring of serum bicarbonate, calcium, and potassium and the urine pH. The urine pH can be measured by immersion of a simple urine dipstick, but this is only reliable on freshly voided urine, unless urine is collected under paraffin (which is difficult to obtain). The target urine pH is >6.5. We recommend discontinuing the bicarbonate-containing solution (but continuing to replete volume with isotonic saline) if the arterial

pH exceeds 7.5, the serum bicarbonate exceeds 31 mEq/L, or the patient develops symptomatic hypocalcemia. Calcium supplementation should be given only for symptomatic hypocalcemia or severe hyperkalemia since early deposition of calcium in muscle is followed by hypercalcemia later in the recovery process. (See "Treatment of hypocalcemia".)

Use of mannitol — If urinary flow is adequate (defined as >20 mL/hour), 50 mL of 20 percent mannitol (1 to 2 g/kg per day [total 120 g], given at a rate of 5 g per hour) may be added to each liter of fluid, providing an increase in urine output is demonstrated following a test dose of mannitol. Among members of the RDRTF-European Renal Best Practice (ERBP) crush recommendation work group, however, there was no consensus regarding mannitol administration, although most experts suggested assessing the response to a test dose first if mannitol were used [27]. A reasonable test dose is 60 mL of a 20 percent solution of mannitol administered intravenously over three to five minutes [27]. If there is no significant increase in the urine output by at least 30 to 50 mL/hour above baseline levels, mannitol should not be continued.

Mannitol should only be used if close monitoring is possible. Mannitol is contraindicated in patients with oligoanuria.

Mannitol should be discontinued if the desired diuresis of approximately 200 to 300 mL/hour cannot be achieved, since there is a risk of hyperosmolality, volume overload, and hyperkalemia with continued mannitol administration under these conditions. (See "Complications of mannitol therapy".)

The mechanism by which mannitol protects against heme pigment-induced ATN is not completely clear. Experimental studies have suggested that mannitol may be protective by causing a diuresis, which minimizes intratubular heme pigment deposition and cast formation [29]. It has also been proposed that mannitol may act as a free radical scavenger, thereby minimizing cell injury [4]. In addition to these beneficial effects on the kidney, mannitol may extract sequestered water from the injured muscles, thus preventing compartmental syndrome [30].

However, at least some studies have shown no amelioration of proximal tubular necrosis with mannitol, and mannitol may cause hyperosmolality and other complications [29]. The available retrospective series, most of which are uncontrolled, report conflicting results regarding the effectiveness of mannitol plus bicarbonate in preventing heme pigment-induced AKI [21,23,31,32]. As an example, 154 of 382 patients with serum CK concentration >5000 units/L were treated with mannitol plus bicarbonate [32]. There was no statistically significant difference in the incidence of AKI (defined as creatinine >2 mg/dL [177 micromol/L]; 22 versus 18 percent), dialysis (7 versus 6 percent), or death (15 versus 18 percent) in patients who were or were not treated with mannitol plus bicarbonate. However, there was a trend toward improved outcomes in patients with extremely high CK levels (>30,000 units/L) treated with mannitol and bicarbonate. This is relevant given that such high levels are not unusual in victims of earthquakes [23,26].

The interpretation of these findings is hampered by the lack of reporting of other elements of treatment, such as adequacy of volume resuscitation, presence of other factors contributing to AKI (eg, drugs, sepsis, hypotension), timing of interventions, and relatively low rate of severe AKI (eg, requiring dialysis).

Unless the patient is carefully monitored and losses are replaced when appropriate, mannitol can lead to both volume depletion and, since free water is lost with mannitol, hypernatremia. Mannitol administered in very high doses or to patients with reduced renal excretion due to renal insufficiency can also raise plasma osmolality sufficiently to cause symptoms of hyperosmolality and volume expansion. The increase in plasma osmolality can also cause passive movement of potassium out of cells and raise the plasma potassium concentration. AKI may occur if patients are treated with more than 200 g of mannitol per day. (See "Complications of mannitol therapy".)

Prevention of hyperkalemia — Although sporadic patients with rhabdomyolysis or the crush syndrome may develop hypokalemia, the large majority are hyperkalemic, which is life threatening [12,33-35]. Hyperkalemia may occur even in the absence of AKI since a large amount of potassium may be released from injured muscle. Since potassium measurements at first triage are seldom available in disaster conditions, transport of victims with a potential crush syndrome to safer areas for more intensive treatment should be started, if possible, after the administration of a preventive oral dose of the potassium-binding resin, sodium polystyrene sulfonate, in combination with 33 percent sorbitol at a 1:3 ratio [22].

Although efficacy of sodium polystyrene sulfonate has been questioned and although sorbitol has sporadically been associated with ulcers of the intestinal wall [36], we suggest their use in disaster crush victims since the risk of fatal hyperkalemia is extremely high. (See "Treatment and prevention of hyperkalemia in adults", section on 'Do not use SPS or other resins'.)

Since a calcium load is to be avoided, sodium polystyrene sulfonate should be preferred to calcium polystyrene sulfonate. (Calcium polystyrene sulfonate is not available in the United States, although it is available elsewhere.)

Many of the isotonic solutions for fluid repletion contain potassium (eg, Ringer's lactate). Because of the risk for life-threatening hyperkalemia, empiric administration of such preparations is absolutely contraindicated in patients at risk for the crush syndrome.

We recommend monitoring plasma potassium several times daily until stabilized. In many victims, fluid administration is initiated in the field or during transportation; but, contrary to all recommendations, these solutions may contain potassium [37]. Therefore, on admission to hospitals, all fluid infusions should be checked, and potassium-containing solutions should be stopped.

Hyperkalemia should be appropriately treated. (See "Treatment and prevention of hyperkalemia in adults".)

If serum potassium concentration cannot be measured due to field conditions, electrocardiography (ECG) can offer useful information, although a normal ECG may be present in spite of overt hyperkalemia. In the 2010 Haiti earthquake, point-of-care devices (eg, iSTAT) were invaluable in disaster-field conditions, providing direct electrolyte and creatinine measurements [38]. These devices or ECG should be used for the early detection of hyperkalemia, which helps with deciding whether dialysis treatment is needed or first volume resuscitation can be attempted. (See "Treatment and prevention of hyperkalemia in adults".)

Urine output goal — Once the patient can be closely monitored (such as hospital or triage setting), the administration of intravenous fluid should be adjusted to maintain the urinary output at approximately 200 to 300 mL/hour. This is done to help ensure adequate renal perfusion and to wash out any obstructing casts. Patients must be followed closely to ensure that fluid overload, as defined by signs of pulmonary congestion, does not occur. As previously mentioned, limb swelling alone may not represent volume overload.

If a bladder catheter has not been placed before hospitalization, it should be inserted to all crush victims, after excluding urethral bleeding and/or laceration, to follow urine flow [27]. Catheters carry a risk of infection, especially in the chaos accompanying most disasters. Therefore, unless there is an obligatory indication, such as unconsciousness, pelvic trauma, possible urethral obstruction, immobilization, or surgery, the catheter should be removed once the patient has established oligoanuric AKI or achieves normal kidney function and monitoring urine production provides no further useful information.

If the urine output goal is achieved, intravenous fluids should be administered until the disappearance of myoglobinuria (either clinically or biochemically). This usually requires several days.

Therapy should be based on physical examination and biochemical analysis, close monitoring of fluid intake and output, and body weight. Although frequently used to determine volume status, absolute central venous pressure (CVP) values can be misleading and often do not predict the response to volume infusion, especially in critically ill patients [39]. Absolute values are increased not only in hypervolemia, but also in other disease states, such as cardiac failure. For that reason, relative changes may be more useful than absolute values in reflecting intravascular volume status [40]. A stable weight may suggest that the appropriate amount of fluid is being administered to the patient.

After serum CK levels begin to return to normal, the volume of administered fluids should be gradually tapered under close clinical and laboratory monitoring. A parallel decrease in urinary output together with normal clinical and biochemical findings indicates that tubular function has been restored.

Dialysis should be initiated in the setting of persistent oligoanuria or other indications. (See 'Treatment of established acute kidney injury' below.)

Total volume administered — The total amount of volume administered depends upon the clinical scenario. A positive fluid balance is always necessary in crush syndrome casualties in the early phase since extreme amounts of fluids can diffuse into the damaged muscles. Fluid solutions can be administered at quantities of up to 12 L/day to an adult weighing 75 kg and with appropriate urine response. Eight liters of urinary output can be expected following an infusion of 12 L of this solution. Therefore, it is reasonable to administer 4 to 4.5 L more fluid than all of the total losses of the previous 24-hour period [2]. Analysis of the Bingol earthquake demonstrated that dialysis was avoided in many patients with crush syndrome by administering more than 20 L of fluid per day to each patient [21]. The relatively low number of victims injured in this particular disaster allowed for more careful monitoring of each victim, which allowed the vigorous volume repletion.

Fluid administration should be individualized and may need to be less aggressive in chaotic disaster circumstances when it is impossible to monitor patients appropriately to avoid volume overload. Under these circumstances, more modest volume repletion is recommended. Although the exact, optimal limit

is unknown, we suggest administering up to a maximum of 6 L of fluid per day under prolonged conditions in which close monitoring may not be possible. More cautious volume repletion is also warranted in victims who are prone to cardiac failure, such as older adults, and in those who are anuric [41].

Calcium — Calcium supplementation should be given only for symptomatic hypocalcemia or severe hyperkalemia because early deposition of calcium in muscle is followed by hypercalcemia later in the injury process. (See "Treatment of hypocalcemia".)

Loop diuretics — Loop diuretics have no impact on outcome in AKI [42,43]. (See "Possible prevention and therapy of ischemic acute tubular necrosis".) In the context of rhabdomyolysis, loop diuretics may worsen the already existing trend for hypocalcemia since they induce calciuria and may increase the risk of cast formation [22,26]. Despite these concerns, however, judicious use of loop diuretics may be justified in older patients, especially if volume overloaded.

TREATMENT OF ESTABLISHED ACUTE KIDNEY INJURY — Other than maintenance of fluid and electrolyte balance and tissue perfusion, there is no specific therapy once the patient has developed AKI. Dialysis is initiated for the usual indications, including volume overload, hyperkalemia, severe acidemia, and uremia. Frequent (twice or even three times daily) hemodialysis may be indicated in patients with crush syndrome, given the high risk of fatal hyperkalemia. A detailed discussion of the indications for dialysis is presented elsewhere. (See "Renal replacement therapy (dialysis) in acute kidney injury in adults: Indications, timing, and dialysis dose".)

Intermittent hemodialysis is suggested over other renal replacement modalities in the setting of crush syndrome. Compared with other modalities, intermittent hemodialysis is most efficient at removing potassium, which is one of the major causes of death [1]. (See "Acute hemodialysis prescription".)

The other renal replacement modalities have the following additional limitations [44]:

- Peritoneal dialysis might be difficult to perform in case of abdominal and/or thoracic trauma, or in patients who cannot lie down due to hypervolemia-related heart failure and/orrespiratory failure. Peritoneal dialysis may also not adequately treat the metabolic and electrolyte derangements caused by rhabdomyolysis (eg, hyperkalemia and other abnormalities), especially in the heavily traumatized patients. Furthermore, peritoneal dialysis may create logistic problems in mass disasters due to the necessity to deliver large loads of bags containing sterile dialysis fluid to the disaster area. (See "Use of peritoneal dialysis for the treatment of acute kidney injury in adults".)
- Continuous dialysis strategies are limited by the need for large amounts of sterile replacement fluid that may be difficult to obtain in disaster conditions. In addition, only one patient can be treated per machine when continuous modalities are used. Finally, continuous anticoagulation by heparin may enhance a bleeding tendency in heavily traumatized patients. Regional citrate anticoagulation avoids the problems associated with anticoagulation but is difficult to monitor in chaotic disaster circumstances. (See "Renal replacement therapy (dialysis) in acute kidney injury in adults: Indications, timing, and dialysis dose" and "Continuous renal replacement therapy in acute kidney injury".)

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute kidney injury in adults".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Acute kidney injury (The Basics)" and "Patient education: Rhabdomyolysis (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Hypovolemia due to various reasons and high circulating levels in the plasma of myoglobin secondary to rhabdomyolysis can directly cause acute tubular necrosis (ATN), resulting in acute kidney injury (AKI). Rhabdomyolysis-associated AKI due to crush injury is a major source of morbidity and mortality in natural or manmade disasters. (See 'Introduction' above.)
- Among entrapped subjects prone to develop the crush syndrome, we suggest the following approach.
- We recommend the intravenous administration of an isotonic solution at a high fluid rate (Grade 1B). We suggest starting intravenous fluid replacement prior to and during extrication of the victim whenever possible (Grade 2B). Among crush victims of mass disasters, we suggest giving isotonic saline rather than an isotonic alkaline solution (Grade 2C). Although the exact rate has not been defined by controlled studies, we suggest administering fluid at 1 L/hour initially. After two liters are given, the rate of administration should be decreased to 500 mL/hour to avoid volume overload. The rate should be adjusted depending on age, body weight, trauma pattern, ambient temperature, urine production, and amount of overall estimated fluid losses.
- Since severe hyperkalemia is relatively common, intravenous solutions containing potassium, such as Ringer's lactate, are contraindicated. (See 'Before and during extrication'above.)
- If no intravenous fluid was given prior to extraction, intravenous isotonic saline at a rate of 1000 mL/hour for adults should be initiated as soon as possible after rescue. After the victim has been removed from the rubble and urine output has been documented, isotonic saline may be switched to an isotonic bicarbonate solution if such fluids are available and alkalosis has been excluded. However, the use of complex solutions such as bicarbonate-containing solutions may be limited by logistic circumstances in mass disasters. The preparation of such

solutions is time consuming and carries the risk of contamination and error in preparation. (See 'Use of bicarbonate' above.)

●The optimal regimen and rate of administration are unknown. Following extrication, we administer the intravenous solution at 500 mL/hour for the first day, if there is no evidence of fluid overload and the patient can be closely monitored. We recommend close monitoring of serum bicarbonate, calcium, potassium, and serum and urine pH. We recommend discontinuing the alkaline solution if symptomatic hypocalcemia develops. (See 'Use of bicarbonate' above.)

- If urinary flow is >20 mL/hour among victims removed from the rubble, we suggest adding mannitol to the intravenous alkaline solution, providing an increase in urine output is demonstrated following a test dose (Grade 2C). A suggested test dose is 60 mL of a 20 percent solution of mannitol administered intravenously over three to five minutes. If urine output increases by at least 30 to 50 mL/hour above baseline levels in response to the test dose, 50 mL of 20 percent mannitol (1 to 2 g/kg per day [total, 120 g]) may be given at a rate of 5 g/hour. Mannitol is contraindicated in patients with oligoanuria.

  We recommend discontinuing mannitol if the desired diuresis cannot be achieved (approximately 200 to 300 mL/hour) (Grade 1B). (See 'Use of mannitol' above.)
- Once the patient can be closely monitored (such as hospital or triage setting), the administration of intravenous fluid should be adjusted to maintain the urinary output at approximately 200 to 300 mL/hour. If the urine output goal is achieved, we suggest continuing fluid therapy until the disappearance of myoglobinuria (either clinically or biochemically). This usually requires several days.

●Once the patient is in a hospital setting, closely monitor input and all losses (urinary volume plus other losses together) of the previous day. In this setting, therapy should be based on physical examination, biochemical analysis, close monitoring of fluid intake and output, and body weight. (See 'Urine output goal' above.)

●We recommend monitoring plasma potassium and calcium several times daily until stabilized. We recommend treating hyperkalemia as discussed elsewhere. (See "Treatment and prevention of hyperkalemia in adults".)

●Patients with symptomatic hypocalcemia or severe hyperkalemia may require calcium supplementation. In patients with asymptomatic hypocalcemia, we suggest not providing calcium supplementation (Grade 2C). (See "Treatment of hypocalcemia", section on 'Therapeutic approach' and "Treatment and prevention of hyperkalemia in adults".)

●Dialysis is initiated for the usual indications, including volume overload, hyperkalemia, severe acidemia, and uremia. Among patients with heme pigment-induced AKI due to crush injury, we suggest intermittent hemodialysis rather than other renal replacement modalities (Grade 2C). (See "Renal replacement therapy (dialysis) in acute kidney injury in adults: Indications, timing, and dialysis dose" and "Acute hemodialysis prescription".)

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