



Volume 14 Number 4
Fall 2004

TraumaCare

The Official Publication of ITACCS

International Trauma Care



The German Air Rescue team in action. (Photo provided by Herbert Kubnigk, MD; copyright, German Air Rescue.)

- Patterns and Characteristics of Trauma in a Developing Country
- Uncontrolled Hemorrhage in Pelvic Fracture
- Brief History and Literature Review of Rhabdomyolysis
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ISSN 1094-1126

Editor-in-Chief

John K. Stene, MD, PhD
Department of Anesthesiology
Milton S. Hershey Medical Center
Hershey, PA 17033 USA
Tel: 717-531-8434; Fax: 717-531-4110
e-mail: jstene@psu.edu

Managing Editor

Linda J. Kesselring, MS, ELS
ITACCS
P.O. Box 4826
Baltimore, MD 21211 USA
Tel: 410-744-7372
e-mail: lkessel112@aol.com

Copy Editor

E. Ann Donaldson, ELS
Tel: 434-973-6776
Fax: 434-973-7775
e-mail: morann@aol.com

Guidelines for Authors available at www.itaccs.com

Send address changes and general inquiries to TraumaCareMail@aol.com

ITACCS World Headquarters

P.O. Box 4826, Baltimore, MD 21211 USA
Fax: 410-235-8084 • www.ITACCS.com

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Publication Date: March 2005
Credit Expiration Date: March 31, 2006

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Wellington School of Medicine

University of Otago, PO Box 7343, Wellington, New Zealand

TRAUMA CARE SYSTEMS

Patterns and Characteristics of Trauma in a Developing Country

Alis Ozcakir, MD,¹ Ganime Sadikoglu,¹ MD,
Erol Armagan, MD,² and Rifat Tokyay, MD³
Uludag University Medical School, Departments of ¹Family
Medicine and ²Emergency Medicine, 16059 Bursa, Turkey,
and ³American Hospital, Istanbul, Turkey
alis_o@yahoo.com
rifatt@amerikanhastanesi.com.tr

Learning Objective: To divulge the importance of trauma epidemiology and trauma registry in the care and prevention of injuries.

Abstract

Objective: The first step in dealing with a problem such as trauma is to identify the injury patterns and characteristics. Therefore, we aimed to demonstrate the current status of trauma admissions to a Level I trauma center in a major city of a developing country to be used as a model in establishing effective interventions for reducing injuries and their adverse consequences. **Design:** Retrospective descriptive study. **Setting:** The emergency department of the Uludag University Medical Center. **Methods:** Data received from the trauma admission forms of all trauma patients presenting to the Emergency Department between January 1, 1996, and December 31, 2000. **Results:** Among the recorded major trauma patients (n = 4,527), 71.7% were men and 28.3% were women. The main cause of trauma was motor vehicle accidents (70.3%) followed by falls (14.8%), interpersonal violence (physical assault, firearm and stab wounds) (7.3%), and machinery or workplace accidents (3.9%). Among all age groups, male sex and motor vehicle accidents were the main causes of trauma. Skin and soft tissue lacerations, ecchymoses, abrasions, and hematomas (23.1%), multiple organ injuries (18.3%), and cranial injuries (15.3%) were the main trauma types. Almost half of all the trauma patients (48.9%) were hospitalized in various wards, 23.5% were sent home, 17.2% transferred to another hospital, and 1.9% died in the hospital. **Conclusion:** Our findings emphasize the importance of motor vehicle accidents and falls as the leading causes of trauma and the need for measures such as educating the public, raising the awareness of the community, and taking legislative action to prevent these trauma patterns. Directing the resources and the education of the health care personnel toward the management of the injuries caused by these trauma patterns can also help in decreasing trauma morbidity and mortality.

Trauma frequently affects the young population and is the leading cause of death in the first four decades of life, a period of maximum productivity. Trauma also causes permanent disability in nearly twice the number of deaths it causes.^{1,2} In the United States, it has been reported that trauma-related injuries are the fourth cause of death after heart diseases, cancer, and stroke among all age groups.^{3,4} In the United Kingdom, it was found that 24% of the survivors of motor vehicle accidents were exposed to disability for at least 6 months. The current picture shows us that we are facing a substantial loss in the productive age group and that trauma is the most expensive public health problem.^{2,5} In other words, apart from leading to death and disability, trauma also presents a substantial problem for a country from the socioeconomic perspective.

Trauma-related admissions to emergency units comprise a rather large group. In order to reduce the number of patients in this group, it is necessary to determine the common trauma patterns to be able to take specific measures such as improving environmental factors and educating families and the public. Improving emergency care systems and developing hospitals selected as regional trauma care centers are the second step to minimize potential trauma-related disabilities and mortality.³

Turkey is a developing country with a population of 67 million. Its gross national product (GNP) per capita is around 2,500 U.S. dollars; it spends only 3.5% of its GNP on health care. Uludag University Medical School has an 800-bed medical center that may be considered as the Level I (600–1,000 beds) trauma center of the Bursa province. Our university hospital serves a population of 11 million, 1 million of which are urban and 10 million of which are rural. Bursa, the fourth largest city and an important industrial region, is located in the west and relatively more developed part of Turkey. In the metropolitan area, there are eight state-owned, one military, and three private hospitals. Four of these state-owned hospitals are general hospitals (two for public and two for labor men and their families) that may be categorized as Level II (400–600 beds) and Level III (150–250 beds) trauma centers; the other four are specialty hospitals, namely, children's, oncology, gynecology and obstetrics, and respiratory disease. In the rural area, there are 12 Level III–IV hospitals (50–150 beds).

Emergency medicine is a fairly new specialty in our medical system (since 1993) and emergency medical services (EMS) have been established in major cities only since 1996. Therefore, many aspects of the emergency care of the trauma patient, including their transfer and transportation, are still in their infancy. The emergency departments of the state-owned or private general hospitals as well as the state ambulance services are staffed with general practitioners. Unfortunately, these physicians usually lack the skills to perform some emergency or life-saving procedures such as endotracheal intubation, cricothyroidotomy, or placement of chest tubes and have to depend on surgeons or anesthesiologists who are usually on-call at home.

In our province, ground ambulances are used for most of the transportation or transfer of trauma patients. Transportation to the hospital takes approximately half an hour within the metropolitan region and 1 to 2 hours from the rural areas.

Keeping in mind the aforementioned status of our prehospital and in-hospital trauma care, this study aims to identify the characteristics and the types of major trauma seen in the Uludag University Medical Center, to compare these characteristics with similar national and international body of evidence, and to review potential efforts needed to minimize trauma-related disabilities and deaths in the region.

Methods

Trauma patients admitted to the emergency department (ED) of the Uludag University Medical Center during a 5-year period (January 1, 1996, to December 31, 2000) were included in the study. The study group that met the trauma center admission criteria comprised 4,527 trauma patients, each of whom completed a "trauma admission form" in the ED.⁶ Patients lacking the necessary information (more than two parameters of the study) in their trauma charts were excluded from the study.

Parameters evaluated in the study included age, sex, prehospital status, admission date and time, mechanism and intent of trauma, nature and severity of injury, and disposition destinations. Items that were missing on the trauma admission forms were documented as missing.

Patients were divided into six age groups: 0–15, 16–25, 26–35, 36–45, 46–55, and 56 years and over. The date of admission was recorded as month and year. Causes of trauma were classified as motor vehicle accidents, falls, interpersonal violence (stabs and gunshot wounds), machinery and workplace accidents, and others (in-house accidents, burns, injuries due to electricity, drowning, airplane crash, and unspecified and multiple causes).

The obtained data were entered into a personal computer and analyzed by Epi Info Version 1.1.2 (Epi Info is a statistical program distributed free by the World Health Organization) and SPSS 9.0 statistical programs (SPSS, Inc., Chicago, IL). Differences were tested by using the chi-square test.

Results

Among the 4,527 patients 71.7% (3,246) were male and 28.3% (1,281) were female. The mean age was 30.1 ± 0.3 years, with the youngest patient being 40 years old and oldest being 87 (median age, 28).

The number of trauma patients admitted to the hospital increased from 393 in 1996 to 1,183 in 2000 (Fig. 1). When monthly distribution of trauma admissions was analyzed, a peak in the summer season was observed (Fig. 2). A statistically significant relationship was found between the causes of trauma and the seasonal trauma peaks ($P = 0.004$).

According to individual analysis of causes of trauma, road traffic accidents were the leading cause (70.3%), followed by falls (14.8%), penetrating injuries that included firearm and stab wounds (7.3%), machinery accidents (3.9%), home/game accidents (0.9%), self-inflicted injuries (0.7%), and all the others (2.1%).

The details of the road traffic accidents, the leading cause of trauma, were in-vehicle traffic accidents affecting driver or passengers (66.5%), traffic accidents affecting pedestrians (21.6%), motorcycle accidents (5.8%), bicycle accidents (2.6%), tractor accidents (1.7%), and others (1.8%). The male sex was dominant in 93.2% of vehicle drivers, 98.7% of motorcyclists, and 91.4% of bicyclists. The sex distribution among pedestrians was 65.6% men and 34.4% women.

Injuries related to falling from high places included falling from trees (13.7%) and falling from balconies, walls, roofs, windows, and buildings under construction (87.3%).

Traumatic injuries caused by suicide attempts included falling from a high place (45.1%), gunshot wounds (22.6%), stab wounds (19.4%), and hanging (12.9%).

When association between sex and age groups was assessed, the number of men injured was higher than women (Fig. 3) in all age groups, but this was significantly higher in the 16- to 25- and 26- to 35-year-old age groups ($P < 0.05$).

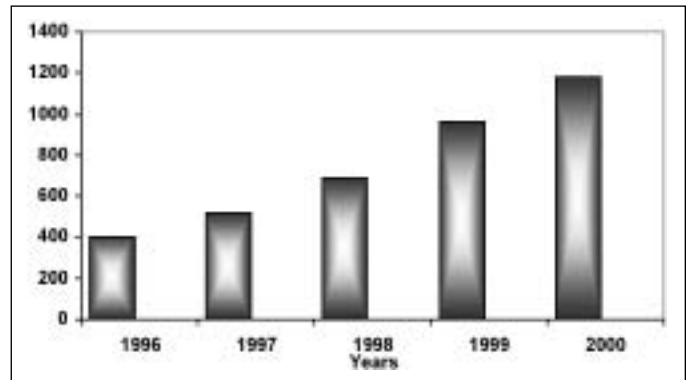


Figure 1. Yearly distribution of trauma admissions to the ED.

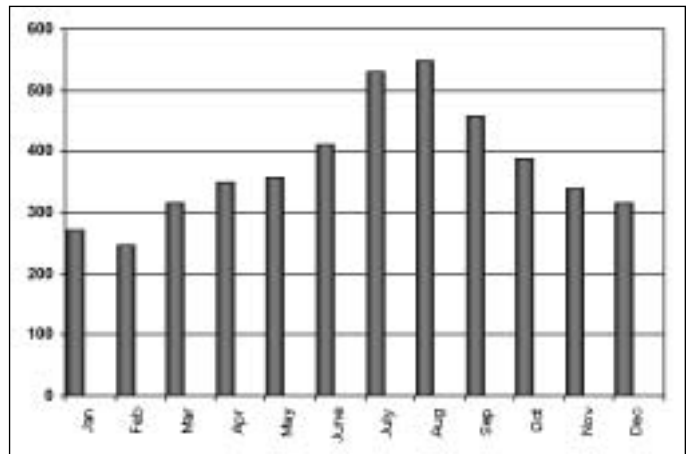


Figure 2. Monthly distribution of trauma admissions to the ED.

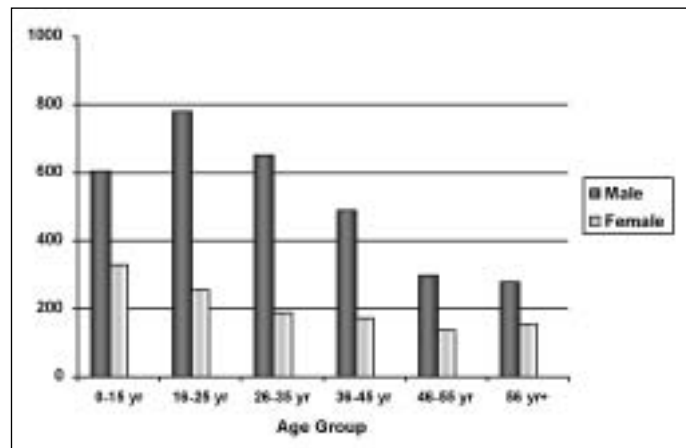


Figure 3. Age and sex distribution of the trauma admissions.

When association between sex and trauma causes was analyzed, it was observed that motor vehicle accidents, falls, workplace accidents, and penetrating injuries including gunshot and stab wounds were significantly more common among men (Table 1) ($P < 0.05$).

The leading cause of trauma in all age groups was motor vehicle accidents. While injuries related to motor vehicle accidents were the number-one cause (61%) in 0- to 15-year-old age group, falling from a high place (31%) was the next. In the 16- to 25-year-old age group, the leading cause of trauma was motor vehicle accidents (71%), followed by gunshot and stab wounds (11%). Motor vehicle accidents (70.1%) and falls (21.9%) were the main causes of trauma among patients 56 years and over.

The most frequent findings due to trauma were lacerations, ecchymoses, abrasions of skin, and swelling or hematoma in soft tissues (23.1%) followed by multiple thoracoabdominal injuries (18.3%), cranial injuries (15.3%), and extremity fractures (11.6%) (Table 2).

Table 1. Association between Sex and Cause of Trauma

Cause of Trauma	Male	Female	Total
Motor vehicle accidents	2,198	965	3,163
Falls	442	222	664
Interpersonal violence	293	35	328
Workplace accidents	165	10	175
All other trauma causes	129	38	167
Unrecorded trauma causes	21	9	30
Total	3,248	1,279	4,527

Table 2. Classification of Trauma Admissions to the ED by Injury Site

Injury Site	Frequency	%
Skin and soft tissue trauma	982	23.1
Multiple organ injuries	777	18.3
Cranial trauma	651	15.3
Extremity fractures	492	11.6
Torso trauma	314	7.4
Vertebral and spinal injuries	184	4.3
Abdominal injuries	122	2.9
Other	140	3.3
No identifiable injury	292	6.9

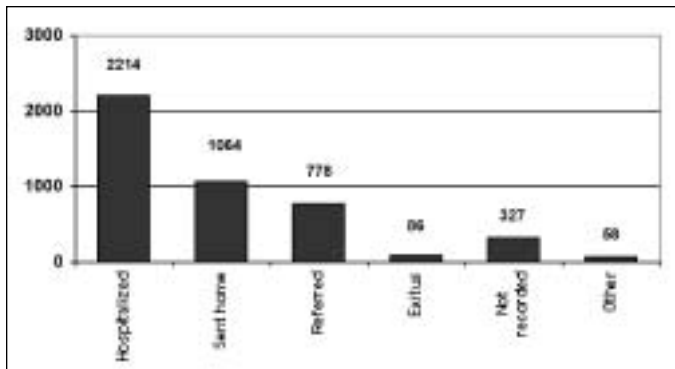


Figure 4. Discharge locations of trauma patients from the ED.

The majority of the trauma patients were sent from the ED to various surgical wards or to the intensive care unit (ICU) (48.9%); 23.5% were sent home, 17.2% were transferred to other hospitals, 1.9% were dead on arrival or died in the ED, and 1.3% refused further investigation or observation in the ED and left the hospital. Final destination was missing in 7.2% of the trauma admission forms. Figure 4 shows the discharge location of this group of patients.

Discussion

The types and causes of trauma may vary from one country to another and also within different regions of a single country. Trauma is the leading cause of death in the young population in Turkey, as in the Western societies, but the pattern is somewhat different in Turkey. As our study points out, the most frequent cause of trauma among all age groups and both sexes was motor vehicle accidents (70.3%) followed by falls, gunshot and stab wounds, and workplace accidents. Another study from Turkey also cited motor vehicle accidents as the leading cause of trauma in its region.⁷ A similar study in Iran reported that the most frequent causes of trauma were also motor vehicle accidents and falls.⁸ Trauma due to road traffic accidents, a problem resulting in substantial economic, social, and emotional loss all over the world, is said to be a more evident public health problem especially in developing countries without adequate infrastructure,^{7,9} but studies from the Western world also cite motor vehicle accidents as the leading cause of trauma.^{5,10} On the other hand, a study from Australia reported that the major type of nonfatal injuries was falls and the major type of fatal injuries was suicide attempts and motor vehicle accidents.¹¹

Injury death rates due to motor vehicle accidents is 3 per 10,000 per year in Turkey. This rate may seem close to the rate in the developed nations, which is 2 per 10,000 per year, but actually it is much higher when the number of motor vehicles per 1,000 people is considered, which is 150 in Turkey as opposed to 500 in developed countries. According to a recent report on police statistics, there were 7,000 immediate deaths due to motor vehicle accidents in 1 year and the cost of the road traffic accidents to the Turkish society was 12 billion dollars.

A number of factors such as the status of the infrastructure, the ratio of the number of motor vehicles to the population, and education level and socioeconomic conditions of the public lead to variations in trauma causes among countries or regions. In our region, the reason for motor vehicle accidents as the leading cause of trauma is probably the result of many factors such as excessive number of motor vehicles, inadequate infrastructure, public ignorance and lack of discipline to obey laws and regulations, inadequate inspections and control mechanisms, increased population, and deep cultural differences among different segments of the society due to rapid urbanization and migration.

The use of safety belts and crash helmets decreases the number of trauma-related injuries and deaths.^{12,13} One finding in our study that proves the detrimental effects of public ignorance and lack of discipline to obey laws and regulations and inadequacy of proper official inspections and control mechanisms on trauma is the rate of safety belt use by in-vehicle trauma patients. The compliance with safety belt use in our region is 5%. We believe that at least some of the major cranial and thoracoabdominal injuries could have been

prevented if this compliance rate were higher. Had there been regulations requiring the presence of airbags in automobiles in Turkey, we are sure that the trauma patient characteristics would also change, and that major cranial and torso trauma would decrease. Although we do not have enough data and studies about seat belt, helmet, and airbag use throughout the country, we believe that increasing public awareness in this matter will decrease deaths and disabilities due to motor vehicle accidents in Turkey.

The percentage of male trauma patients admitted to the ED is nearly 2.5 times higher than that of female patients (71.7% vs. 28.3%, respectively). This ratio is consistent with the literature. A study done in Uganda reported that 72.3% of the 5,210 admissions from trauma were male and 27.7% were female.¹⁴ This follows World Health Organization data, which report that injuries and traumatic deaths are more common in men than women.⁹

More men were injured as a result of trauma compared with women, and the association between sex and age was significant in this respect. Traumatized individuals are primarily young and middle-aged men. Other studies have also reported that trauma mainly affects productive age group and men.^{8,9,11} The reason that men are more affected by trauma may partially be explained by the high number of male drivers compared with female drivers, despite an increase in female drivers in recent years.

Motor vehicle accidents are the leading cause of injury in all age groups. In order to reduce mortality and morbidity related to motor vehicle accidents in childhood, it would be useful to educate the parents to use baby and child restraints and to supervise or accompany child pedestrians.

The second major cause of trauma after motor vehicle accidents in the 0- to 15-year-old age group is all types of falls. The number of falls decreases with advancing age and rises again in the elderly (56 years and over). The literature reports are similar, with falls being more frequent in childhood.^{15,16} Developing various protection mechanisms for target age groups at risk would be effective in decreasing the incidence of falls. Educating mothers and families and caretakers, eliminating potential causes of falls, placing barriers in appropriate settings, and adequate supervision would be useful in helping to prevent falls.¹⁷ Factors implicated in the excess number of morbidity and mortality due to falls in advanced age include chronic health problems in the elderly, environmental conditions posing high risk, and delay in medical care.¹⁸

Falling from trees constitutes 13.7% of all the falls. This is because of the number of falls from olive trees while harvesting the fruit in the late summer and early fall season and is a unique epidemiologic factor for the Bursa region. If these workers can be provided with better means of harvesting olives, many of these unfortunate injuries can be prevented.

It is evident that motor vehicle accidents and falls are more frequent in the summer season. Only 13.7% of falls are from trees, which, as mentioned, are more frequent in the late summer and early fall (adult falls). The rest of the falls are from windows and balconies and they are more frequent in the summer season (child falls). No significant seasonal difference was observed for other causes of trauma. There are other studies in which are found a similar correlation between the summer season and a high incidence of injuries due to road traffic accidents and falls. On the other hand, a study from Iran reported that motor vehicle accidents mainly occurred in the winter.⁸ In a study conducted in Brazil to

determine the incidence of childhood injuries, it was reported that accidents occurred more in the summer season (38.1%) when schools were closed.¹⁹ There are other studies reporting that falls in children occur more commonly in the summer season,^{20,21} but Benoit et al²² found a significantly higher number of childhood falls in the spring. The seasonal increase in trauma admissions in our study is from two reasons, one of which is the increased traffic on the roads in the summer. Bursa is on the main highway from Istanbul to Izmir, the first and third largest cities of the country, respectively. The other reason is also unique to the region. Injuries due to adult falls are increased in the late summer, especially those reported in the rural areas, because at this time of the year people climb up the trees to collect olives and other fruits.

The number of trauma patients admitted to the ED of the Uludag University Medical School within the last 5 years (1999–2004) has increased significantly. The reason for this increase is probably twofold. First, Bursa is a developing area undergoing rapid economic change and urbanization and, parallel with this, the rate of trauma is also increasing in the region. Second, our trauma unit was established in 1994 and the state EMS system was started in Bursa in 1995; both systems gradually developed, which also increased our trauma admissions.

The most frequent types of injuries reported in the trauma admission forms were skin and soft tissue lacerations, ecchymoses, abrasions, and hematoma, followed by multiple organ injuries, cranial injuries, and extremity fractures.

Moini et al⁹ reported the most frequently injured body sites as external body surfaces (53%), head/neck (43%), and extremities (42%). Differences in the classification and evaluation of anatomic localization of injuries in different studies may lead to a variation among the results. There are a number of studies investigating the relationship between injury site and age or injury mechanism. In most of these studies, however, the primary injury sites were the head and the extremities.^{19,23–25}

Nearly one-fourth (24%) of the patients admitted to our ED were discharged from the ED and sent home with discharge instructions such as to go to a hospital if they have headache, vomiting, weakness of a limb, or a change in their condition. Nearly half of the patients (49%) were hospitalized in different wards, and the remaining one-fourth were referred to other hospitals, died, or lost to follow-up with outcomes unknown. A study conducted in Jamaica by McDonald et al²⁶ reported that 16% of the trauma patients admitted within 1 year (1996) were hospitalized. On the other hand, in a study conducted in two separate hospitals of Uganda, 61% of 5,210 injured patients admitted to the ED were sent home after appropriate treatment, 37% were hospitalized, and 0.8% were dead on arrival.¹⁴ Hospitalization rate among trauma patients admitted to our hospital appears to be high. The reason for this is that our center is the biggest in the region and there are many severe and complicated trauma cases referred from other hospitals.

Conclusion

Currently, trauma constitutes a major health problem in Turkey. For appropriate trauma care, the EMS system and regionalized trauma care must be established throughout the country, but this is expensive and will take time. Therefore, development of effective trauma-preventive strategies should be the major thrust in developing countries. The first step in

developing such strategies is to identify the patterns and characteristics of trauma patients in various regions.

This study has revealed the trauma profile of our region. Road traffic accidents and falls are the major trauma types encountered in our region. A few simple measures such as appropriate intervention and referrals, education of physicians and medical personnel, and increasing public awareness in these types of trauma causes can significantly reduce injury-related burden, suffering, and mortality.

This study has also revealed the importance of keeping medical records of trauma patients. We know that this study would have been much better if we had had all the information pertaining to the trauma patients in their trauma charts. Trauma registry should be taken more seriously in our institution and in our country as well as in other developing countries.

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CLINICAL ISSUES

Uncontrolled Hemorrhage in a Patient with Pelvic Fracture: A Case Report

Magnus Södergren, MD, and Robert G. Hahn, MD, PhD

Department of Anesthesiology & Intensive Care, South Hospital, S-118 83 Stockholm, Sweden
robert.hahn@sodersjukhuset.se

Learning Objectives: 1) To be aware of the potential influence of episodic rebleeding on hemodynamic stability in patients with traumatic pelvic fracture, and 2) to be aware that animal experiments demonstrate a better outcome if fluid resuscitation does not completely restore the arterial blood pressure in the presence of major vascular injury.

Neither author has any conflicts of interest to disclose.

Abstract

A 73-year-old woman arrived at hospital with multitrauma, including a nonoperative pelvic fracture. Fluid resuscitation aimed at restoring normal hemodynamics was started, but hypotensive events developed on four occasions when intensive fluid resuscitation had raised the systolic pressure to just above 100 mm Hg. The blood volume expansion resulting from transfusion of erythrocytes and plasma and the infusion of clear fluid corresponded to six times her blood volume during the first 21 hours in hospital. The clinical course suggests the presence of episodic rebleeding from the pelvic fracture.

Pelvic fractures are often accompanied by major bleeding, which is potentially life-threatening.^{1,2} Current recommendations for treatment are to stabilize the bony pelvis (if anatomically possible) while restoring normal tissue perfusion through administration of fluids and blood products.^{3,4} In recent years, however, animal experiments have raised concerns as to

whether such fluid treatment may aggravate ongoing acute bleeding or lead to rebleeding from surgically inaccessible vessels.^{5,6} While most orthopaedic injuries will stop bleeding spontaneously, allowing for completion of resuscitation, venous bleeding from the posterior presacral plexus is a notable exception. We report on a patient with pelvic fracture whose clinical course showed a striking resemblance to the “transient responders” seen in animal studies of aggressive volume resuscitation during acute hemorrhage.

Case Report

A 73-year-old woman was found below a third-floor window after an attempted suicidal jump. At the arrival of the ambulance she was conscious, not in pain, but confused. Her left arm had two open fractures (wrist and elbow) and was severely distorted. The left thigh was bruised. The blood pressure was unrecordable and the heart rate high. Breathing was not affected at first, but she became slightly dyspneic during transport to hospital, and was treated with 10 liters of O₂ 100% delivered by a nonrebreather face mask. On arrival in the emergency department (ED), her systolic blood pressure was 45 mm Hg (external cuff); SaO₂, 75%; body temperature, 37°C; and capillary Hb, 12.1 g/dL. Gross examination revealed a malpositioned left shoulder, an open wrist fracture of the radius and ulna, crepitational fracture of costa IV, and an unstable fracture of the pelvis involving the sacrum and the left acetabulum, ala of ilium, and inferior ramus. Past medical history was not available.

Fluid resuscitation began with 1 liter of Ringer’s acetate solution and, within 10 minutes, the systolic pressure rose to 95 mm Hg. During the subsequent 30 minutes, another 1 liter of Ringer’s solution and 2 liters of a Ringer’s-dextran mixture were infused. After tracheal intubation under ketamine anesthesia, the patient was transferred to the operating room (OR), where the pelvic fracture was stabilized with a Hoffman instrument. Bilateral pleural drainage was also applied, without significant return of blood or air from either chest cavity. Ultrasound showed minimal fluid in the abdominal cavity. Hemodynamic instability persisted and was treated with ongoing fluid resuscitation; angiographic embolization was not an available option at that time. During the operation, the patient developed ventricular fibrillation, which required four defibrillations.

Four hours later, the patient was transferred to the intensive care unit (ICU) where intravascular catheters for monitoring the arterial and central venous pressures were inserted. Computed tomography (CT) on day 2 showed anterior displacement of the spleen and left kidney owing to massive retroperitoneal hematoma. There was no damage to the internal organs, including the aorta. Peripheral edema was particularly pronounced around the shoulders. On day 5, the fracture of the humerus was fixed and the dislocated shoulder was repositioned. The patient was weaned off the ventilator after a long period in the ICU, but eventually died 4 months after the injury, owing to respiratory failure.

After the initial fluid resuscitation, the patient had four markedly hypotensive events despite liberal volume support, which, during the first 21 hours in hospital, comprised 10.8 liters of erythrocytes, 7.2 liters of stored plasma, 3.2 liters of fresh-frozen plasma, 8 liters of Ringer’s solution, 2 liters of Ringer-dextran, 1 liter of glucose 2.5%, 600 mL of bicarbonate buffer, and 350 mL of thrombocytes (Fig. 1). The total fluid losses in surgical drains and external bleeding amounted to 3.6 liters.

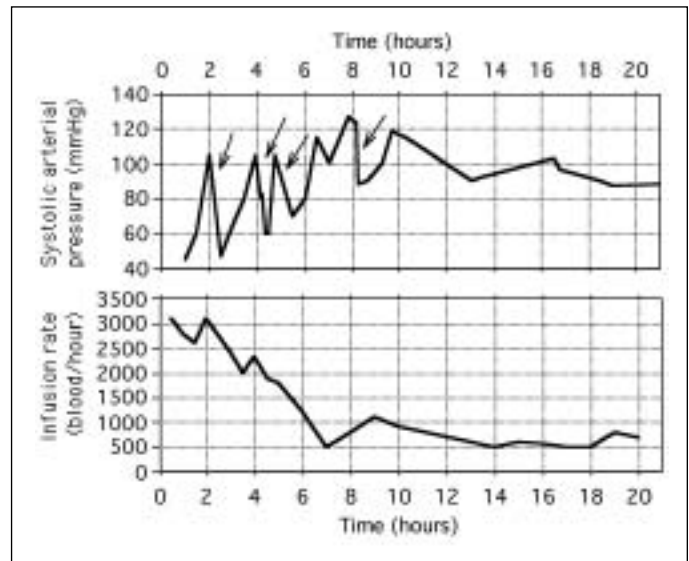


Figure 1. Systolic arterial pressure (top) and the rate of volume support (bottom) in a multitraumatized woman with pelvic fracture. To obtain the latter parameter, we converted each type of fluid into its corresponding blood volume effect by using the following weights: erythrocytes and plasma = 1, Ringer-dextran = 0.5, and Ringer’s solution = 0.3. The result is expressed as the sum of the volume effect of all fluids given per hour. Arrows indicate sudden development of hypotension after intensified fluid therapy.

Discussion

The survival of patients with a pelvic fracture is greatly affected by their hemodynamic stability on arrival in hospital.⁷ While there is a general consensus that an aggressive multidisciplinary approach to hemorrhage control is mandatory,¹ the immediate goals of fluid resuscitation are controversial. Restoration of intravascular volume and composition is clearly important in the long term to sustain tissue perfusion, yet clinical trials have not consistently documented improved survival with prehospital volume support in patients with uncontrolled hemorrhage.^{8,9} A large body of animal research suggests that early aggressive volume support, in the presence of ongoing hemorrhage, possibly increases mortality through rebleeding, dilution of clotting factors and the hematocrit, and induced hypothermia.^{5,6,10-14}

Stern et al⁶ resuscitated pigs with a 4-mm laceration in the lower aorta to mean arterial pressures of 40, 60, and 80 mm Hg and found that attempts to restore a normal blood pressure markedly increased mortality. Even when the arterial pressure remained low, survival could be improved by limiting resuscitation with crystalloid⁵ and hypertonic¹⁰ fluid to between 30% and 50% of the recommended amount, and by infusing the fluid at a lower rate.^{10,11} The benefits of a limited fluid program in pigs received support from experiments in rats.¹²⁻¹⁴ The increased blood flow rate and/or increased transmural pressure following fluid resuscitation apparently disturbs immature blood clots in the walls of bleeding vessels^{6,14,15} and the subsequent rebleeding is characterized by a sudden drop in flow rate after the initial rise.^{10,16} These experiences from animal experiments are similar to the clinical course of the patient reported here, to whom fluid was given vigorously. The volume support administered during the first 21 hours in hospital was sufficient to expand the blood volume to 30 liters, six times her normal blood volume. The measured blood loss was quite small. The clinical course,

together with the CT scan, suggests that “third-space” loss of fluid was substantial, while blood gradually accumulated in the extravascular retroperitoneal space. The blood pressure curve shows that the patient repeatedly became hypotensive despite (or perhaps because of) the rapid administration of fluids. These data are consistent with repeated rebleeding from surgically inaccessible wounds.

Figure 1 illustrates the intensity of the volume support and the systolic pressure during the day of admission. Apart from the short period of cardiac arrest, four events with a rapid fall in blood pressure occurred when enough volume support was given to raise the systolic pressure to 100 mm Hg. These events were most probably due to relative hypovolemia, which is surprising as the rate of infusion of fluid was high, accessible sources of bleeding had been arrested, and a Hoffman instrument had been applied early on to fix the pelvic fracture. Stabilization using an external frame, a pelvic binder, or percutaneous fixation is often employed to stop bleeding from a pelvic fracture, although in a lateral compression injury such as this patient's, it may not be of great benefit. Early stabilization does allow for improved nursing care and earlier patient mobility. Damage to major arteries may require a direct surgical approach² or angiographically directed embolization; these options could have been helpful in the present case, but were not available in the hospital at the time.¹⁷ The patient eventually stabilized at a systolic pressure of 90 mm Hg and was allowed to remain at this level without further fluid administration.

Vigorous fluid therapy, resulting in a rise of arterial pressure followed by a marked drop—the classic “transient responder” pattern—causes the disruption of immature blood clots. Such disturbances result in rebleeding, which increases the total blood loss and prolongs the period of hemodynamic instability. Hemodilution-induced changes in hemostasis and blood viscosity may contribute to such rebleeding, but mechanical forces associated with a rise in the blood flow rate and/or arterial pressure associated with vigorous fluid resuscitation constitute the most important mechanism.^{5,10-15,18}

Hypoperfusion leading to organ system failure is a significant concern in any patient, particularly an elderly one, and older age is a relative contraindication to deliberate hypotensive resuscitation. In this case of difficult-to-control pelvic bleeding, however, where there were no surgical or angiographic options available, targeting a lower than normal blood pressure early in the resuscitation might have prevented significant rebleeding and avoided the necessity for such massive resuscitation. Hypotensive resuscitation is already being practiced by many clinicians in patients with gastric bleeding or a ruptured aorta, but its application in unselected trauma patients is controversial.^{19,20} The advent of systemic procoagulant agents (e.g., recombinant human factor VIIa) may someday contribute to the care of patients such as the one reported here, but at present this therapy is expensive and unproven.²¹

Summary

In summary, this case presents an interesting and all too common clinical dilemma, which invites a solution in contradiction to the usual standard for resuscitation from shock. Tolerance of a lower-than-normal blood pressure and deliberate slowing of fluid administration should be considered in any case of ongoing hemorrhage in which an immediate anatomic solution is not available. In all patients,

but particularly the elderly, close clinical observation and moment-to-moment titration of therapies is required. Early and frequent assessment of arterial blood gases and serum lactate level will provide evidence of the depth of shock, and can help the clinician to achieve a balance between adequate perfusion and the risk of rebleeding. New monitoring technology currently under clinical study may make this process more rapid and reliable in the near future.^{22,23} While individual resuscitation strategy will always depend on details of the patient and presentation, deliberate hypotension is one option the clinician should consider when confronted by persistent or recurrent hemorrhage that is not anatomically correctable.

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Rhabdomyolysis: A Historical Review with Two Illustrative Cases

Roya Yumul, MD, PhD, Stephen N. Steen, SCD, MD, Adebambo Osibamiro-Sedun, MD, Adejare Windokun, MD, and Rebecca L. Sapien, BS

Department of Anesthesiology

Martin Luther King, Jr., Hospital

Charles R. Drew University of Medicine and Science

Los Angeles, CA 90059 USA

ryumul@dhs.co.la.ca.us

Learning Objectives: 1) To identify the indicators of rhabdomyolysis, 2) to review the options for the management of patients with rhabdomyolysis, and 3) to appreciate the need for clinical vigilance and repeated examinations.

Abstract

Rhabdomyolysis is not an uncommon occurrence; it has been observed from antiquity. The etiology of this long-standing condition is diverse. We report two classic cases that were managed successfully.

Rhabdomyolysis refers to disintegration of striated muscle.¹ The rhabdomyolysis syndrome was initially observed in the 13th century^{2,3} BCE⁴ and was presumed to be caused by the human ingestion of migratory quail that had eaten hemlock seeds.^{5,6} In 1884, the first report of a presumptive metabolic disorder was reported in which horses developed weakness, bilateral paresis, and muscular tremors, and then myoglobinuria.⁷ The first cases of crush syndrome and acute renal failure (ARF) were reported during the Sicilian earthquake in Messina⁸ in 1908, and in the German medical literature during World War I.⁹ In 1910, the classic trial of symptoms consisting of muscle pain, weakness, and brown urine was reported by Meyer-Betz.^{10,11}

In 1924, physicians near Könisberger Haff shores along the Baltic coast recognized an outbreak of an illness manifested by sudden, severe muscular rigidity.¹²⁻¹⁵ Other outbreaks resembling Haff disease were reported from Sweden and the Soviet Union from 1934 until 1984.¹⁶⁻¹⁹ Similar outbreaks occurred in the following 9 years and affected approximately 1,000 individuals. Recently, Buchholz and associates¹² described in detail six U.S. cases that occurred in two clusters and as one sporadic case in California and Missouri, respectively. Haff disease has been identified as being caused by persons eating Bigmouth Buffalo fish (*Ictiobus cyprinellus*), a bottom-feeding freshwater fish similar to carp.²⁰

Bywaters and Beall²¹ identified the first causative association between rhabdomyolysis and ARF during World War II, following the observation of victims of the bombing of

London during the Battle of Britain in 1940. Bywaters²² later published an overview of this syndrome.

The term “coturnism” was coined in 1972 by Samuel Bessman for this dietary-toxicologic syndrome. The articles written by Grivetti²³ and by Poels and Gabreels²⁴ describe in detail the fascinating history of this disease.

We present two cases of rhabdomyolysis that show its successful management.

Case Report 1

A 29-year-old man presented to the emergency department with the following history, which he reported was of an unknown period of time, and after heavy alcohol use the preceding day. He was noted to have a swollen, severely tender, firm right buttock that was nonerythematous with no drainage and no sensory deficits. He was unable to dorsiflex or plantar flex the right big toe. He had no significant medical or surgical histories. Initial laboratory values were Na, 128; K, 5.9; Cl, 87; BUN, 61; CR, 3.4; Ca, 7.0; glucose, 187; CK, 21,985, with elevated liver enzymes; Hgb, 19.8 g/dL; Hct, 58; WBC, $17.3 \times 10^3/\mu\text{L}$; and platelets, $224 \times 10^3/\mu\text{L}$. The blood alcohol level was 29 mg/dL and he tested positive for cocaine. The urine was dark brown and positive for myoglobin. After hydration with approximately 4 liters of crystalloid, a repeat set of laboratory determination showed Na, 128; K, 5.9; BUN, 33; CR, 1.4; CK, 41,779; Hgb, 7.4 g/dL; Hct, 21; and platelets $92 \times 10^3/\mu\text{L}$. At this time, arterial blood gas analyses showed a pH of 7.3, paCO_2 of 33 mm Hg, paO_2 of 92.4 mm Hg, HCO_3^- of 15.2 mEq/L, base deficit of -9.3 mEq/L, and O_2 saturation of 96% on room air.

A diagnosis of compartment syndrome was made and the anesthesia department was notified. Aggressive fluid resuscitation was initiated after a large-bore intravenous (IV) and an arterial line were placed with approximately 6 liters of crystalloid being administered to this acidotic patient. He was transferred to the operating room for a surgical decompression fasciotomy under general anesthesia. A rapid-sequence induction technique was performed using fentanyl, midazolam, etomidate, and rocuronium with isoflurane for maintenance. Surgery lasted 40 minutes. Intraoperatively, the patient received 3,500 mL of lactated Ringer's solution/normal saline. The gluteus maximus was exposed and normal tissue with no evidence of necrosis was noted. The wound was packed and the patient was brought to the postanesthesia care unit and kept intubated for further resuscitation.

Postoperative laboratory values revealed progressive renal failure with BUN of 73, CR of 3.2, and hypocalcemia. The patient later became anuric and developed renal failure and atrial fibrillation. He was treated with diltiazem HCl by IV drip and then transferred to the intensive care unit and hemodialyzed. After 30 days, he was discharged home with resolved renal failure (BUN, 18; CR, 1.1; K, 3.9; Na, 140) and medicated with diltiazem HCl and vitamins.

Case Report 2

A 21-year-old man was brought into the emergency department on 8/13/2002 with fracture of the left femur following a motor vehicle crash. He was noted to have a medical history of hip screws at age 7 and 15 for slipped femoral growth plates. Physical examination at time of presentation revealed broken glass shards over the head and neck, slurred speech, and the smell of ethanol on his breath.

None of the authors have any conflicts of interest to disclose.

Vital signs were a blood pressure of 130/80 mm Hg, pulse rate of 113 beats per minute, respiratory rate of 26 per minute, and a temperature of 98.7°F. Examination of the cranial nerves revealed no deficit. The chest was clear to auscultation bilaterally. Examination of the cardiovascular system was normal with a regular rate and rhythm and heart sounds S₁ and S₂ only; there were no murmurs. The abdomen was obese, soft, nontender; bowel sounds were normal and there was no organomegaly. Rectal examination was within normal limits.

Examination of the extremities revealed a comminuted fracture of the left femur, comminuted fractures of the distal third of the left fibula and tibia, and a right midshaft fracture of the tibia and fracture, which were all painful and tender to palpitation. The dorsalis pedis was 2+ on the left and positive using a Doppler signal on the right. Computerized tomography studies of the abdomen, pelvis, cervical spine, and head were all within normal limits. Initial laboratory determinations were Na, 139; K, 3.5; CR, 102; HCO₃, 26; BUN, 14; CR, 1.4; glucose, 126; Ca, 9.6; Hb, 15.1; Hct, 43.4; WBC, 13.3 x 10³/mL; platelets, 307 x 10³/μL. The ECG showed normal sinus rhythm. At the preoperative anesthesia visit, the patient was scheduled for open reduction and internal fixation of the left femur and intramedullary rodding of the left and right tibia under general anesthesia.

Preinduction vital sign values were blood pressure of 129/65 mm Hg, pulse rate of 129 beats per minute, respiratory rate of 20 per minute, and temperature of 99.1°F. Induction was with etomidate and fentanyl; suxamethonium was used to facilitate endotracheal intubation with a size 8.0 cuffed tube under direct vision. Rocuronium was used to facilitate ventilation. Anesthesia was maintained with oxygen in nitrous oxide 50% with desflurane and intermittent doses of fentanyl. Standard and invasive monitoring devices were placed. The patient was positioned on an Amsco-OrthoVision orthopaedic and fracture table (Steris Corp., Mentor, Ohio) for the surgery. Vital signs ranged from 80–140, 40–80, and 90–130 mm Hg. Normal saline, 9,500 mL, was infused. The surgery lasted 7 hours and 10 minutes. Blood loss was estimated to be 2,000 mL and the patient was transfused with 4 units of packed red blood cells. The patient was transferred, intubated, to the postanesthetic recovery room.

At 03:30 on 8/16/02, the patient was noted to have the following vital signs: blood pressure, 124/72 mm Hg; pulse rate of 155 beats per minute, respiration of 12 on ventilator settings of A/C RR 12, V_T 800, F_IO₂ 1.0, and PEEP of 5 cm H₂O. The arterial blood gas values were pH, 7.33; PaCO₂, 51 mm Hg; and PaO₂, 249 mm Hg. The laboratory determination revealed Na, 138; K, 4.5; Cl, 110; HCO₃, 23; BUN, 17; CR, 1.8; glucose, 105; AST, 765; ALT, 185; bilirubin, 1.1; alkaline phosphatase, 28; CPK, 78,000; WBC, 10.4 x 10³/μL; Hgb 7.9, g/dL; Hct, 27.3; platelets, 110 x 10³/mL; PT/PTT, 13.4/36.9; and INR, 1.6. Examination of the extremities revealed that the left lower extremity was warm, with a palpable dorsalis pedis; the extremity was edematous, with a capillary refill >2 seconds. The right lower extremity was cold from the middle lower leg to the foot, with no pulses noted. The urine was dark. A diagnosis of right anterior compartment syndrome was made and the surgeon was notified. The patient was resuscitated with hydration and prepared for fasciotomy under general anesthesia, and a four-compartment fasciotomy was performed in the postanesthetic recovery room. The surgical findings were muscles under tension with evidence of unhealthy muscle within the compartments.

The postfasciotomy results revealed that the posterior tibial artery was positive with Doppler but the dorsalis pedis was absent. Postoperatively, the patient was maintained on the ventilator (paralyzed). His right lower limb compartment syndrome worsened and he underwent above-knee amputation on the right leg on 8/24/02. He subsequently developed respiratory insufficiency, as characterized by increased airway pressures and hypoxemia. The arterial blood gas values on 100% O₂ were 7.309, 49, 55, 24.7, -1.2, and 86.8%.

The patient's respiratory failure worsened and he developed clinical features of adult respiratory distress syndrome. He was maintained on ventilator support. There was worsening of renal failure, with oliguria (160 mL over 24 hours) and BUN of 79 and CR of 5.5. Dialysis was started on 8/26/02. Following a tracheostomy under general anesthesia on 9/17/02, the patient gradually improved and was transferred for further rehabilitation.

Etiology

Rhabdomyolysis is not an uncommon disorder and its etiology may be diverse.²⁴ Rhabdomyolysis may be inherited (Table 1) or acquired. The most common hereditary cause of rhabdomyolysis is McArdle disease, which is related to myophosphorylase deficiency. If rhabdomyolysis is acquired, it may be subdivided with some overlap into the groups shown in Table 2. Table 3 shows some causes primarily related to drugs and toxins. As can be seen from these tables, a multitude of factors may cause this condition; almost anything may produce rhabdomyolysis!

Crush injuries following earthquakes are a major cause of rhabdomyolysis. An average of 1,000 earthquakes with intensities of 5.0 or greater on the Richter scale are recorded each year.²⁵ With wars and an increase in terrorist activities, one may expect further instances of rhabdomyolysis, which will overwhelm presently available resources of personnel and equipment (e.g., dialysis equipment) for treating the injured.

Table 1. Inherited Causes of Rhabdomyolysis

Deficiencies of Glyco(Geno)Lytic Enzymes

- Myophosphorylase (McArdle disease)
- Phosphorylase kinase
- Phosphofructokinase (Tarui's disease)
- Phosphoglycerate mutase
- Phosphoglycerate kinase
- Lactate dehydrogenase

Abnormal Lipid Metabolism

- Carnitine palmitoyltransferase deficiency I and II
- Carnitine deficiency

Other Genetic Disorders

- Idiopathic rhabdomyolysis
- Myoadenylate deaminase deficiency
- Malignant hyperthermia
- Neuroleptic malignant syndrome

Table 2. Acquired Causes of Rhabdomyolysis

<i>Traumatic: Direct Muscle Injury</i>	
	Crush
	Burning, freezing
	Electric shock, lightning stroke
<i>Ischemic Injury</i>	
	Compression
	Vascular occlusion
	Sickle cell trait
<i>Metabolic/Metabolic Disorders</i>	
	Diabetic ketoacidosis
	Nonketotic hyperosmolar coma
	Hypothyroidism
	Hypophosphatemia
	Hyponatremia
	Hypokalemia
<i>Infectious/Infections</i>	
	Bacterial
	Viral
<i>Inflammatory</i>	
	Polymyositis
	Dermatomyositis
<i>Exercise/Excessive Muscle Exercise</i>	
	Sports and military training
	Status epilepticus
	Status asthmaticus
	Convulsions
	Prolonged myoclonus, acute dystonia
<i>Heat-related Syndromes</i>	
	Toxic shock syndrome
	Heat stroke

Under ischemic injury, we may consider compartment syndrome. This condition results from a confined swelling within a muscular compartment, which, if untreated, may result in a cessation of capillary circulation, ischemia, and necrosis of muscle and nerves. Tiwari et al²⁶ recently published a detailed review of acute compartment syndrome with reference to the abdominal compartment syndrome and the limb compartment syndrome, describing the etiology, treatment, and outcome of each of these syndromes.

In the leg, the anterior compartment is commonly affected and "the commonest fractures in limb compartment syndrome are those of the tibial shaft."²⁷ Comminuted fractures are most prone to compartment syndrome and may reflect the high energy required to cause this type of fracture; operative treatment of fractures with intramedullary nailing can lead to limb compartment syndrome.^{26,27} This situation occurred in the second case report presented here, and was diagnosed by clinical vigilance and repeated examinations.

Alcoholism is a common cause of rhabdomyolysis. This may be secondary to alcohol-related trauma, seizures, or coma or may be due to the direct effect of ethanol on skeletal

Table 3. Drugs and Toxins Known To Cause Rhabdomyolysis

Alcohol (ethanol)	Loxapine
Amoxapines	LSD (lysergic acid diethylamide)
Amphetamines	
Amphotericin B	
Anticholinergic syndrome	Malignant hyperthermia
Antihistamines	Mercuric chloride
	Methadone
Barbiturates	Morphine
Benzene	
Bezafibrate	Neuroleptics
Carbenoxolone	Oxprenolol
Carbon monoxide	
Chloralose	Paracetamol
Chlorpromazine	Paraphenyl diamine
Clofibrate	Pentamidine
Copper sulfate	Phencyclidine
	Phenformin
Diazepam	Phenylpropanolamine
Dihydrocodeine	Phenylzene
Diuretics	
L-Dopa withdrawal	Quail ingestion
	Haff disease
Ethylene glycol	Brown spider bite
	Snake bite
Fenfluramine	Hornet/wasp sting
Fluphenazine	
	Rohypnol
Gasoline sniffing	
Glutethimide	Salicylates
	Stelazine
Haloperidol	Strychnine
Heroin	Suxamethonium
Isoniazid	Theophylline
Isopropyl alcohol	Toluene (paint sniffing)
Lindane	Vasopressin
Lithium	
Liquorice	Zinc phosphide

muscle, resulting in both chronic myopathy and acute rhabdomyolysis. It is believed that ethanol causes direct sarcolemmal injury, leading to increased sodium permeability and subsequent accumulation of calcium. Hypophosphatemia may also be an important precipitant because the ability of muscle cells is reduced.

There are many reports on rhabdomyolysis following propofol use by children and adults, but the authors question a direct cause-and-effect relationship (not having observed or heard of same from colleagues). Drugs such as lipid-lowering agents and antibiotics have been implicated as etiologic agents in statin-associated rhabdomyolysis,^{28,29} which may occur in patients with normal creatine levels.³⁰ Prolonged immobilization, as for a patient in the lithotomy position³¹⁻³³ or the Lloyd-Davies position,^{34,35} may result in a compartment syndrome.

Complications

Complications are due to the local effects of muscle injury and the systemic effects of released muscle components. These complications include 1) hypovolemia from hemorrhage and influx of fluid to necrotic muscle, 2) cardiac arrest and arrhythmia (due to hyperkalemia, which is potentiated by hypocalcemia resulting from calcium deposition in necrotic muscle), 3) compartment syndrome, 4) disseminated intravascular coagulation, and 5) ARF.

Treatment

As indicated by Dhawan et al,³⁶ treatment consists of the following six steps: 1) hydration, in order to maintain adequate hydration and urinary output, 2) alkalinization of the urine to prevent dissociation of myoglobin to its nephrotoxic metabolites, 3) diuretic therapy to dilute the nephrotoxic metabolites, 4) normalization of electrolyte disturbances (e.g., hyperkalemia [when >6.5 mEq/L] by the administration of glucose and insulin, hyperphosphatemia by oral administration of CaCO_3 or $\text{Ca}[\text{OH}]_2$), 5) dialysis, if indicated (e.g., in uncontrolled hyperkalemia, acidosis, uremic encephalopathy), and 6) supportive therapy (e.g., fresh-frozen plasma is indicated in the event of disseminated intravascular coagulation when associated with bleeding, and decompressive fasciotomy, in the case of a compartment syndrome to prevent further local tissue necrosis).

Discussion

Myoglobin, a 17,000 molecular weight oxygen-binding protein, is present in skeletal muscle at a concentration of 1 g/kg. Upon skeletal muscle damage, myoglobin is released into the bloodstream and filtered therefrom by the kidneys. The visible discoloration of urine by myoglobin indicates both massive and acute muscle destruction (rhabdomyolysis). The kidneys may be occluded, with resultant damage (e.g., tubular necrosis or kidney failure). Myoglobinuric renal failure occurs within the clinical scenario of rhabdomyolysis in about 30% of patients.

At a urine pH less than 5.6, myoglobin is transformed to ferrihematin, which precipitates in the proximal tubule. Renal damage is facilitated by hypovolemia and acidic urine. Oligonuria is associated with hyperkalemia, hypocalcemia, anion-gap acidosis, and rapid azotemia because of the hypercatabolic state. Early and aggressive fluid hydration may prevent complications by rapidly eliminating the myoglobin from the kidneys. The hydration needs with muscle necrosis may approximate the massive fluid volume needs of a severely burned patient.

Evidence of rhabdomyolysis can range from a subclinical rise of creatine levels to a medical emergency comprising interstitial and muscle cell edema, contraction of intravascular volume, and pigment-induced ARF.

Serum creatine kinase ≥ 5 times the normal (reference ranges: males, 38-174 \bar{U} ; females, 96-140 \bar{U}) is a primary diagnostic indication of rhabdomyolysis, as observed in both case reports presented here. This elevation is so great that other causes (e.g., myocardial infarction) may be excluded. In addition, the CK-MM isoenzymes constitute at least 98% of the total volume. Other significant biochemical findings are hyperkalemia, hypocalcemia, hyperphosphatemia, and

hyperuricemia. Metabolic acidosis may result from release of phosphate, sulfate, uric acid, and lactic acid from the muscle. The pathogenesis and management of rhabdomyolysis have been well described in detail by Dhawan et al³⁶; the search for the toxic mechanisms has also been well described by Grivetti.²³

Conclusions

Rhabdomyolysis is not an uncommon event and may result from a variety of conditions. The complications thereof can be life-threatening. As Dhawan et al³⁶ determined, "The treatment in the acute phase consists of maintaining an adequate circulating volume and sufficient diuresis to prevent renal complications. The prognosis of adequately treated rhabdomyolysis is excellent."

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Guidelines for Management of Mechanical Ventilation in Critically Injured Patients

Maureen McCunn, MD, MIPP,¹ Anne J. Sutcliffe, MBChB, Walter Mauritz, MD, PhD, and the ITACCS Critical Care Committee*

*Medical Director, Neurotrauma ICU
Physician Director, Continuous Renal Replacement Therapies
Acting Medical Director, Kernan Rehabilitation Hospital ICU
R Adams Cowley Shock Trauma Center
22 South Greene Street
Baltimore MD 21201 USA
mmccunn@umm.edu*

Premise

Patients suffering severe trauma are at high risk of developing respiratory failure: both acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) (Appendix 1). Management strategies for these patients should begin upon arrival at the trauma center/emergency department by initially identifying who is most likely to develop severe respiratory insufficiency. The goal is to institute therapies early (e.g., “open lung” or “protective” lung ventilation) in the emergency department, operating room, and in the intensive care unit (ICU) in an effort to lessen the degree or to prevent the formation of atelectasis and/or parenchymal damage to the lung.

Statement of the Issue

One of the most basic and paradoxically advanced clinical skills in the practice of anesthesiology and critical care medicine is the management of mechanical ventilation. Ideally,

*ITACCS Critical Care Committee Guidelines Participants: Michael J. A. Parr, FRCP, FRCA, FANZCA, FJFICM, Richard P. Dutton, MD, MBA, Lewis J. Kaplan, MD, FACS, James G. Cain, MD, Linda Pelinka, MD, PhD, Charles E. Smith, MD, Keiichi Tanaka, MD, Adolph H. Giesecke, MD, Heather Lee Bailey, MD, Freddy Lippert, MD, John K. Stene, MD, PhD, Eran Talor, MD, and Mary Hyder, MD

Dr. McCunn, representing the authors, does not have any conflicts of interest to disclose.

mechanical ventilation should potentiate alveolar recruitment, optimizing intrapulmonary gas distribution, and narrowing time-constant discrepancies. Ideal ventilator management should distribute pressure and volume to dependent and nondependent regions proportionally.

Recommendations for ventilator management from several randomized, prospective trials are suggested in Table 1. These recommendations refer to ALL locations where patients following injury may be located: the emergency department, operating theatre, and ICUs. For patients with respiratory failure who require surgery, *if the ventilator settings in the ICU exceed the capability of the operating room ventilator, then the patient should be taken to the operating room on the ICU ventilator, and remain on the ICU ventilator for the surgical procedure.* The goal, from admission onward in these high-risk patients, is to do no further harm.

Table 1. Recommendations for Ventilator Settings

- Tidal volumes 6–8 mL/kg
- PEEP higher than the lower inflection point
- Limit peak/plateau pressure to <35 cm H₂O
- Adjust I:E ratio and respiratory rate as needed to achieve above
- Wean FiO₂ to obtain PaO₂ 80–100 mm Hg (or an oxygenation saturation of 93–97%)
- Early conversion to pressure-limited modes of ventilation

Atelectasis

Recent studies provide data that support the use of positive pressure and low oxygen concentrations to minimize or reverse the formation of atelectasis during mechanical ventilation and general anesthesia. Atelectasis formation is also seen in the ICU in dependent lung zones.

Within 5 minutes of induction of general anesthesia, increased densities appear in the dependent regions of both lungs.¹ They develop with both intravenous and inhalational anesthesia and whether the patient is breathing spontaneously or is paralyzed and ventilated mechanically.² Although atelectasis may not appear to be severe on chest radiograph

(CXR) or computed tomography (CT) scan, collapsed lung comprises four times more lung tissue than aerated regions. For this reason, a seemingly small amount of compressed lung tissue can account for a significant increase in shunt fraction. Of the three basic mechanisms of atelectasis formation that have been proposed, compression and absorption atelectasis, rather than loss-of-surfactant atelectasis, seem to be the major offenders during anesthesia.³ Another contributor to the formation of atelectasis is high-inspired oxygen concentration. An FiO₂ of 1.0 preinduction and prior to extubation both contribute to atelectasis formation,⁴ and may explain a significant part of hypoxia seen in the postanesthesia care unit (PACU).⁴ Inspired oxygen concentrations of 0.8 and 0.3 during anesthesia have been studied, and both concentrations result in a decrease in atelectasis formation and shunt fraction.⁵ However, during the acute trauma resuscitation phase, patients in hemorrhagic shock may require 100% oxygen to augment O₂ delivery to ischemic tissues. In addition, the potential for a difficult airway may be magnified in patients with vomiting, facial injuries, or major cervical spine, tracheal, or soft tissue neck injury. For these reasons, preoxygenation with 100% O₂, or early hyperoxygenation postintubation is routinely practiced.

Fortunately, atelectasis formation with high-inspired oxygen concentrations can be avoided or minimized through the use of either vital capacity maneuvers⁶ or positive end-expiratory pressure (PEEP).⁷

Ventilator-Associated Lung Injury

A contributing variable to the development of acute respiratory failure may be iatrogenic:ventilator-associated lung injury. There is increasing evidence that “traditional” high-volume, low PEEP ventilator settings induce parenchymal damage through overdistension or “stretch” of the aerated lung and repeated opening and closing or “shear” of the collapsed derecruited lung.^{8,9} This may result in disruption of the normal alveolar integrity and can actually perpetuate the inflammatory response and lead to “bio-trauma.”¹⁰ These phenomena have been shown to occur in healthy lungs^{11,12} and in previously damaged lungs.

Several researchers have published data that show that ventilator management using low tidal volumes (6–8 mL/kg), limiting distending pressure (transpulmonary, or plateau pressure <35 mm Hg), and setting PEEP above the lower inflection point on the pressure-volume curve may decrease mortality, decrease ICU length of stay, and decrease ventilator days.^{13,14} The largest prospective, randomized study to be published to date is the multicenter ARDSnet trial.¹⁵ Patients with ALI/ARDS were randomized in a multicenter trial to either “traditional” tidal volume ventilation (12 mL/kg) and end-inspiratory plateau pressure <50 cm H₂O or to “low volume” ventilation (6 mL/kg) with end-inspiratory plateau pressure <30 cm H₂O. The study was stopped early, after the enrollment of 861 patients, because of a significant decrease in mortality in the study arm group of patients (39.8 vs. 31%, respectively; *P* = 0.007).

ARDS in Trauma

Trauma is second only to sepsis in regard to risk factors for ARDS; the incidence of ARDS in the trauma population is

Table 2. Risk Factors for ARDS in Trauma Patients

- Shock
- Pulmonary contusion
- Fractures
- Multiple transfusions
- Pneumonia
- Injury severity score >16
- Trauma score <13
- +/- admission lactate, pH, base deficit, serum bicarbonate
- Gastric aspiration
- Near-drowning
- Smoke inhalation
- Fat embolism
- Sepsis
- Blunt injury
- Surgery to head
- Disseminated intravascular coagulation

12% to 39%.¹⁶ Of the 14 risk factors identified as highly associated with subsequent development of ARDS (Table 2), 8 factors (pulmonary contusion, fractures, shock, multiple transfusions, gastric aspiration, near-drowning, smoke inhalation, and fat embolism) may be seen *early* in the trauma patient and 3 may be seen *late* (several days or weeks) following admission to the trauma center (pneumonia, sepsis, disseminated intravascular coagulation). In a study by Hoyt et al,¹⁷ a total of 3,289 trauma patients were followed prospectively and those who later developed ARDS were compared with those in the cohort who did not develop ARDS. Logistic regression analysis between these groups showed blunt mechanism of injury, Injury Severity Score, >16; Trauma Score, <13; and surgery to the head to be significant risk factors. A more recent publication demonstrated that the initial metabolic acidosis on presentation predicts the development of acute lung injury in trauma patients.¹⁸ Prior studies had shown inconsistent findings when evaluating base deficit, lactate, pH, and serum bicarbonate concentration on admission in multiply injured patients.^{19–21} Early ARDS (<48 hours after admission) has been characterized by hemorrhagic shock and capillary leak, while late ARDS (>48 hours after admission) follows pneumonia and is associated with multiple-system organ failure.²²

During the initial stages of ARDS, increased capillary permeability results in lung edema. Positive pressure must exceed the sum of interstitial pressures and superimposed hydrostatic pressure to reopen lung units. Following the initial phase of injury, alveolar edema becomes organized and is replaced by fibrinous material. Recruitment maneuvers to open collapsed alveoli become less effective as the response to pressure increases on the ventilator begin to favor overdistension. Therefore, *lung recruitment needs to be instituted early in the course of respiratory failure.*

Recruitment

Frequently during mechanical ventilation, ALI/ARDS patients are managed in the supine position. Hypoxemia and hemodynamic instability often discourage medical staff from changing patient position. In general, hospital beds are

designed specifically to accommodate the tradition of minimizing patient movement. The supine position maximizes the compressive effect of the heart, mediastinal structures, and rib cage. Supine positioning concentrates the weight of the abdominal organs posteriorly and cephalad. As a result, the abdominal contents displace the crural portion of the diaphragm cephalad, encroaching upon the thoracic cavity.

The greatest frequency of opening of lung units occurs at around 25 cm H₂O, with the maximal frequency of estimated transpulmonary opening pressures seen at pressures between 20 and 25 cm H₂O.²³ Crotti et al²⁴ have also shown that recruitment occurs in a Gaussian, or normal, distribution mode such that different regions of the lung are recruited at differing pressures, ranging from 10 to 45 cm H₂O.

The majority of derecruitment occurs at PEEP values spanning 0 to 15 cm H₂O, which is in the range of superimposed pressure. Indeed, the average PEEP levels needed to maintain oxygen saturation were 16.7 ± 2.3 cm H₂O in ARDSexp and 15.6 ± 2.5 cm H₂O in ARDSp in a recent randomized, prospective trial.²⁴

Overdistension creates dead space. Progressive overdistension initiates capillary compression and blood flow is redistributed to less-ventilated regions, aggravating hypoxemia. Recruitment of lung tissue requires sufficient airway pressures to exceed the critical opening pressure of the airways. Lung recruitment also requires *time* in addition to critical opening *pressure*. As this pressure is reached and maintained, time allows redistribution of delivered gas volume.

Early investigations in the research of ARDS looked at physiologic changes in gas exchange, hemodynamic variables, and respiratory system mechanics. More recently, a new body of literature has given us an enhanced understanding of these variables as correlated with findings seen on CT scans. This has enabled us to further delineate *pulmonary* ("primary" or "direct" insult) ARDS (ARDSp) from the *extrapulmonary* ("secondary" or "indirect" insult) form (ARDSexp). ARDSp is primarily a process of consolidation, with alveolar filling of fibrin, edema, blood cells, and collagen, as opposed to ARDSexp, which presents with atelectasis of alveolar architecture accompanied by microvascular congestion.^{25,26} This corresponds to the finding that ARDSp represents a "stiffer" lung, which may not improve with PEEP, while in ARDSexp there is a stiffer thoracoabdominal cage and a more compliant lung, both of which improve with PEEP.²⁷

Spontaneous Breathing

Spontaneous breathing is a much ignored and yet crucial aspect to improve ventilation/perfusion (V/Q) matching, as there is a significant difference in the distribution of gas flow (V) between controlled mechanical ventilation (CMV) and spontaneous breathing. Mechanical ventilation results in a tidal volume delivered to nondependent, poorly perfused lung units (West's Zone I), whereas spontaneous breathing is preferentially directed to dependent lung regions where blood flow (Q) is higher.²⁸⁻³⁰ In addition, allowing the diaphragm to move helps to maintain its muscle and it is then able to perform one of its functions: keeping the abdominal contents out of the thorax. Relaxation of the diaphragm into the posterior (dependent) chest in a supine patient exacerbates alveolar collapse. Underventilation of these lung units can then lead to shunt. Spontaneous breathing does not lead to an increase in oxygen consumption (VO₂).³¹

Traditionally, spontaneous breathing in ALI/ARDS patients is discouraged. Controlled ventilation frequently mandates neuromuscular blockade or heavy sedation, which eliminates the diaphragm's potential to facilitate dependent lung ventilation.³² Furthermore, lack of diaphragmatic tone compounds the cephalad displacement of the diaphragm.³³ The summation of these forces results in disproportionate underventilation of dependent lung regions. Therefore, initial lung injury combined with traditional management practices may further amplify lung heterogeneity.

Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation (NIPPV) is increasingly popular, particularly for patients with chronic respiratory diseases. Recently, several researchers have shown improved outcomes when patients with acute respiratory failure are managed in this manner. Trauma patients may also benefit from this therapy.

A retrospective review of trauma patients with acute respiratory failure showed an improvement in the PaO₂/FiO₂ ratio, an increase in tidal volume, and a decrease in respiratory rate with mean pressure support level of 12 cm H₂O and PEEP 4.5 cm H₂O applied by face mask. The length of time for the use of NIPPV was 6 to 144 hours.³³

NIPPV may be an alternative to endotracheal intubation in certain trauma patients (i.e., those without facial injuries, a mental status that permits both cooperation and the ability to protect the airway, and a low suspicion of aspiration risk). Either a nasal mask or a face mask may be used.

Oxygen Toxicity

In addition to its contribution to the formation of atelectasis, oxygen used in high concentrations has been shown to cause pulmonary damage indistinguishable from ARDS. High concentrations of oxygen given during fluid resuscitation may increase free radical formation and contribute to reperfusion injury. Consequently, it should be administered in doses sufficient to maintain adequate tissue oxygenation, but not in excess. Most intensive care practitioners aim to maintain PaO₂ between 8 and 9 kPa (60–80 mm Hg). Although direct evidence is lacking, these levels do not lead to tissue hypoxia unless tissue perfusion is compromised by hypovolemia or hypotension. The only exception to this rule is the management of patients with severe head injuries. For these patients, provided cerebral perfusion is maintained, a PaO₂ of 10 kPa is sufficient.

Adequate Nutrition/Source Control of Infection/Fluid and Electrolyte Management

While the purpose of these guidelines is to outline goals to achieve with regard to mechanical ventilation in trauma patients, it is well recognized that manipulation of the ventilator alone (i.e., without meticulous care of the patient) is not enough. For this reason, it is imperative to ensure early nutrition, infection control, and fluid and electrolyte management.

Recommendations

- *PEEP should be applied early.* Suggested initial setting is a PEEP > 10 cm H₂O, since most patients in the supine position derecruit at PEEP levels between 10 and 15 cm H₂O. Patients who have undergone massive fluid resuscitation, those with pulmonary contusions or direct pulmonary injuries, and the morbidly obese may require higher settings. Hypotension in the face of PEEP suggests under-resuscitation, and volume replacement should continue. Some traumatic disease processes (i.e., neurogenic shock, blunt myocardial injury, cardiac disease) may require vasoactive support.
- *Patients at risk of ALI/ARDS should have “open-lung” techniques instituted before deterioration of blood gases or findings on chest radiograph.* PEEP, or mean airway pressure, should be increased as needed to preserve a PaO₂/FiO₂ ratio at the highest possible value.
- *Plateau pressure should be limited to <35 cm H₂O.* Ventilator-associated lung injury is known to occur at transpulmonary pressures >35 to 40 cm H₂O and at low PEEP settings. Since it is not practical to measure transpulmonary pressure clinically, a plateau pressure is an acceptable correlate. (How to decrease tidal volume, decrease respiratory rate, increase inspiratory time, change to pressure modes of ventilation, and/or inverse-ratio ventilation.)
- *Tidal volumes should be set at 6 to 8 mL/kg.* Volutrauma caused by overdistension (TV 10–15 mL/kg) causes lung injury. This typically occurs at the upper end of the pressure-volume curve, above the upper inflection point. Volutrauma may be a result of high tidal volumes, leading to overdistension injury, or to high PEEP without concurrent limitation in tidal volume settings (e.g., if an increase in PEEP is necessary in order to improve oxygenation, PIP/plateau pressures should be limited by decreasing tidal volume or converting to a pressure-limited mode of ventilation).
- *Spontaneous breathing should be allowed as much as possible.* This is true in the ICU and in the OR. Spontaneous breathing improves V/Q matching, cardiac output, and renal blood flow. In addition, it may prevent deconditioning of the respiratory muscles. (Many operative procedures do not require neuromuscular blockade.)
- *NIPPV is a useful adjunct.* NIPPV may be possible instead of intubation, and will decrease the risk of pneumonia. Current studies show a proven benefit only in patients with chronic obstructive pulmonary disease (COPD) exacerbation. NIPPV may be beneficial in congestive heart failure and in patients with pulmonary contusion, but a large prospective randomized trial has yet to be completed.
- *Recruitment maneuvers should be done when attempting to open collapsed alveoli.* Because the opening, or distending, pressure that is necessary to open collapsed alveoli is higher than that required to keep recruited alveoli open, pressure can be decreased following the maneuver. A recruitment maneuver is performed by continuous or sustained pressure of 30 to 45 cm H₂O for 30 seconds, as tolerated (i.e., continuous monitoring and acceptable values of blood pressure, heart rate, oxygen saturation, and intracranial pressure, if applicable). After a recruitment maneuver, PEEP should be *increased* from its previous level in order to maintain alveolar patency. (Returning PEEP to the baseline level will not ensure continued recruitment.)
- *Supplemental oxygen in high concentrations is toxic to the lungs and should only be administered in doses sufficient to maintain normal arterial oxygenation.* When oxygen is administered in high doses, arterial blood gases should be measured as soon as possible and the inspired concentration of oxygen should be adjusted accordingly.
- *During manual ventilation, each manual breath should be administered so that it is just possible to see the chest rising and falling.* Excess volumes and pressures are easily administered and are just as dangerous as those delivered by a ventilator. If available, peripheral oxygen saturation and end-tidal carbon dioxide monitors are useful guides to the adequacy of ventilation. Aim for SpO₂ of 93–97% and ETCO₂ of 3.5–4kPa (35–40 mm Hg).
- *Permissive hypercapnia.* Several studies have shown that patients will tolerate a pH greater than 7.2 without cardiovascular compromise. In patients with a marginal PaO₂/FiO₂ ratio, acceptance of higher PaCO₂, in exchange for maintaining an adequate mean airway pressure and limiting peak/plateau pressure, is reasonable.
- *Patient positioning should optimize ventilation.* Frequent turning, suctioning, and chest physiotherapy will promote ventilation/perfusion matching and improve gas exchange. Patients can be mobilized and lifted out of bed even with devices such as chest tubes, pulmonary artery catheters, and vacuum-assisted suction dressings while on mechanical ventilation.
- *Role of intermittent prone positioning therapy.* Although the largest randomized trial to investigate the role of intermittent prone positioning therapy (IPPT) did not show an overall benefit in mortality, subgroup analysis demonstrated that some patients do respond to this intervention with improved outcome: specifically, those with high TV ventilation (12–15 mL/kg), a Simplified Acute Physiology Score >40, or a PaO₂/FiO₂ ratio <150 (that is, the most critically ill patients).³⁵ In addition, a recent editorial suggested that IPPT is an intervention that should be considered to improve V/Q matching in patients who do not respond to other methods of recruitment. It is both a safe and an effective method that may decrease mortality in trauma patients.

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Appendix 1. Acute Respiratory Failure

Acute Lung Injury (ALI) is defined as

1. Acute onset
2. Bilateral infiltrates on chest radiograph
3. PaO₂/FiO₂ ratio ≤300
4. Noncardiogenic pulmonary edema

Acute Respiratory Distress Syndrome (ARDS) is defined as

1. Acute onset
2. Bilateral infiltrates on chest radiograph
3. PaO₂/FiO₂ ratio ≤200
4. Noncardiogenic pulmonary edema

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Editor

John K. Stene, MD, PhD
Department of Anesthesia
The Milton S. Hershey Medical Center
Hershey, PA 17033 USA
jstene@psu.edu

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
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the balance is in the solution.

- HEXTEND (6% Hetastarch in Lactated Electrolyte injection) is indicated in the treatment of hypovolemia when plasma volume expansion is desired. It is not a substitute for blood or plasma.
- Solutions containing hetastarch are contraindicated in patients with known sensitivity to hydroxyethyl starch, bleeding disorders or with congestive heart failure where volume overload is a potential problem.
- Solutions containing hetastarch should not be used in renal disease with oliguria or anuria not related to hypovolemia.

Please see brief summary of Prescribing Information on following page.

BRIEF SUMMARY

HEXTEND® 6% Hetastarch in Lactated Electrolyte Injection Flexible Plastic Container

INDICATIONS AND USAGE

HEXTEND (6% Hetastarch in Lactated Electrolyte Injection) is indicated in the treatment of hypovolemia when plasma volume expansion is desired. It is not a substitute for blood or plasma.

CONTRAINDICATIONS

Solutions containing hetastarch are contraindicated in patients with known hypersensitivity to hydroxyethyl starch or with bleeding disorders or with congestive heart failure where volume overload is a potential problem. Solutions containing hetastarch should not be used in renal disease with oliguria or anuria not related to hypovolemia.

Solutions containing lactate are NOT FOR USE IN THE TREATMENT OF LACTIC ACIDOSIS.

WARNINGS

Solutions containing calcium should not be administered simultaneously with blood through the same administration set because of the likelihood of coagulation.

Life threatening anaphylactic/anaphylactoid reactions have been rarely reported with solutions containing hetastarch; death has occurred, but a causal relationship has not been established. Patients who develop severe anaphylactic/anaphylactoid reactions may need continued supportive care until symptoms have resolved.

Hypersensitivity reactions can occur even after solutions containing hetastarch have been discontinued.

Solutions which contain potassium should be used with great care, if at all, in patients with hyperkalemia and severe renal failure and in situations in which potassium retention is present.

Solutions containing sodium ions should be used with great care, if at all, in patients with congestive heart failure and severe renal insufficiency and in clinical states in which edema with sodium retention occurs.

In patients with diminished renal function, administration of solutions containing sodium or potassium ions may result in sodium or potassium retention.

Solutions containing lactate ions should be used with great care in patients with metabolic or respiratory alkalosis. The administration of lactate ions should be performed with great care when dealing with conditions in which an increased level or an impaired utilization of these ions occurs, such as severe hepatic insufficiency.

DO NOT USE IN LEUKAPHERESIS.

Usage in Plasma Volume Expansion

Large volumes of isotonic solutions containing 6% hetastarch (HEXTEND or Hetastarch Injection) may transiently alter the coagulation mechanism due to hemodilution and a mild direct inhibitory action on Factor VIII. Hemodilution by isotonic solutions containing 6% hetastarch may also result in a 24 hour decline of total protein, albumin, and fibrinogen levels and in transient prolongation of prothrombin, activated partial thromboplastin, clotting, and bleeding times.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of isotonic solutions containing 6% hetastarch. Administration of packed red cells, platelets, and fresh frozen plasma should be considered if excessive dilution occurs.

In randomized, controlled, comparative studies of Hetastarch Injection (n = 92) and Albumin (n = 85) in surgical patients, no patient in either treatment group had a bleeding complication and no significant difference was found in the amount of blood loss between the treatment groups.

HEXTEND has not been adequately evaluated to establish its safety in situations other than treatment of hypovolemia in elective surgery. In some cases, the use of isotonic solutions containing 6% hetastarch has been associated with coagulation abnormalities in conjunction with an acquired, reversible von Willebrand's-like syndrome and/or Factor VIII deficiency when used over a period of days. Replacement therapy should be considered if a severe Factor VIII or von Willebrand deficiency is identified. If a coagulopathy develops, it may take several days to resolve. Certain conditions may affect the safe use of isotonic solutions containing 6% hetastarch on a chronic basis. For example, in patients with subarachnoid hemorrhage where an isotonic solution containing 6% hetastarch is used repeatedly over a period of days for the prevention of cerebral vasospasm, significant clinical bleeding may occur. Intracranial bleeding resulting in death has been reported with the use of Hetastarch Injection.

PRECAUTIONS

General

The possibility of circulatory overload should be kept in mind. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated and in clinical states in which edema with sodium retention occurs.

Indirect bilirubin levels of 8.3 mg/L (normal 0.0-7.0 mg/L) have been reported in 2 out of 20 normal subjects who received multiple infusions of Hetastarch Injection. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering isotonic solutions containing 6% hetastarch to patients with a history of liver disease.

If a hypersensitivity effect occurs, administration of the drug should be discontinued and appropriate treatment and supportive measures should be undertaken (see **WARNINGS**).

Caution should be used when administering solutions containing hetastarch to patients allergic to corn because such patients can also be allergic to hetastarch.

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, acid-base balance, and coagulation parameters during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation.

Solutions containing dextrose should be used with caution in patients with known subclinical or overt diabetes mellitus.

Caution must be exercised in the administration of parenteral fluids, especially those containing

sodium ions, to patients receiving corticosteroids or corticotropin.

Potassium containing solutions should be used with caution in the presence of cardiac disease, particularly in digitalized patients or in the presence of renal disease.

Solutions containing lactate ions should be used with caution as excess administration may result in metabolic alkalosis.

Elevated serum amylase levels may be observed temporarily following administration of solutions containing hetastarch although no association with pancreatitis has been demonstrated. Serum amylase levels cannot be used to assess or to evaluate for pancreatitis for 3-5 days after administration of solutions containing hetastarch. Elevated serum amylase levels persist for longer periods of time in patients with renal impairment. Solutions containing hetastarch have not been shown to increase serum lipase.

One report suggests that in the presence of renal glomerular damage, larger molecules of hetastarch can leak into the urine and elevate the specific gravity. The elevation of specific gravity can obscure the diagnosis of renal failure.

Hetastarch is not eliminated by hemodialysis. The utility of other extracorporeal elimination techniques has not been evaluated.

If administration is by pressure infusion, all air should be withdrawn or expelled from the bag through the medication port prior to infusion.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies of animals have not been performed to evaluate the carcinogenic potential of hetastarch.

Teratogenic Effects: Pregnancy Category C.

Hetastarch Injection has been shown to have an embryocidal effect on New Zealand rabbits when given intravenously over the entire organogenesis period in a daily dose 1/2 times the maximum recommended therapeutic human dose (1500 mL) and on BD rats when given intraperitoneally, from the 16th to the 21st day of pregnancy, in a daily dose 2.3 times the maximum recommended therapeutic human dose. When Hetastarch Injection was administered to New Zealand rabbits, BD rats, and Swiss mice with intravenous daily doses of 2 times, 1/3 times, and 1 times the maximum recommended therapeutic human dose, respectively, over several days during the period of gestation, no evidence of teratogenicity was evident. There are no adequate and well controlled studies in pregnant women. HEXTEND should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether hetastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HEXTEND is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of HEXTEND in pediatric patients have not been established. Adequate, well-controlled clinical trials to establish the safety and effectiveness of HEXTEND in pediatric patients have not been conducted. However, in one small double-blind study, 47 infants, children, and adolescents (ages 1 year to 15.5 years) scheduled for repair of congenital heart disease with moderate hypothermia were randomized to receive either Hetastarch Injection or Albumin as a postoperative volume expander during the first 24 hours after surgery. Thirty-eight children required colloid replacement therapy, of which 20 children received Hetastarch Injection. No differences were found in the coagulation parameters or in the amount of replacement fluids required in the children receiving 20 mL/kg or less of either colloid replacement therapy. In children who received greater than 20 mL/kg of Hetastarch Injection, an increase in prothrombin time was demonstrated (p = 0.006). There were no neonates included in this study.

Geriatric Use

Of the total number of patients in clinical trials of HEXTEND (n=119), 30% were 65 or older while 12% were 70 or older. Other reported experience with Hetastarch Injection has not identified differences in responses between elderly and younger patients, but greater senescence of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

In clinical trials comparing the plasma volume expanding properties of HEXTEND (n=60) with those of Hetastarch Injection (n=59), there were no significant differences in the number of adverse or serious adverse events between the two groups.

Reported adverse reactions with isotonic solutions containing 6% hetastarch include:

General

Hypersensitivity (see **WARNINGS**).

Death, life-threatening anaphylactic/anaphylactoid reactions, cardiac arrest, ventricular fibrillation, severe hypotension, non-cardiac pulmonary edema, laryngeal edema, bronchospasm, angioedema, wheezing, restlessness, tachypnea, stridor, fever, chest pain, bradycardia, tachycardia, shortness of breath, chills, urticaria, pruritus, facial and periorbital edema, coughing, sneezing, flushing, erythema multiforme, and rash.

Cardiovascular

Circulatory overload, congestive heart failure, and pulmonary edema (see **PRECAUTIONS**).

Hematologic

Intracranial bleeding, bleeding and/or anemia due to hemodilution (see **WARNINGS**) and/or Factor VIII deficiency, acquired von Willebrand's-like syndrome, and coagulopathy including rare cases of disseminated intravascular coagulopathy and hemolysis. With extensive clinical use of Hetastarch Injection, rare cases of disseminated intravascular coagulopathy and hemolysis have been observed.

Metabolic

Metabolic acidosis.

Other

Vomiting, peripheral edema of the lower extremities, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, and muscle pains. Hydroxyethyl starch-associated pruritus has been reported in some patients with deposits of hydroxyethyl starch in peripheral nerves.

Caution: Federal (USA) law prohibits dispensing without prescription.

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Reference 58-0851-R2-Rev. September, 1999

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.....
Careful inquiry should be made concerning previous hypersensitivity reaction, as serious and occasionally fatal anaphylactic reactions have been reported in patients receiving therapy with penicillins. ZOSYN is contraindicated in patients with a history of these reactions to any of the penicillins, cephalosporins, or β -lactamase inhibitors.

While ZOSYN possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, during prolonged therapy is advisable.

During clinical trials, pseudomembranous colitis has been rarely reported (<1%).

The most commonly reported adverse events in clinical trials, irrespective of relationship to therapy, included diarrhea (11.3%), headache (7.7%), constipation (7.7%), nausea (6.9%), and insomnia (6.6%).

Please see adjacent brief summary of Prescribing Information.

ZOSYN^{IV}
(piperacillin sodium/tazobactam sodium)

EMPIRIC THERAPY FOR SERIOUS INFECTIONS



ZOSYN® (Piperacillin and Tazobactam for Injection) Brief Summary

See package insert for full prescribing information.

CONTRAINDICATIONS ZOSYN is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or β -lactamase inhibitors.

WARNINGS SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC/ANAPHYLACTOID) REACTIONS (INCLUDING SHOCK) HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH PENICILLINS INCLUDING ZOSYN. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ZOSYN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, ZOSYN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTIC/ANAPHYLACTOID REACTIONS (INCLUDING SHOCK) REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ZOSYN, and may range in severity from mild to life-threatening. Consider this diagnosis in patients who present with diarrhea after antibacterial agent administration. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, initiate therapeutic measures. Mild cases usually respond to drug discontinuation alone. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis may be necessary.

PRECAUTIONS General: Bleeding manifestations have occurred in some patients receiving β -lactam antibiotics, including piperacillin. These reactions have sometimes been associated with coagulation test abnormalities such as clotting time, platelet aggregation, and prothrombin time and are more likely to occur in renal failure patients. If bleeding manifestations occur, discontinue ZOSYN and institute appropriate therapy. The possibility of the emergence of resistant organisms that might cause superinfections should be kept in mind. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

ZOSYN is a monosodium salt of piperacillin and a monosodium salt of tazobactam, containing 2.35 mEq (54 mg) of Na⁺ per gram of piperacillin; consider this when treating patients requiring restricted salt intake. Perform periodic electrolyte determinations in patients with low potassium reserves; the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

As with other semisynthetic penicillins, piperacillin has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

In patients with renal insufficiency or in hemodialysis patients, the intravenous dose should be adjusted to the degree of renal function impairment. (See Full Prescribing Information—**DOSE AND ADMINISTRATION**.)

Laboratory Tests: Perform periodic assessment of hematopoietic function, especially with prolonged therapy, ie, ≥ 21 days. (See **ADVERSE REACTIONS—Adverse Laboratory Events**.)

Drug Interactions: Aminoglycosides—The mixing of ZOSYN with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside. (See Full Prescribing Information—**DOSE AND ADMINISTRATION—Compatible Intravenous Diluent Solutions**.)

When ZOSYN was co-administered with tobramycin, the area under the curve, renal clearance, and urinary recovery of tobramycin were decreased by 31%, 32%, and 38%, respectively. Pharmacokinetic alterations of tobramycin when administered with ZOSYN may be due to in vivo and in vitro inactivation of tobramycin in the presence of piperacillin/tazobactam. The inactivation of aminoglycosides in the presence of penicillin-class drugs has been recognized. It has been postulated that microbiologically inactive penicillin-aminoglycoside complexes of unknown toxicity form. In patients with severe renal dysfunction (ie, chronic hemodialysis patients), tobramycin pharmacokinetics are significantly altered when administered with piperacillin. The alteration of tobramycin pharmacokinetics and the potential toxicity of the penicillin-aminoglycoside complexes in patients with mild to moderate renal dysfunction who are administered an aminoglycoside with ZOSYN are unknown.

Probenecid—Probenecid administered with ZOSYN prolongs the half-life of piperacillin by 21% and of tazobactam by 71%.

Vancocin—No pharmacokinetic interactions with ZOSYN have been noted.

Heparin—Coagulation parameters should be tested more frequently and monitored regularly during simultaneous administration of high doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function.

Vecuronium—Piperacillin used with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. ZOSYN could produce the same phenomenon if given with vecuronium. Due to their similar mechanism of action, the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. (See package insert for vecuronium bromide.)

Methotrexate—Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid drug toxicity.

Drug/Laboratory Test Interactions: As with other penicillins, ZOSYN may result in a false-positive reaction for glucose in the urine using a copper-reduction method (CLINITEST[®]). Glucose tests based on enzymatic glucose oxidase reactions (such as DIASTIX[®] or TES-TAPE[®]) are recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term carcinogenicity studies in animals have not been conducted with piperacillin/tazobactam, piperacillin, or tazobactam. Piperacillin/tazobactam was negative in the following mutagenicity tests/assays up to the concentrations noted: microbial mutagenicity assay (14.84/1.86 μ g/plate), unscheduled DNA synthesis (UDS) test (5689/711 μ g/mL), mammalian point mutation (Chinese hamster ovary cell HPRT) assay (8000/1000 μ g/mL), and a mammalian cell (BALB/c-3T3) transformation assay (8/1 μ g/mL). In vivo, piperacillin/tazobactam did not induce chromosomal aberrations in rats dosed I.V. with 1500/187.5 mg/kg; this dose is similar to the maximum recommended human daily (MRHD) dose on a body-surface-area basis (BSA) (mg/m²).

Piperacillin was negative in the following mutagenicity tests/assays up to the concentrations noted: microbial mutagenicity assays (50 μ g/plate), UDS test (10,000 μ g/mL), and a cell (BALB/c-3T3) transformation assay (3000 μ g/mL). There was no DNA damage in bacteria (Rec assay) exposed to piperacillin at concentrations up to 200 μ g/disk. In a mammalian point mutation (mouse lymphoma cells) assay, piperacillin was positive at concentrations ≥ 2500 μ g/mL. In vivo, piperacillin did not induce chromosomal aberrations in mice at I.V. doses up to 2000 mg/kg/day or rats at I.V. doses up to 1500 mg/kg/day. These doses are half (mice) or similar to (rats) the MRHD dose based on BSA (mg/m²). In another in vivo test, there was no dominant lethal effect when piperacillin was administered to rats at I.V. doses up to 2000 mg/kg/day, which is similar to the MRHD dose based on BSA (mg/m²). When mice were administered piperacillin at I.V. doses up to 2000 mg/kg/day, which is half the MRHD dose based on BSA (mg/m²), urine from these animals was not mutagenic when tested in a microbial mutagenicity assay. Bacteria injected into the peritoneal cavity of mice administered piperacillin at I.V. doses up to 2000 mg/kg/day did not show increased mutation frequencies. Tazobactam was negative in the following mutagenicity assays up to the concentrations noted: microbial mutagenicity assays (333 μ g/plate), UDS test (2000 μ g/mL), mammalian point mutation (Chinese hamster ovary cell HPRT) (5000 μ g/mL), a cell (BALB/c-3T3) transformation assay (900 μ g/mL). In another mammalian point mutation (mouse lymphoma cells) assay, tazobactam was positive at concentrations ≥ 3000 μ g/mL. In an in vitro cytogenetics (Chinese hamster lung cells) assay, tazobactam was negative at concentrations up to 3000 μ g/mL. In vivo, tazobactam did not induce chromosomal aberrations in rats at I.V. doses up to 5000 mg/kg, which is 23 times the MRHD dose based on BSA (mg/m²).

Pregnancy: Teratogenic effects—Pregnancy Category B: Piperacillin/tazobactam: Reproduction studies in rats have revealed no evidence of impaired fertility due to piperacillin/tazobactam administered up to a dose which is similar to the MRHD dose based on BSA (mg/m²).

Teratology studies in mice and rats have revealed no evidence of harm to the fetus due to piperacillin/tazobactam administered up to a dose which is 1 to 2 times and 2 to 3 times the human dose of piperacillin and tazobactam, respectively, based on BSA (mg/m²). Piperacillin and tazobactam cross the placenta in humans.

Piperacillin: Reproduction and teratology studies in mice and rats have revealed no evidence of impaired fertility or fetal harm due to piperacillin administered up to a dose which is half (mice) or similar to (rats) the MRHD dose based on BSA (mg/m²).

Tazobactam: Reproduction studies in rats have revealed no evidence of impaired fertility due to tazobactam administered at doses up to 3 times the MRHD dose based on BSA (mg/m²).

Teratology studies in mice and rats have revealed no evidence of fetal harm due to tazobactam administered at doses up to 6 and 14 times, respectively, the human dose based on BSA (mg/m²). In rats, tazobactam crosses

the placenta. Concentrations in the fetus are less than or equal to 10% of those found in maternal plasma. There are no adequate and well-controlled studies with the piperacillin/tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Use this drug during pregnancy only if clearly needed.

Nursing Mothers: Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Exercise caution when ZOSYN is administered to a nursing woman.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Patients over 65 years are **not** at an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See Full Prescribing Information—**DOSE AND ADMINISTRATION**.)

ADVERSE REACTIONS During the initial clinical investigations, 2621 patients worldwide were treated with ZOSYN in phase 3 trials. In the key North American clinical trials (n=830 patients), 90% of the adverse events reported were mild to moderate in severity and transient in nature. However, in 3.2% of the patients treated worldwide, ZOSYN was discontinued because of adverse events primarily involving the skin (1.3%), including rash and pruritus; the gastrointestinal system (0.9%), including diarrhea, nausea, and vomiting; and allergic reactions (0.5%).

Adverse local reactions that were reported, irrespective of relationship to ZOSYN therapy, were phlebitis (1.3%), injection site reaction (0.5%), pain (0.2%), inflammation (0.2%), thrombophlebitis (0.2%), and edema (0.1%).

Adverse Clinical Events: Based on patients from the North American trials (n=1063), the events with the highest incidence in patients, irrespective of relationship to ZOSYN therapy, were diarrhea (11.3%); headache (7.7%); constipation (7.7%); nausea (6.9%); insomnia (6.6%); rash (4.2%); including maculopapular, bullous, urticarial, and eczematoid; vomiting (3.3%); dyspepsia (3.3%); pruritus (3.1%); stool changes (2.4%); fever (2.4%); agitation (2.1%); pain (1.7%); moniliasis (1.6%); hypertension (1.6%); dizziness (1.4%); abdominal pain (1.3%); chest pain (1.3%); edema (1.2%); anxiety (1.2%); rhinitis (1.2%); and dyspnea (1.1%).

Additional adverse systemic clinical events reported in 1.0% or less of the patients in the initial North American trials are listed below within each body system. **Autonomic nervous system**—hypotension, ileus, syncope. **Body as a whole**—rigors, back pain, malaise. **Cardiovascular**—tachycardia, including supraventricular and ventricular; bradycardia; arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction. **Central nervous system**—tremor, convulsions, vertigo. **Gastrointestinal**—melena, flatulence, hemorrhage, gastritis, hiccup, ulcerative stomatitis. Pseudomembranous colitis was reported in one patient during the clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **Warnings**.) **Hearing and Vestibular System**—tinnitus. **Hypersensitivity**—anaphylaxis. **Metabolic and Nutritional**—symptomatic hypoglycemia, thirst. **Musculoskeletal**—myalgia, arthralgia. **Platelets, Bleeding, Clotting**—mesenteric embolism, purpura, epistaxis, pulmonary embolism. (See **Precautions, General**.) **Psychiatric**—confusion, hallucination, depression. **Reproductive, Female**—leukorrhea, vaginitis. **Respiratory**—pharyngitis, pulmonary edema, bronchospasm, coughing. **Skin and Appendages**—genital pruritus, diaphoresis. **Special senses**—taste perversion. **Urinary**—retention, dysuria, oliguria, hematuria, incontinence. **Vision**—photophobia. **Vascular (extracardiac)**—flushing.

In a completed study of nosocomial lower respiratory tract infections, 222 patients were treated with ZOSYN in a dosing regimen of 4.5 g every 6 hours in combination with an aminoglycoside and 215 patients were treated with imipenem/cilastatin (500 mg/500 mg q6h) in combination with an aminoglycoside. Twenty-five (25, 11.0%) patients in the piperacillin/tazobactam group and 14 (6.5%) in the imipenem/cilastatin group ($p > 0.05$) discontinued treatment due to an adverse event. Adverse events that occurred in more than 1% of patients and were considered by the investigator to be drug-related were: diarrhea (17.6%), fever (2.7%), vomiting (2.7%), urinary tract infection (2.7%), rash (2.3%), abdominal pain (1.8%), generalized edema (1.8%), moniliasis (1.8%), nausea (1.8%), oral moniliasis (1.8%), BUN increased (1.8%), creatinine increased (1.8%), peripheral edema (1.8%), abdomen enlarged (1.4%), headache (1.4%), constipation (1.4%), liver function tests abnormal (1.4%), thrombocytopenia (1.4%), exocoriation (1.4%), and sweating (1.4%).

Drug-related adverse events reported in 1% or less of patients in the nosocomial pneumonia study of ZOSYN with an aminoglycoside were: acidosis, acute kidney failure, agitation, alkaline phosphatase increased, anemia, asthenia, atrial fibrillation, chest pain, CNS depression, colitis, confusion, convulsion, cough increased, thrombocytopenia, dehydration, depression, diplopia, drug level decreased, dry mouth, dyspepsia, dysphagia, dyspnea, dysuria, eosinophilia, fungal dermatitis, gastritis, glossitis, grand mal convulsion, hematuria, hyperglycemia, hypernatremia, hypertension, hypertonia, hyperventilation, hypochromic anemia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia, hypoxia, ileus, injection site edema, injection site pain, injection site reaction, kidney function abnormal, leukocytosis, leukopenia, local reaction to procedure, melena, pain, prothrombin decreased, pruritus, respiratory disorder, SGOT increased, SGPT increased, sinus bradycardia, somnolence, stomatitis, stupor, tremor, tachycardia, ventricular extrasystoles, and ventricular tachycardia.

In a previous nosocomial pneumonia study conducted with a dosing regimen of 3.375 g given every 4 hours with an aminoglycoside, the following adverse events, irrespective of drug relationship, were observed: diarrhea (20%); constipation (8.4%); agitation (7.1%); nausea (5.8%); headache (4.5%); insomnia (4.5%); oral thrush (3.9%); erythematous rash (3.9%); anxiety (3.2%); fever (3.2%); pain (3.2%); pruritus (3.2%); hiccup (2.6%); vomiting (2.6%); dyspepsia (1.9%); edema (1.9%); fluid overload (1.9%); stool changes (1.9%); anorexia (1.3%); cardiac arrest (1.3%); confusion (1.3%); diaphoresis (1.3%); duodenal ulcer (1.3%); flatulence (1.3%); hypertension (1.3%); hypotension (1.3%); inflammation at injection site (1.3%); pleural effusion (1.3%); pneumothorax (1.3%); rash, not otherwise specified (1.3%); supraventricular tachycardia (1.3%); thrombophlebitis (1.3%); and urinary incontinence (1.3%).

Adverse events irrespective of drug relationship observed in 1% or less of patients in the above study with ZOSYN and an aminoglycoside included: aggressive reaction (combative), angina, asthenia, atelectasis, balanoposthitis, cerebrovascular accident, chest pain, conjunctivitis, deafness, dyspnea, earache, ecchymosis, fecal incontinence, gastric ulcer, gout, hemoptysis, hypoxia, pancreatitis, perineal irritation/pain, urinary tract infection with trichomonas, vitamin B12 deficiency anemia, xerosis, and yeast in urine.

Additional adverse events reported from worldwide marketing experience with ZOSYN, where causal relationship to ZOSYN is uncertain: **Gastrointestinal:** hepatitis, cholestatic jaundice. **Hematologic:** hemolytic anemia, anemia, thrombocytosis, agranulocytosis, pancytopenia. **Immune:** hypersensitivity reactions, anaphylactic/anaphylactoid reactions (including shock). **Infections:** candidal superinfections. **Renal:** interstitial nephritis, renal failure. **Skin and Appendages:** erythema multiforme and Stevens-Johnson syndrome; toxic epidermal necrolysis.

Adverse Laboratory Events (Seen During Clinical Trials): Of the studies reported, including that of nosocomial lower respiratory tract infections in which a higher dose of ZOSYN was used in combination with an aminoglycoside, changes in laboratory parameters, without regard to drug relationship, include: **Hematologic:** decreases in hemoglobin and hematocrit, thrombocytopenia, increases in platelet count, eosinophilia, leukopenia, neutropenia. The leukopenia/neutropenia appears to be reversible and most frequently associated with prolonged administration, ie, ≥ 21 days of therapy. These patients were withdrawn from therapy; some had accompanying systemic symptoms (eg, fever, rigors, chills). **Coagulation:** positive direct Coombs' test, prolonged prothrombin time, prolonged partial thromboplastin time. **Hepatic:** transient elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin. **Renal:** increases in serum creatinine, blood urea nitrogen. **Urinalysis:** proteinuria, hematuria, pyuria.

Additional laboratory events include abnormalities in electrolytes (ie, increases and decreases in sodium, potassium, and calcium), hyperglycemia, decreases in total protein or albumin, blood glucose decreased, gamma-glutamyltransferase increased, hypokalemia, and bleeding time prolonged.

The following adverse reaction has also been reported for PIPRACIL[®] (sterile piperacillin sodium): **Skeletal:** prolonged muscle relaxation. (See **PRECAUTIONS—Drug Interactions**.)

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

OVERDOSAGE There have been post-marketing reports of overdose with piperacillin/tazobactam. The majority of those events experienced including nausea, vomiting, and diarrhea have also been reported with the usual recommended dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment should be supportive and symptomatic according to the patient's clinical presentation. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by hemodialysis. (See Full Prescribing Information—**CLINICAL PHARMACOLOGY**.)

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This Brief Summary is based on ZOSYN direction circular CI 7876-1 (Revised April 2003).

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105023-01



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Educational Objectives

This publication/activity is designed to provide trauma care professionals interested in the treatment of critically ill trauma patients with a regular overview and critical analysis of the most current, clinically useful information available, covering strategies and advances in the diagnosis of traumatic injuries and the treatment of trauma patients. Controversies, advantages, and disadvantages of diagnosis and treatment plans are emphasized. There are no prerequisites for participation in this activity.

After reading each issue, participants should have a working familiarity with the most significant information and perspectives presented and apply what they have learned promptly in clinical practice. Specific learning objectives are listed at the opening of each article.

CME QUESTIONS

This issue of *TraumaCare* can be used to earn 10 CME credit hours.

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CME QUESTIONS

1. In the United States, among all age groups, trauma-related injuries are the fourth cause of death after heart diseases, cancer, and stroke.
 - a. True
 - b. False
2. Trauma due to road traffic accidents, a problem resulting in substantial economic, social, and emotional loss all over the world, is said to be a more evident public health problem especially in developing countries without adequate infrastructure, but studies from the Western world also cite motor vehicle accidents as the leading cause of trauma.
 - a. True
 - b. False
3. Improving emergency care systems and developing hospitals selected as regional trauma care centers do not decrease trauma-related disabilities and mortality.
 - a. True
 - b. False
4. According to World Health Organization, injuries and traumatic deaths are more common in men than women.
 - a. True
 - b. False
5. The most frequently injured body sites are external body surfaces, head and neck, and extremities.
 - a. True
 - b. False
6. The following diagnosis may be followed by episodic rebleeding in the presence of aggressive fluid resuscitation:
 - a. Fracture of the humerus.
 - b. Rupture of an aortic aneurysm.
 - c. Fracture of the femoral neck.
 - d. Inguinal hernia.
 - e. All of the above.
7. What is the most typical clinical evidence of episodic rebleeding?
 - a. Sudden drop in arterial pressure during aggressive volume replacement.
 - b. No increase in arterial pressure during aggressive volume replacement.
 - c. Loss of consciousness during aggressive volume replacement.
 - d. Sudden increase in heart rate during aggressive volume replacement.
 - e. None of the above.
8. What is the mechanism of episodic rebleeding?
 - a. Vasoconstriction in venous vessels markedly increases the capillary pressure.
 - b. An immature blood clot is washed away by increased blood flow/pressure.
 - c. Vagal reflexes increase parasympathetic tone, which overdistends the large veins.
 - d. Coagulation factors are consumed, causing blood clots to dissolve.
 - e. An immature blood clot is washed away by increased blood flow/pressure.
9. Which of the following proposals about episodic rebleeding is correct?
 - a. It is known to worsen the outcome of trauma patients.
 - b. It occurs when the blood pressure is normal.
 - c. The risk increases with the time from injury.
 - d. It implicates that a major blood vessel has been injured.
10. Which one of the following proposals about episodic rebleeding is false:
 - a. Pelvic fracture may be associated with episodic rebleeding.
 - b. Stabilizing the pelvis is the most important means of reducing subsequent blood loss in traumatic pelvic fracture.
 - c. Measuring coagulation factors is a viable means of monitoring rebleeding.
 - d. Rebleeding increases total blood loss and prolongs the period of hemodynamic instability.
 - e. More often follows penetrating trauma than blunt trauma.
11. Treatment of rhabdomyolysis includes
 - a. Hydration
 - b. Alkalinization of the urine
 - c. Diuretic therapy
 - d. Fresh-frozen plasma
 - e. All of the above

12. Which of the following complications is seen in rhabdomyolysis?
 - a. Renal failure
 - b. Hyperkalemia
 - c. Hyperphosphatemia
 - d. DIC
 - e. All of the above
13. To prevent renal failure in a patient with rhabdomyolysis, the following can be performed.
 - a. Maintain adequate circulatory volume
 - b. Use of osmotic diuretics
 - c. Mannitol, 0.25 g/kg
 - d. Lasix, 10-100 mg IV
 - e. Bicarbonate
14. A 21-year-old male patient undergoes bilateral tibia fracture repair under general anesthesia. Postoperatively, the patient develops tachycardia, mild hypotension, and acidosis on ABG, and severe pain in the lower limbs is not relieved by the PCA he is on. You should
 - a. Increase the PCA morphine dose
 - b. Administer bicarbonate to correct the acidosis
 - c. Send for laboratory check for serum creatinine levels
 - d. Do nothing; the patient is malingering
 - e. Check compartmental pressures in the legs
15. Alcoholism can cause rhabdomyolysis.
 - a. True
 - b. False
16. If the ICU ventilator settings exceed the capabilities of the OR ventilator for an ICU patient who requires surgery, it is recommended that:
 - a. The patient should be weaned from the ICU ventilator before surgery.
 - b. The operating room ventilator settings should be approximated in the ICU before transport to the OR, then the patient taken to the OR on ambuventilation.
 - c. The patient should be taken to the OR on the ICU ventilator and remain on that ventilator during the surgical procedure.
17. Which of the following basic mechanisms of atelectasis formation seem(s) to be the major offender(s) during anesthesia?
 - a. Compression and absorption atelectasis.
 - b. Loss-of-surfactant atelectasis.
18. In a categorization of ARDS based on physiologic changes and CT findings, a process of consolidation, with alveolar filling of fibrin, edema, blood cells, and collagen, representing a "stiffer" lung, which may not improve with PEEP, describes which of the following?
 - a. Pulmonary ("primary" or "direct" insult) ARDS (ARDSp)
 - b. Extrapulmonary ("secondary" or "indirect" insult) ARDS (ARDSexp)
19. In a categorization of ARDS based on physiologic changes and CT findings, the presentation of atelectasis of alveolar architecture accompanied by microvascular congestion, as well as a stiffer thoracoabdominal cage and a more compliant lung, which improve with PEEP, describes which of the following?
 - a. Pulmonary ("primary" or "direct" insult) ARDS (ARDSp)
 - b. Extrapulmonary ("secondary" or "indirect" insult) ARDS (ARDSexp)
20. Recruitment of lung tissue requires all but which of the following?
 - a. A high-inspired fraction of oxygen.
 - b. Airway pressure that exceeds the critical opening pressure of the airways.
 - c. Time to allow redistribution of delivered gas volume.

Evaluation Form: Please rate this self-study activity by marking one response for each statement.

Did the articles meet their stated objectives? Yes No

How do you rank the quality of this educational activity? 5 (high) 4 3 2 1 (low)

Comments: _____

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Answer Form: Please circle the one best answer for each question.

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1. a b
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14. a b c d e
15. a b
16. a b c
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18. a b
19. a b
20. a b c

I certify that I have completed the "TraumaCare/Fall 2004" activity as designed and claim 10 credit hours in Category 1 of the Physicians Recognition Award of the American Medical Association.

Signature _____ Date _____

Mail answer form and check (\$100, members; \$200, nonmembers) to ITACCS Department of CME Credit, P.O. Box 4826, Baltimore, MD 21211. Allow 4 to 6 weeks for processing.

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References:

- 1) BMJ Volume 320, 18 March 2000
- 2) To Err is Human: Building a Safer Health System, Linda T. Kohn, Janet M. Corrigan, and Molla S. Donaldson, Editors, © 2000 by the National Academy of Sciences.

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