EMERGENCY MEDICINE REPORTS

Practical, Evidence-Based Reviews in Emergency Care

January 11, 2015 VOL. 36, NO. 2

AUTHORS

Jay H. Shubrook, DO, FACOFP, FAAFP, Associate Professor of Family Medicine, Director, Diabetes Fellowship Program, The Diabetes Institute at Ohio University

Nancy Mora Becerra, MD, Ohio State University, Columbus, OH

Sarah E. Adkins, PharmD, BCACP, Faculty, The Ohio State University College of Pharmacy; Assistant Professor of Pharmacology, Ohio University Heritage College of Medicine, Athens, OH

Aili Guo, MD, Assistant Professor of Specialty Medicine, Ohio University Heritage College of Osteopathic Medicine

PEER REVIEWER

Jeff Unger, MD, ABFP, FACE, Director, Unger Primary Care Concierge Medical Group, Rancho Cucamonga, CA

STATEMENT OF FINANCIAL DISCLOSURE

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Shubrook (author) reports he receives grant/research support from Sanofi and is a retained consultant for Eli Lilly. Dr. Unger (peer reviewer) reports he receives grant/research support from Novo Nordisk, Sanofi-Aventis, Lilly, Dance Pharma, GSK, and Janssen; is a retained consultant for Novo Nordisk, Sanofi-Aventis, Valeritas, Dance Pharma, and Janssen; is on the speakers bureau for Novo Nordisk, Lilly, Valeritas, and Janssen; and is a stockholder at Novo Nordisk. Dr. Farel (CME question reviewer) owns stock in Johnson & Johnson. Dr. Schneider (editor) is a retained consultant for Logical Images. Dr. Stapczynski (editor) owns stock in Pfizer, Johnson & Johnson, AxoGen, Walgreen Company, and Bristol Myers Squibb. Dr. Adkins (author), Dr. Guo (author), Dr. Mora Becerra (author), Dr. Wise (editor), Ms. Coplin (executive editor), Ms. Kimball (managing editor). Mr. Landenberger (editorial director), and Ms. Mark (executive editor) report no financial relationships with companies related to the field of study covered by this CME activity.

AHC Media

Insulin: A Primer

Introduction

Prior to the discovery of insulin, type 1 diabetes was a uniformly fatal disease. The first use of exogenous insulin in a dog by Banting and Macloed resulted in the Nobel Prize in Physiology or Medicine.[1] In January 1922, they injected exogenous insulin in a 14-year-old boy who was dying at the Toronto General Hospital. After receiving the insulin he desperately needed, he improved and by the end of that month his glucosuria and ketonuria normalized.[1]

Initially, bovine and porcine insulins were purified from animal pancreatic tissues and were used to treat people with diabetes. Since they were foreign to the human body, immune reactions were common, which resulted in an unpredictable treatment effect and duration. In 1958, Frederick Sanger won a Nobel Prize in Chemistry for the discovery of the molecular structure of insulin.[1] Dorothy Hodgkin, who won a Nobel Prize in Chemistry in 1964, discovered the tertiary structure of insulin.[2] These discoveries allowed for the pharmacologic development of human insulin.

The development of human insulin was a significant advancement as it decreased immunogenic reactions and provided longer duration of action. Human insulin is produced by recombinant DNA technology, introducing the proinsulin gene into *Escherichia coli* or yeast. These organisms replicate and produce insulin.

Human insulins include regular (R) and neutral protamine hagedorn (NPH), lente (L), and ultralente (U). Only R and NPH are still available today. R insulin is used most commonly as mealtime insulin. It should be dosed 30-45 minutes before a meal. NPH insulin has a longer duration of action, can be dosed 4-6 hours before a meal, and is used 1 meal in advance (taken before breakfast to cover lunch) or as a basal insulin 2-3 times per day. NPH has a prolonged effect due to the addition of a positively charged protamine.

Today there are three rapid-acting analog insulins (aspart, lispro, glulisine) and two long-acting analogs (glargine, fetemir).

Insulin and C-peptide Physiology

Insulin is produced and released specifically by the ß cells of the pancreatic islet cells within the pancreas. Insulin is a polypeptide hormone that consists of two chains (chain A with 21 amino acid residues and chain B with 30 amino acid residues) linked by two disulfide bridges. The first form is preproinsulin. Soon after production, it is released from the rough endoplasmic reticulum when proteolytic enzymes cleave into pro-insulin. Pro-insulin converts to insulin when other proteolytic action cleaves the

EXECUTIVE SUMMARY

- Patients starting on insulin in the ED should be started on a basal insulin 0.1-0.2 U/kg.
- Patients being treated for acute hyperglycemia (not previously on insulin) should receive 2 U for every 50 mg/dL elevation of glucose over 150 mg/dL.
- Patients who present acutely ill with an active insulin pump should have the pump turned off and supplemental insulin given IV.
- Patients who present with unexplained hypoglycemia should have a c-peptide and insulin level drawn. High insulin levels without equal elevation of c-peptide suggest exogenous insulin administration.

C chain (c-peptide) and leaves the active insulin molecule in the vesicle for secretion. This physiologic feature is convenient in that one molecule of c-peptide is produced for each insulin molecule. This makes c-peptide a good measure of endogenous insulin production.[3]

While the cause of hypoglycemia in most patients is apparent, in patients with unexplained hypoglycemia, measurement of insulin and c-peptide, and in some cases sulfonylurea, can be important. The most important causes of hypoglycemia are shown in Table 1. In most cases the cause of the hypoglycemia will be apparent — sepsis, known excessive use of insulin, etc.

Patients who have an excess of exogenous insulin, such as overdose on insulin (intentional or unintentional) will have low c-peptide levels and high insulin levels. Patients with an insulin-producing tumor such as insulinoma will have high insulin levels (< 100 uU/mL) and high c-peptide levels. These tumors tend to be very small (< 2 cm) and are often missed on imaging. Patients who have an inadvertent or intentional overdose of sulfonylurea drugs will have very high levels of insulin and c-peptide exceeding those seen with insulinoma.[4] Exogenous sulfonylurea levels can be measured.

Insulin secretion is based on the glucose level presenting to the pancreas. There is a diurnal pattern as well whereby insulin secretion is lowest in the middle of the night and greatest first thing in the early morning. In a fasting state, insulin secretion suppresses glycogenolysis and stimulates gluconeogenesis and lipogenesis.

Insulin secretion is also modulated by the intake of nutrients (bolus secretion). In response to meal ingestion, insulin secretion is biphasic. There is a large and rapid first-phase insulin secretion followed by a slower and more sustained second-phase secretion. The incretin system stimulates insulin release and suppresses glucagon release from the pancreas. The incretin effect provides a much larger increase in insulin secretion than glucose levels.

Table 1: Important Causes of Hypoglycemia

- Intentional or unintentional overdose of insulin
- Intentional or unintentional overdose of oral hypoglycemic
- Insulinoma, multiple endocrine neoplasias
- Liver disease
- End stage renal disease
- Hypopituitarism
- Hypothyroidism
- Inborn errors of metabolism
- Starvation
- Sepsis
- ETOH
- Reactive after gastric surgery

The liver removes at least 50% of insulin released. The remainder is taken up into systemic circulation where it interacts with target site receptors. At the target sites, insulin binds to receptor sites on plasma membranes. This binding begins a cascade of intracellular reactions that trigger significant cellular responses such as glucose uptake, glycogen synthesis, and lipogenesis.[5]

The insulins discussed are currently FDA approved in the United States for use in diabetes (*see Table 2*).

Rapid-Acting Insulins

There are three FDA-approved, rapid-acting insulin analogs available in the United States today: glulisine, lispro, and aspart. Timing of meals and monitoring for hypoglycemia are important with rapid-acting insulins.

Insulin lispro was approved in 1996 by Lilly with the brand name HumaLOG®. Upon injection, insulin lispro is quickly absorbed, faster than regular injected human insulin. Lispro also has a shorter duration of action compared to regular insulin. The recommended time of administration for insulin lispro is 15 minutes prior to a meal.[6]

Insulin aspart (NovoLOG®) by Novo Nordisk was approved in 2000. This insulin is recommended for subcutaneous administration approximately 5-10 minutes before a meal.[7]

Insulin glulisine (Aprida®) is a human insulin analog. This insulin can be given either prior to the meal or up to 20 minutes after the meal. Insulin glulisine was approved for use in 2004.[8]

Short-Acting Insulin

Regular insulin, which was FDA-approved in 1982, is a short-acting human insulin that is produced using recombinant DNA techniques. Regular insulin is normally administered 30-45 minutes prior to a meal and tends to last longer than rapid-acting insulins,

Table 2: Pharmacokinetic Profiles of Currently Available Insulins and Insulin Analogs

Insulin	Brand Name	Manufacturer	Species Source	Concentration	Time of Action (hours)		
					Onset	Peak Effect	Duration
Rapid							
Glulisine	Apidra	Sanofi-Aventis	human analog	U100	0.2-0.5	1.6-2.8	3-4
Lispro	HumaLOG	Lilly	human analog	U100	0.25-0.5	0.5-2.5	≤ 5
Aspart	NovoLOG	Novo Nordisk	human analog	U100	0.2-0.3	1-3	3-5
Short-Acting							
Regular	HumuLIN R NovoLIN R	Lilly Novo Nordisk	human	U100	0.5	2.5-5	4-12
Intermediate							
NPH	HumuLIN N NovoLIN N	Lilly Novo Nordisk	human	U100	1-2	4-12	14-24
Intermediate/Short-Acting Mixed							
70 NPH 30 regular	HumuLIN 70/30 NovoLIN 70/30	Lilly Novo Nordisk	human	U100	0.5	regular 0.8-2 NPH 6-10	18-24
Intermediate/Rapid-Acting Mixed							
50 lispro protamine 50 lispro	HumaLOG Mix 50/50	Lilly	human analog	U100	0.25-0.5	0.8-4.8	14-24
75 lispro protamine 25 lispro	HumaLOG Mix 75/25	Lilly	human analog	U100	0.25-0.5	1-6.5	14-24
70 aspart protamine 30 aspart	NovoLOG Mix 70/30	Novo Nordisk	human analog	U100	10-20 minutes	1-4	18-24
Long							
Detemir	Levemir	Novo Nordisk	human analog	U100	3-4	3-9	6-23
Glargine	Lantus	Sanofi-Aventis	human analog	U100	3-4	none	average 24
Miscellaneous Long							
Regular	HumuLIN R U500 (concentrated)	Lilly	human	U500	0.5	2.5-5	up to 24

anywhere from 4-12 hours. Regular insulin, which can be given subcutaneously or intravenously, is particularly useful as an intravenous infusion and is frequently used in hyperglycemic crises such as diabetic ketoacidosis and hyperglycemic hyperosmolar nonketosis syndrome.[9]

Intermediate-Acting Insulin[11]

Neutral protamine hagedorn (NPH), or isophane, is a cloudy suspension that contains insulin and protamine. The addition of protamine creates a longer duration of action. When administered, enzymes slowly break down the protamine to allow for the slow absorption of insulin. NPH absorption is often variable, having an onset from 1-5 hours, and duration of action from 4-12 hours.[10] NPH insulin, which has been available since 1982, is available as HumuLIN N® (Lilly) or NovoLIN N® (Novo Nordisk). In the clinical setting, NPH is typically given one meal in advance or as 2-3 doses per day to serve as a basal insulin. The availability of long-acting insulins has led to decreased use of NPH insulin.

Premixed Insulins[9,10-12]

Human insulin regular and NPH can be mixed into a single syringe for administration. The two commercially available human insulin mixes are HumuLIN® 70/30 or NovoLIN N® 70/30 (70% NPH and 30% regular). The 70/30 mix is a cloudy suspension (as NPH is cloudy). The onset is around 30-45 minutes, with a peak effect in 4-12 hours. This insulin is typically dosed 2-3 times per day with pre-breakfast and pre-dinner dosing. This is convenient for patients who want to limit the number of injections. Responses to

this insulin, though, can be less reliable dose to dose. Regular insulin can precipitate out in the NPH insulin.

Other mixed insulins available include rapid-acting analog insulin and protamined rapid-acting analog insulin. The protaminated rapid-acting analog will delay absorption and give a prolonged effect. The HumaLOG® 75/25 and NovoLOG® 70/30 mixes have a more rapid onset of action and a shorter peak effect. This allows them to be dosed immediately before mealtime, which may result in more reliable clinical effects and reduced post-meal hypoglycemia. These rapid-acting mixed insulins came to market in the mid-to-late 1990s.

Long-Acting Analog Insulin

Insulin glargine (Lantus®) came on the market in 2000, followed by the release of insulin detemir (Levemir®) in 2005. The introduction of a steady, long-acting insulin closely mimics the basal rate of endogenous insulin. These agents alone have a lower risk of hypoglycemia due to the lack of a peak response and the continuous release of low levels of insulin.

Insulin glargine is a long-acting analog of human insulin. The insulin structure was modified by attaching two arginine amino acids to the terminal end of the B chain and changing asparagine to glycine at the terminal end of the A chain. These modifications form a precipitate upon subcutaneous injection. This precipitate dissolves slowly, creating a continuous, steady release of insulin. Because of this mechanism, insulin glargine has no defined peak. Glargine is injected subcutaneously once daily and should not be administered intravenously or intramuscularly.[13] Given that glargine has an acidic pH, it should not be mixed with other insulins.

Insulin detemir is a long-acting human analog insulin. The onset of action is generally 1-2 hours. It can be given once daily. Insulin detemir is administered subcutaneously, but should not be administered intravenously or intramuscularly.[14]

Concentrated Insulin

Currently there is only one concentrated insulin clinically available in the United States (HumuLIN U500) but there are more emerging.

Table 3: Basal Insulin Algorithms

Measure	ADA/EASD	AACE/ACE	IDF	CDA
Algorithm				
Initial dosage	10 U/d	10 U/d	Not specified	10 U/d
Titration	2 U every 3 days	1-3 U every 2-3 days	2 U every 3 days	1 U every day
Target FBG, mg/dL	70-130	< 110[a]	<110	72-126

[a]Fasting blood glucose (FBG) target recommendation from the American Association of Clinical Endocrinologists (AACE) 2011 guidelines.

Abbreviations: ACE, American College of Endocrinology; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; EASD, European Association for the Study of Diabetes; A1c, glycated hemoglobin; IDF, International Diabetes Federation.

Adapted from: LaSalle JR, Berria R. Insulin therapy in type 2 diabetes: A practical approach for primary care physicians and other health professionals. *J Am Osteopath Assoc* 2013;113:152-162.

Starting Insulin in the ED

In most cases, patients with severe hyperglycemia will be admitted, and treatment with insulin will be initiated by the primary care physician or endocrinologist. However, some patients with diabetic ketoacidosis are now kept in observation or in the ED until discharge. Increasingly, patients with new onset diabetes are discharged home directly or placed in an observation unit under the care of an emergency physician, who then starts insulin treatment. Traditional "diabetic teaching," which includes diet, foot care, and eye care, is either completed in the ED or as an outpatient.

Patients with type 1 diabetes (those who present with diabetic ketoacidosis) will require insulin treatment. Many patients with type 2 diabetes (metabolic syndrome, obese, later onset) can be tried on an oral hypoglycemic, with insulin used in refractory cases. Some advocate insulin as the first treatment for type 2 diabetes.[15,16] The underlying principle behind early intensive insulin use is that "resting" the pancreas in early diabetes may provide not only more rapid control of glucose but also a lasting or "legacy" effect on glucose control. While this is promising, this method of treatment requires further exploration.

How to Start Insulin? For most patients, starting insulin usually means starting a basal insulin, glargine, detemir, or NPH. Basal insulins allow for suppression of hepatic glucose production overnight and can help normalize morning blood glucose. Therefore, controlling fasting glucose is a logical first step. By removing glucose toxicity, the remaining functioning ß cells are better able to address prandial hyperglycemia.

The ADA/EASD recommend a starting dose of 0.1-0.2 units/kg as a single dose. This starting dose is rarely enough insulin to normalize morning glucose, so patients should be instructed to see their doctor within a few days to adjust their dose. Table 3 compares basal insulin titration recommendations from major diabetes organizations.

Patient-driven titrations have proven to be more effective than physician-driven titrations.[17,18] Agreed upon stopping points include when the basal dose reaches 0.5 units/kg or when the patient experiences a hypoglycemic episode.[19]

Since diabetes is very common, many patients may already be familiar with insulin injections. In other patients, nursing can teach the proper injection technique.

As mentioned earlier, there are two long-acting basal insulins and one intermediate-acting insulin that can serve as a basal insulin. All three formulations work well to suppress hepatic glucose production. The analog insulins (glargine, detemir) have numerous benefits over NPH insulin,[20-22] including less hypoglycemia,

especially nocturnal hypoglycemia; less weight gain; and less frequent dosing. The downside is the expense. Analog insulins are 3-5 times more expensive than generic human insulin. When dosing a basal insulin analog, it is recommended to start with a weight-based dose once daily. Many physicians have stayed with the initial recommendations to dose glargine at bedtime, but dosing can, in fact, be any time of day based on the patient's schedule and preference.

When NPH is used as a basal insulin, it is most commonly dosed 2-3 times per day. Twice-daily dosing, before breakfast and before dinner, is best. This minimizes hypoglycemia between meals and overnight. Use of three times daily dosing insulin will result in a very complex set of insulin actions and unpredictable hypoglycemia in a person who may not fully understand the dynamics of these insulins.

Premixed insulin allows a person to take fewer injections than a basal bolus regimen. However, it is more often associated with hypoglycemia and results in an inflexible daily and meal schedule to prevent hypoglycemic episodes.

Premixed insulin can be used for someone who has poor control but who is not motivated to engage in three or more shots per day.

Adjusting Insulin in the ED

Hyperglycemia is often noted in diabetic patients who come to the ED. If the elevation is mild, say under 300 mg/dL, and not related to the acute disease, the patient may require simple adjustment of their insulin. This is best done by the PCP, but in some cases that cannot be done. The ED provider should be able to start the insulin adjustment until the patient can see his or her physician. It is good to draw an A1c in the ED to help guide future adjustments.

If the patient is only on a basal regimen, increase the basal dose 1-3 U per day and have the patient check fasting glucose levels. If a patient has a good fasting glucose but the later glucose levels are elevated, consider adding a newer oral agent (DPP-4 inhibitors, SGLT-2 inhibitors), older agent such as the glinides or alpha-glucosidase inhibitors, or the shorter acting injectable GLP-1 receptor analogs.[23] The use of non-insulin injectables or oral agents is beyond the scope of this paper. Rapid-acting insulin analogs, which include aspart, lisine, and glulisine, can also be used.

The Endocrine Society, in cooperation with a number of other professional organizations, developed a decision tool for mealtime dosing. This reference (Accurate insulin decisions) is freely available for clinicians.[19]

The goal of using mealtime insulin is to replicate physiologic insulin release. The patient takes an injection of mealtime insulin with each meal. The typical starting dose is 0.1 unit/kg per meal. If the patient is well-controlled in the morning, the physician may need to subtract 10% of the basal dose to prevent hypoglycemia that could result from treating daytime hyperglycemia more effectively by using a mealtime dose of insulin.

Recent studies support the principle of a basal plus 1 insulin schedule. In this scenario, the patient continues basal insulin, but only takes mealtime insulin with the largest meal of the day. For most people in the United States, this corresponds to the evening meal. When using a basal plus 1 regimen, the mealtime dose may be bigger at 0.1-0.2 units per kg.[24]

The term "sliding scale" has been replaced by "correction scale" to identify a different way to use insulin when current insulin needs are unknown.

Correction scale insulin may be used alone for initial treatment if the person's insulin needs are unknown. However, it is intended that after 24 hours, the "correction insulin" needed the previous day would be converted to scheduled insulin the next day that will prevent the need for ongoing "sliding scale insulin." Correction scale insulin is used in addition to scheduled mealtime insulin to supplement the current meal dose and correct a hyperglycemic reading in specific situations.

To make a specific correction scale, the physician can use the rule of 1800 (the constant may vary from 1500-1900 based on the source). To estimate the amount of glucose reduction for 1 unit of insulin, take the total daily dose of all insulin injections and then divide this into the constant of 1800.[25] An example is listed below.

Example 1. A person presents to the hospital with community-acquired pneumonia. He has no history of diabetes but he is hyperglycemic at the time of admission with a glucose of 212 mg/dL and no history of diabetes. Because this patient is acutely ill, sliding scale insulin is started using 2 units for every 50 mg/dL above 150 mg/dL. After the first 24 hours, he needs 20 units of insulin from the scale. Using the correction scale correctly, on day 2 the physician takes the total of the previous correction scale insulin from day 1 and converts it to scheduled insulin. Typically, half the insulin would be once-daily basal insulin (10 units) and the remaining scale insulin would be used to cover the meal content, divided equally among the meals (about 3 units per meal). This is repeated daily until the correction insulin need is negligible.

Insulin Delivery

At present, all insulin products are delivered via subcutaneous insulin injections in addition to a syringe and insulin drawn from a vial. Insulin pens are available as reusable devices (pens) with replaceable insulin cartridges or disposable single-use pens.

Patients who currently use or plan to start insulin usually prefer insulin pens[26] because they are more portable and allow for attachment of pen needles, thus reducing the necessary equipment the patient has to carry. Insulin pens hold 3 mL (or 300 units) of insulin, so they need to be replaced more often than vials, which hold 10 mL (1000 units). Additionally, adherence is improved for insulin pens compared to vials and syringe.[27]

Writing Insulin Prescriptions

Most insulin products in the United States are U100 insulin (100 units/mL), which translates as 100 units in each mL of insulin. Each "unit" is standardized for a similar clinical response

Table 4: Recommended Mealtime Insulin Titrations

Measure	ADA/ EASD	AACE/ ACE	IDF	CDA[a]
Algorithm Initial dosage	4 U	5 U	Not specified	Total daily dose of 0.3-0.5 U/kg; 40% of total = basal; 20% of total = bolus (3 times/d) 1 U every day
Titration	2 U every 3 days	2-3 U every 2-3 days	2 U every 3 days	NA

Adapted from: LaSalle JR, Berria R. Insulin therapy in type 2 diabetes: A practical approach for primary care physicians and other health professionals. *J Am Osteopath Assoc* 2013;113:152-162.

— one unit of lispro, aspart, and glulisine should each have similar glucose-lowering effects — which allows for accurate prescribing and dosing, even when switching between insulins. A vial of U100 insulin holds 10 mL or 1000 units. An insulin pen holds 3 mL or 300 units.

Prescriptions for insulin pens also need to include pen needles, which come in regular (8 mm), short (5 mm), mini (4 mm), and nano (3 mm). Recent evidence has shown that all needle lengths are equally effective.[28]

Errors in insulin prescription and/or dosing are among the most common in inpatient and outpatient settings.[29] To minimize the chance for error a few general rules should always be followed:

1. Always write out the word "unit" — do not use the abbreviation U as it can be mistaken for a 0.
2. The current recommended nomenclature (http://www.ismp.org/tools/tallmanletters.pdf) is to capitalize the last three letters of a brand name to limit confusion between similarly named products. For example: HumaLOG vs HumuLIN or NovoLOG vs NovoLIN.
3. Specify whether the prescription is for pens or vials.
4. Write NovoLIN R 6 units before each meal three times per day instead of writing Novolin R take as directed at mealtimes.
5. If a patient needs to take a correction dose, it should be spelled out on the prescription: Write HumaLOG 6 units per meal plus correction 1 unit for every 50 mg/dL above 150 mg/dL.
6. Always include the maximum dose per day on the prescription so the pharmacist can dispense the correct total volume.

The following is an example of what a prescription might look like: Apidra SolostarR pens, Take ApidraR 6 units per meal plus 1 unit for every 50 mg/dL above 150 mg/dL for a maximum of 40 units per day, 30-day supply, 5 refills.

Determining the Prescription Dose

Estimating the volume on the prescription is based on daily dose. Each vial of U100 insulin holds 1000 units. Dividing by a typical 30-day month corresponds to approximately 1 vial per month. If a person typically takes 40 units per day of insulin by vial, write for two vials. When prescribing vials, insulin syringes will also be needed. The current sizes for insulin syringes include 0.3 mL, 0.5 mL, and 1 mL, which allow for injections of 30 units, 50 units, and 100 units, respectively. Insulin pens hold 300 units of insulin and typically come in a box of five, for a total of 1500 units. This means that a person who uses 45 units per day of insulin will use one box of five pens per month.

Concentrated Insulins

Patients who are obese and have type 2 diabetes typically need more insulin for a therapeutic effect, which often means very large doses of daily insulin (200-300 units per day). Once a person needs more than 300 units of insulin per day, the number of injections increases and the pharmacokinetics of the insulin can be less consistent due to potential depot effects at the injection site. Concentrated insulins are a potential solution to this challenge.

Regular human insulin is available in a concentrated form, HumuLIN R U500, with the same mechanism of action as U100 regular insulin. However, increased concentrations create more aggregation of insulin molecules into dimers/hexamers, thus prolonging absorption. A single dose of concentrated U500 regular insulin may have effects up to 24 hours. HumuLIN R U500 is recommended for subcutaneous administration 30 minutes prior to a meal and is typically administered 2-3 times per day based on the dose.[30]

Emerging Insulin Products

Researchers are constantly searching for innovative insulins and insulin delivery methods. Products currently in development include inhaled and oral insulin as well as insulin with different pharmacokinetics that allows it to be even more physiologic. In January 2006, an inhaled insulin product (Exubera®, Pfizer) came to market, but sales were not robust enough to continue its production.[31]

In June 2014, the FDA approved Afrezza® (MannKind Corporation),[32,33] an rDNA human dry powder insulin indicated for both type 1 and type 2 diabetes. This inhaled insulin is combined with an inert excipient and used with the Technosphere® Inhalation System. An "ultra-rapid mealtime insulin," Afrezza is designed to reach peak insulin levels 12-15 minutes after inhalation and it is cleared faster than rapid-acting insulin. Therefore, it is dosed with meals. Afrezza is expected to be available in the United States in 2015. The most common side effects are cough, throat pain, headaches, and higher rates of hypoglycemia.[32] This medication should not be used in people who smoke or have problems with moderate-to-severe asthma or COPD symptoms. In these patients, there is a black box warning for bronchospasm.

Dance 501 (Dance Biopharm Inc.) is an inhaled insulin device in development that releases an insulin mist with an appropriate inhalation from the patient.[34] Dance 501 is being studied in adult patients with type 2 diabetes.

Table 5: Available Insulin Products and Delivery Methods

Insulin Product	Regular Insulin	NPH	Glulisine	Aspart	Lispro	Detemir	Glargine	Afrezza
Vial	X	X	X	X	X	X	X	
Permanent refillable insulin pen				X Echo pen Novo Jr. pen Novopen 3	X Luxura HD			
Disposable insulin pen		X	X Solostar pen	X Flexpen	X Kwikpen	X Flexpen, Flextouch	X Solostar pen	
Inhaler								X

In addition, several novel concentrated insulins, including U200 and U300 basal insulins, are in development for patients who take large volumes of insulin. These concentrated insulins will most likely have longer durations of action.

Degludec (Novo Nordisk), a basal insulin with a duration of 42 hours, has been studied in a U100 and a U200 concentration.[35,36] Although it is available in Europe, the FDA is requiring the manufacturer to produce additional cardiovascular outcome data.[35] PEGylated insulin lispro (Lilly)[35,37] is insulin lispro attached to a polyethylene glycol, which makes this molecule have a large hydrodynamic size and prolonged duration of action. This insulin may also have preferential hepatic uptake and may more closely approximate normal endogenous insulin physiology.

In addition, emerging "ultra-fast insulins" that may provide faster insulin coverage for meals and correction are in development to help prevent formation of dimers and hexamers. One promising approach is the use of hyaluronidase to speed absorptions and time to onset. Another option is to add excipients to speed insulin absorption or insulin dispersion.[38]

A new area of insulin technology is biosimilar insulin.[15] Since many insulin analogs will go off patent in the coming years, manufacturers have the opportunity to make close copies, called biosimilars. Although the compounds may have the same amino acid sequence, they may have slightly different clinical characteristics when produced under different conditions. Biosimilars are available in other countries, but there are not enough data from controlled clinical trials to adequately compare them.

The final products in development are "smart insulins," which have built-in glucose sensors that allow the insulin delivery component according to the ambient glucose. These have the potential to resolve the serious issue of hypoglycemia, which is a concern with current insulin formulations. Examples of smart insulins include protein-binding ligands (lectins) that can reversibly bind to carbohydrates and nanotechnology and nanoplugs that sense glucose levels and control insulin release from microgels or bioactive membranes. In addition, bulk hydrogel matrices, microgel sponges, and phenyl boronic acid in hydrogel have been reported to work like closed-loop insulin delivery devices. These hydrogels will swell in the face of hyperglycemia and in turn release insulin from its pores until the glucose normalizes. Although these technologies are exciting, they have only been researched in animal models at this time.[39]

Advanced Insulin Delivery

V-Go is a disposable patch insulin delivery device specifically designed for use in adults with type 2 diabetes.[40] The V-Go includes many of the advantages of an insulin pump and it comes in a non-motorized plastic device that is disposable. V-Go is not an insulin pump as others that will be described below, and is best used only in type 2 diabetes.

Unlike pumps, V-Go has a mechanical power source that delivers insulin with button presses rather than an electronic motor. Each disposable patch is used for 24 hours. The V-Go is waterproof to a depth of about 3 feet for 24 hours, so there is no need to remove the patch while swimming or bathing.

Similar to insulin pumps, V-Go uses a rapid-acting insulin. Only U100 lispro and aspart insulin are approved to use with this device. V-Go pumps are available in three different sizes based on the basal doses patients will receive in a 24-hour interval. For example, the V-Go-20 pump delivers 20 units of insulin over 24 hours (20/24 units = 0.83 units per hour). The delivery devices are also available in 30- and 40-unit systems. Each pump is capable of delivering an additional 36 units of prandial insulin throughout the day through the discrete depression of a bolus button on the side of the pump.

Some people require less insulin with this system for the same clinical effect compared with MDI because the delivery method is more effective. The NDC code for each pump size indicates that the device should be dispensed as a drug rather than as a device. As such, the V-Go is covered by most insurance companies, including Medicare and Medicaid.

Disadvantages of the V-Go include the potential for insurance coverage issues, the potential for skin irritation from the adhesive pad, and a risk for infections at the infusion site. It is also less specific than an insulin pump, providing only one non-adjustable basal rate and fixed dosed boluses in 2-unit increments. Finally, this device should

be removed before any magnetic resonance imaging (MRI) testing.[40]

Insulin Pumps

Insulin pumps were first introduced more than 30 years ago in the United States. Approximately 400,000 people use insulin pump therapy in the United States today.[41] Insulin pumps are a good option for people who are on multiple daily insulin injections.

Insulin is delivered from a reservoir in the insulin pump and provides a basal amount of a single insulin dose through a transcutaneous catheter. Further boluses of insulin can be manually provided in response to carbohydrate ingestion. Insulin pumps are battery-powered devices with software that allow patients to program in advance, temporarily adjust, or suspend insulin basal infusion rates. In addition, insulin pumps can deliver precise boluses. Insulin pumps deliver different basal insulin rates throughout the day based on changes in insulin sensitivity, which allows for greater precision for bolus insulin dose delivery relative to carbohydrate intake and absorption from the gastrointestinal tract. Rapid- or short-acting insulin should be used in the pump. Although not FDA-approved, Humulin R U500 insulin has been used successfully off label in insulin pumps to improve A1c without an increase in hypoglycemia.[42,43] Insulin pumps are attached to patients by one of two means: 1) an infusion set consisting of long, thin, flexible tubing with a catheter or a stainless steel needle on the end that is inserted into the patient's subcutaneous tissue, or 2) a tubing-free pump, also known as a patch pump, that is attached with a subcutaneous needle-inserted catheter and self-adhesive tape. The patient programs and operates the pump or the pump's remote control device to deliver insulin doses that match individual needs.

Programmable Settings on an Insulin Pump

Basal rates are programmed by the provider. The basal insulin release is intended to replicate physiologic insulin release. For patients on subcutaneous injections, this replaces their glargine or detemir dose.

Typically, patients who switch from injections to a pump need less insulin. It is customary to set the first pump dose at 75-80% of the previous injection dose to reduce the chance of hypoglycemia.

Many patients with type 1 diabetes and some with type 2 diabetes utilize carbohydrate counting to make the mealtime insulin match what they are about to eat. Then patients can estimate what they are about to eat and count the carbohydrate grams (or exchanges) at the meal. This number can be input into the pump and the insulin pump will calculate what dose of insulin is needed for that amount of carbohydrates. .

Most people who are on subcutaneous injections have a "sliding scale" or correction scale. This is set to correct to a desired target range. For example, if target glucose is 100 and the correction factor is 50, then the patient will take correction insulin when he/she is above 100, 1 unit for every 50 mg/dL above 100. A pump can dispense a fraction of a unit, e.g., 0.5 units if the glucose is 125 mg/dL.

At a meal, a person can enter information for the carbohydrate content and current glucose into the pump. If the glucose is below the target range, the pump will automatically subtract insulin from the dose about to be given, allowing the person to bolus for a meal if below target and allowing him not to drop immediately.

Suspend Feature. Patients with an insulin pump who have a hypoglycemic episode first should suspend the pump so that no additional insulin is administered until it is safe again, and then treat the low. An ED patient who is acutely ill or injured should have their insulin pump suspended until they are stabilized. Glucose metabolism is often quite variable in acute disease and it is best to treat any significant hyperglycemia with subcutaneous or intravenous insulin.

Often after patients take a correction dose of insulin, their glucose is still high. If the second correction is given before the first correction has taken full effect, patients are at higher risk for dropping low by "stacking their insulin." Patients taking injections cannot know how much of the insulin from their meal is still working, so they make an educated guess about much additional insulin to take. With an insulin pump, the amount of time that insulin is acting can be programmed, which limits the amount of additional insulin that can be given with subsequent boluses within that window of time. In other words, this feature prevents patients from taking repeated injections while the previous injection is still acting, thus avoiding "stacking insulin."

The pump allows patients to increase or decrease the current basal for a set amount of time to respond to a change in their activity, physical state, or glucose. Often, the programmed basal rates will work for normal days but there will be exceptions that necessitate more or less insulin. For example, when a person gets sick with a respiratory illness or when a woman is menstruating, the glucose levels will rise significantly. Under these circumstances, patients can change their basal rate to a set level or by a percentage.

Advantages and Disadvantages of Insulin Pump Therapy

Intensive glucose control has clearly been shown to reduce microvascular complications in type 1 and type 2 diabetes as well to reduce macrovascular complications later in the disease.[45-47] Intensive insulin therapy can include multiple daily insulin injections (MDI) or insulin pump therapy (CSII). Multiple studies have shown that insulin pump therapy with rapid-acting analog insulin improves glucose control and reduces hypoglycemia compared to MDI in type 1 diabetes.[48-54] Insulin pump therapy is also equally effective in type 2 diabetes. The majority of patients (93%) with type 2 diabetes prefer insulin pump therapy over MDI.[55,56]

A 2010 Cochrane review compared insulin pump therapy to MDI and found that insulin pump therapy has better A1c reduction, improves quality of life, and appeared to reduce overall hypoglycemia rates.[57]

Complications associated with CSII include potential skin reactions to tape, diabetic ketoacidosis risk if the pump malfunctions, infusion-site problems (tunneling of insulin or clogged infusion set), and inactivated insulin (due to heat) that can lead to ketoacidosis in a few hours.[58]

Insulin pump patients must be familiar with the use of multiple daily

injections in case of mechanical failure. In addition, pump patients should always carry rapid-acting insulin pens and needles in case the insulin pump malfunctions.

Problem Solving with Insulin Pumps

Patients who are pumping need to keep backup supplies, such as quick-acting insulin pens, in case of pump failure. In the case of mechanical failure, patients should contact the pump company directly. Most companies will replace the pump within 24 hours.

The Future of Insulin Pump Therapy

Currently, only one company in the United States has a commercially available integrated system that links glucose monitoring to insulin pump therapy. However, most insulin pump companies are working on this capacity. One pump in the United States has a sensor augmented system in which the pump will shut off for 2 hours if the glucose drops low.[60] This technology has been shown to reduce the risk of severe hypoglycemia and nocturnal hypoglycemia with similar glucose-lowering effects.[60,61]

Manufacturers are constantly developing new technologies to improve insulin pumps. Researchers are designing artificial intelligence software to recognize glucose patterns and to alert patients and providers to possible need for changes in basal or bolus doses. In the future, there likely will be simplified and more rapid data downloading and improved connectivity. Transmission of CGM and control of insulin infusion rates by small devices with remote displays and alarms also are in development.[61,62] Smartphones will be able to act as data integrators to allow sharing of information from multiple meters, CGM, and pumps between patients and clinicians. Modified smartphones with built-in glucose testing and pump controllers are also in development.[62]

A recent study tested a "bionic" pancreas with a linked sensor and dual hormone (insulin and glucagon) pump for people with type 1 diabetes.[63] This system improved glucose control and reduced hypoglycemia compared to current insulin pump therapy. With these advances, the future of insulin pump therapy appears to be very bright.

Summary

Insulin is an increasingly important component of diabetes treatment. The number of people requiring insulin is likely to rise dramatically in response to the pandemic of obesity facing our nation and the increased rates of type 2 diabetes. The use of insulin, with new more physiologic insulins and advanced delivery methods, can be effective and convenient across a wide profile of patients. With the continued development of "smarter" pumps, the management of one of the most common chronic conditions is becoming safer and more effective.

Acknowledgements: The authors would like to thank Samantha Shubrook, MA, for her extensive editorial assistance in this manuscript.

References

1. Joshi SR, et al. Insulin — history, biochemistry, physiology and pharmacology. *J Assoc Physicians India* 2007;55 (Suppl):19-25.
2. Wikipedia. Insulin. Available at http://en.wikipedia.org/wiki/Insulin. Accessed June 8, 2014.
3. Hall JE. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders Elsevier. 2011; 939-954.
4. Fasano CJ, Rowden AK, O'Malley GF. Quantitative insulin and c-peptide levels among emergency department patients with sulfonylurea-induced hypoglycemia — a prospective case series. *Am J Emerg Med* 2010;28:952-955.
5. Powers AC. Diabetes Mellitus. In: Longo DL, et al, eds. *Harrison's Principles of Internal Medicine* New York: McGraw-Hill; 2012.
6. HumaLOG® (insulin lispro) prescribing information. Eli Lilly and Company. Indianapolis, IN. [updated 2013 Nov 14; cited 2014 Feb 28]. Available from: http://pi.lilly.com/us/humalog-pen-pi.pdf.
7. NovoLOG® (insulin aspart) prescribing information. Novo Nordisk. Bagsvaerd, Denmark. [updated 2013 Oct; cited 2014 Feb 28] Available from: http://www.novo-pi.com/novolog.pdf.
8. Aprida® (insulin glulisine) prescribing information. Sanofi-Aventis LLC. Bridgewater, NJ. [updated 2013 Oct; cited 2014 Feb 28] Available from: http://products.sanofi.us/apidra/apidra.html#S1.
9. HumuLIN R® (regular insulin) prescribing information. Eli Lilly and Company. Indianapolis, IN. [updated 2013 March 9; cited 2014 Feb 28]. Available from: http://pi.lilly.com/us/humulin-r-pi.pdf and http://www.humulin.com/Pages/index.aspx.
10. HumaLOG 75/25 package insert. Eli Lilly and Company. Indianapolis, IN. Available at http://pi.lilly.com/us/humalog7525-pi.pdf. Accessed June 8, 2014.
11. NovoLOG 70/30 product information. Available at http://www.novologmix70-30.com/toolsresources/faqs.aspx. Accessed June 8, 2014.
12. HumaLOG 50/50 package insert. Available at http://pi.lilly.com/us/humalog5050-pi.pdf. Accessed June 8, 2014.
13. Lantus® (insulin glargine) prescribing information. Sanofi-Aventis. Bridgewater, NJ. [updated 2013 Dec; cited 2014 Feb 28]. Available at: http://products.sanofi.us/lantus/lantus.html#section-13
14. Levemir® (insulin detemir) prescribing information. Novo Nordisk. Bagsvaerd, Denmark. [updated 2013 Oct; cited 2014 Feb 28]. Available at: http://www.novo-pi.com/levemir.pdf.
15. Presswala LS, Shubrook JH. Intensive insulin therapy as the primary treatment of type 2 diabetes. *Clinical Diabetes* 2011;29:151-153.
16. Rolla AR. What about insulin as an immediate first step for type 2 diabetes? *Diabetes Obes Metab* 2009;11(Suppl 5): 19-22.
17. Blonde L, et al, for TITRATE study group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: An assessment of two different fasting plasma glucose targets — the TITRATE study. *Diabetes Obes Metab* 2009;11:623-631.
18. Davies M, et al; ATLANTUS Study Group. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: Comparison of two treatment algorithms using insulin glargine. *Diabetes Care* 2005;28:1282-1288.
19. Accurate Insulin Decisions. The Endocrine Society website. Available at: http://www.accurateinsulin.org/. Accessed May 23, 2014.
20. Rosenstock J, et al. Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH)

insulin in patients with type 2 diabetes: A long-term, randomized, open-label study. *Diabetologia* 2009;52:1778-1788.

21. Riddle MC, et al; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080-3086.
22. Philis-Tsimikas A, et al. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 2006;28:1569-1581.
23. Diabetes Self-Management. Postprandial hyperglycemia. Available at: http://www.diabetesselfmanagement.com/Articles/Diabetes-Definitions/postprandial_hyperglycemia/. Accessed June 22, 2014.
24. Riddle MC, et al. Comparison of 3 intensified insulin regimens added to oral therapy for type 2 diabetes: Twice-daily aspart premixed vs glargine plus 1 prandial glulisine or stepwise addition of glulisine to glargine [abstract 409-PP]. *Diabetes* 2011;60(suppl 1):A113.
25. Stoller WA. Individualizing insulin management. Three practical cases, rules for regimen adjustment. *Postgrad Med* 2002;111:51-54.
26. Summers KH, et al. Preference for insulin delivery systems among current insulin users and nonusers. *Clin Ther* 2004;26:1498-1505.
27. Lee WC, et al. Medication adherence and the associated health-economic impact among patients with type 2 diabetes mellitus converting to insulin pen therapy: An analysis of third-party managed care claims data. *Clin Ther* 2006;28:1712-1725.
28. Frid A, et al. New injection recommendations for patients with diabetes. *Diabetes Metab* 2010;36(Suppl 2):S3-S18.
29. Geller AI, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. *JAMA Intern Med* 2014;174:678-686.
30. Humulin U500 product information. Available at: http://www.humulinhcp.com/pages/index.aspx?WT.srch=1&WT.mc_id=4994-44806-567. Accessed June 8, 2014.
31. Exubera information. Available at: http://en.wikipedia.org/wiki/Inhalable_insulin. Accessed June 8, 2014.
32. Afrezza manufacturer webpage. MannKind Corporation. Valencia, CA. [updated 2013; cited 2014 June 2] Available at: http://www.mannkindcorp.com/product-pipeline-diabetes-afrezza.htm. Accessed June 8, 2014.
33. Afrezza. FDA Briefing Document. [updated 2014 April; cited 2014 June 2] Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf. Accessed June 8, 2014.
34. Dance 501 product information. Available at http://dancebiopharm.com. Accessed June 8, 2014.
35. Zinman B. Newer insulin analogs: Advances in basal insulin replacement. *Diabetes Obes Metab* 2013;15(Suppl 1):6-10.
36. Insulin degludec product information. Available at: http://www.novonordisk.com/press/rd_pipeline/rd_pipeline.asp?showid=1. Accessed June 8, 2014.
37. Caparrotta TM, Evans M. PEGylated insulin Lispro (LY2605541) — a new basal insulin analogue. *Diabetes Obes Metab* 2014;16;388-395.
38. Heinemann L, Muchmore DB. Ultrafast-acting insulins: State of the art. *J Diabetes Sci Technol* 2012;6:728-742.
39. Kalra S. Smart insulins. *J Pak Med Assoc* 2014;64:95-97.
40. VGO product information. Available at https://www.go-vgo.com/about-vgo. Accessed June 8, 2014.
41. JDRF and BD collaborate to improve insulin pump delivery. Juvenile Diabetes research Foundation. Available at: www.bd.com/contentmanager/b_article.asp?Item_ID=24402&ContentType_ID=1&BusinessCode=20004&d=us&s=us&dTitle=&dc=us&dcTitle=United+States. Accessed July 20, 2014.
42. Lane WS, et al. A prospective trial of U500 insulin delivered by Omnipod in patients with type 2 diabetes mellitus and severe insulin resistance. *Endocr Pract* 2010;16:778-784.
43. Reutrakul S, et al. Clinical use of U500 regular insulin: Review and meta-analysis. *J Diabetes Sci Technol* 2012;6:412-420.
44. Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists/American College of Endocrinology insulin pump management task force. *Endocr Pract* 2014;20:463-489.
45. Diabetes Control and Complications Trial Research Group. Implementation of treatment protocols in the Diabetes Control and Complications Trial. *Diabetes Care* 1995;18:361-376.
46. Nathan DM, et al; DCCT/EDIC Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643-2653.
47. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-853. Erratum: *Lancet* 1999;354:602.
48. Boland EA, et al. Continuous subcutaneous insulin infusion: A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 1999;22:1779-1784.
49. Jeha GS, et al. Insulin pump therapy in preschool children with type 1 diabetes mellitus improves glycemic control and decreases glucose excursions and the risk of hypoglycemia. *Diabetes Technol Ther* 2005;7:876-884.
50. Kaufman FR, et al. Insulin pump therapy in type 1 pediatric patients: Now and into the year 2000. *Diabetes Metab Res Rev* 1999;15:338-352.
51. Nielsen S, et al. Use of continuous subcutaneousinsulin infusion pump in patients with type 2 diabetes mellitus. *Diabetes Educ* 2005;31:843-848.
52. Radermecker RP, Scheen AJ. Continuous subcutaneous insulin infusion with short-acting insulin analogues or human regular insulin: Efficacy, safety, quality of life, and cost-effectiveness. *Diabetes Metab Res Rev* 2004;20:178-188.
53. Melki V, et al. Improvement of HbA1c and blood glucose stability in IDDM patients treated with lispro insulin analog in external pumps. *Diabetes Care* 1998;21:977-982.
54. Klingensmith GJ, et al. The use of insulin pump therapy in adolescents. *Pediatrician* 1983;12:220-228.
55. Wainstein J, et al. Insulin pump therapy vs multiple daily injections in obese type 2 diabetic patients. *Diabet Med* 2005;22:1037-1046.
56. Raskin P, et al. Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: A randomized, parallel-group, 24 week study. *Diabetes Care* 2003;26:2598-2603.
57. Misso ML, et al. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev* 2010;CD005103.
58. Walsh J, Roberts R. *Pumping Insulin*. 4th ed. San Diego, CA: Torrey Pines Press; 2006.
59. US CMS Insulin pump patient eligibility criteria. AACE 2014, and Centers for Medicare and Medicaid Services. Publication #100-03 Medicare National Coverage Determinations. Available at

http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS014961.html. Accessed Aug. 10, 2014.

60. Bergenstal RM, et al. Threshold-based insulin pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224-232.
61. Bergenstal RM, et al. Effectiveness of sensor augmented insulin pump therapy in type 1 diabetes. *N Engl J Med* 2010;363:311-320.
62. Bequette BW. Challenge and recent progress in the development of a closed-loop artificial pancreas. *Ann Rev Control* 2012;36:255-266.
63. Russell SJ, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N Engl J Med* 2014;371:313-325.

CME Questions

1. What is the best measure of endogenous insulin production?
   A. serum insulin level
   B. finger stick insulin level
   C. c-peptide
   D. fasting insulin level
2. Which of the following is a basal insulin?
   A. glulisine
   B. detemir
   C. aspart
   D. lispro
3. Which of the following is a rapid mealtime insulin analog?
   A. lispro
   B. detemir
   C. glargine
   D. regular
4. A nurse presents comatose to the ED with severe hypoglycemia. She responds to D 50. She denies taking any medication but is under treatment for depression. Vital signs are normal and she appears well. The best workup for the patient is:
   A. Draw insulin and c-peptide levels.
   B. Order a CT scan for insulinoma.
   C. Draw blood cultures and start broad spectrum antibiotics.
   D. Discharge the patient without further workup and have her eat frequent small meals.
5. Which of the following insulins *cannot* be given IV?
   A. regular
   B. NPH
   C. glargine
   D. All insulins can be given IV.
6. Which of the following insulins is FDA approved as an "inhaled" insulin rather than by subcutaneous injection?
   A. detemir (Levemir)
   B. glulisine (Apidra)
   C. lispro (HumaLOG)
   D. technospheres (Afrezza)
   E. neutral protamine hagedorn
7. Insulin pump therapy has *not* been associated with:
   A. improved glucose control in type 1 diabetes
   B. reduction in hypoglycemia in type 1 and type 2 diabetes
   C. greater patient preference and quality of life in type 2 diabetes
   D. universal insurance coverage
8. You are starting a patient on insulin from the ED. What is an appropriate starting dose?
   A. 0.1-0.2 U/kg NPH once a day
   B. 1.0-2.0 U/kg NPH once a day
   C. 0.1-0.2 U/kg regular once a day
   D. 0.1-0.2 U/kg regular 4 times a day
9. A patient presents with urosepsis and a glucose of 300 mg/dL. He has no history of prior diabetes. What dose of insulin should he receive?
   A. 2 U regular
   B. 6 U regular
   C. 10 U regular
   D. 2 U/kg regular
10. When writing a prescription for insulin, which of the following is *not* recommended?
    A. Capitalize the last 3 letters of the name.
    B. Write out the word "units."
    C. Specify pens or syringes.
    D. Use the term "as needed" to allow the patient to titrate the insulin dose.

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the references for further research.
2. Scan the QR code to the right or log on to www.cmecity.com.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After completing the test, your browser will be directed to the activity evaluation form.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

EMERGENCY MEDICINE REPORTS

CME Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

EMERGENCY MEDICINE REPORTS™
(ISSN 0746-2506) is published biweekly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Telephone: (800) 688-2421 or (404) 262-7436.

Editorial Director: Lee Landenberger
Executive Editor: Shelly Morrow Mark

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Emergency Medicine Reports,*** P.O. Box 550669, Atlanta, GA 30355.

Back issues: $31. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

SUBSCRIBER INFORMATION

CUSTOMER SERVICE: 1-800-688-2421

Customer Service E-Mail Address:
customerservice@ahcmedia.com

Editorial E-Mail Address:
shelly.mark@ahcmedia.com

World-Wide Web page:
www.ahcmedia.com

SUBSCRIPTION PRICES

1 year with 65 ACEP/65 AMA/39 AAFP Category 1/Prescribed credits: $564

1 year *without* credit: $419
Add $19.99 for shipping & handling

MULTIPLE COPIES:
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

One to nine additional copies:
$359 each;
10 or more additional copies:
$319 each.

All prices U.S. only. U.S. possessions and Canada, add $30 plus applicable GST. Other international orders, add $30.

ACCREDITATION

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 65 *AMA PRA Category 1 Credits™*. Each issue has been designated for a maximum of 2.50 *AMA PRA Category 1 Credits™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Approved by the American College of Emergency Physicians for a maximum of 65.00 hour(s) of ACEP Category I credit.

This Enduring Material activity, Emergency Medicine Reports, has been reviewed and is acceptable for up to 39.00 Prescribed credits by the American Academy of Family Physicians. Term of approval begins 01/01/2015. Term of approval is for one year from this date. Each monograph is approved for 1.50 Prescribed credits. Credit may be claimed for one year from the date of each monograph. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Each issue is approved for 1.50 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 65 AOA Category 2-B credits.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This CME activity is intended for emergency and family physicians. It is in effect for 36 months from the date of the publication.

EMERGENCY MEDICINE REPORTS

Insulin: A Primer

Important Causes of Hypoglycemia

- Intentional or unintentional overdose of insulin
- Intentional or unintentional overdose of oral hypoglycemic
- Insulinoma, multiple endocrine neoplasias
- Liver disease
- End stage renal disease
- Hypopituitarism
- Hypothyroidism
- Inborn errors of metabolism
- Starvation
- Sepsis
- ETOH
- Reactive after gastric surgery

Pharmacokinetic Profiles of Currently Available Insulins and Insulin Analogs

					Time of Action (hours)		
Insulin	**Brand Name**	**Manufacturer**	**Species Source**	**Concentration**	**Onset**	**Peak Effect**	**Duration**
Rapid							
Glulisine	Apidra	Sanofi-Aventis	human analog	U100	0.2-0.5	1.6-2.8	3-4
Lispro	HumaLOG	Lilly	human analog	U100	0.25-0.5	0.5-2.5	≤ 5
Aspart	NovoLOG	Novo Nordisk	human analog	U100	0.2-0.3	1-3	3-5
Short-Acting							
Regular	HumuLIN R NovoLIN R	Lilly Novo Nordisk	human	U100	0.5	2.5-5	4-12
Intermediate							
NPH	HumuLIN N NovoLIN N	Lilly Novo Nordisk	human	U100	1-2	4-12	14-24
Intermediate/Short-Acting Mixed							
70 NPH 30 regular	HumuLIN 70/30 NovoLIN 70/30	Lilly Novo Nordisk	human	U100	0.5	regular 0.8-2 NPH 6-10	18-24
Intermediate/Rapid-Acting Mixed							
50 lispro protamine 50 lispro	HumaLOG Mix 50/50	Lilly	human analog	U100	0.25-0.5	0.8-4.8	14-24
75 lispro protamine 25 lispro	HumaLOG Mix 75/25	Lilly	human analog	U100	0.25-0.5	1-6.5	14-24
70 aspart protamine 30 aspart	NovoLOG Mix 70/30	Novo Nordisk	human analog	U100	10-20 minutes	1-4	18-24
Long							
Detemir	Levemir	Novo Nordisk	human analog	U100	3-4	3-9	6-23
Glargine	Lantus	Sanofi-Aventis	human analog	U100	3-4	none	average 24
Miscellaneous Long							
Regular	HumuLIN R U500 (concentrated)	Lilly	human	U500	0.5	2.5-5	up to 24

Basal Insulin Algorithms

Measure	ADA/EASD	AACE/ACE	IDF	CDA
Algorithm Initial dosage	10 U/d	10 U/d	Not specified	10 U/d
Titration	2 U every 3 days	1-3 U every 2-3 days	2 U every 3 days	1 U every day
Target FBG, mg/dL	70-130	< 110[a]	<110	72-126

[a]Fasting blood glucose (FBG) target recommendation from the American Association of Clinical Endocrinologists (AACE) 2011 guidelines.

Abbreviations: ACE, American College of Endocrinology; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; EASD, European Association for the Study of Diabetes; A1c, glycated hemoglobin; IDF, International Diabetes Federation.

Adapted from: LaSalle JR, Berria R. Insulin therapy in type 2 diabetes: A practical approach for primary care physicians and other health professionals. *J Am Osteopath Assoc* 2013;113:152-162.

Recommended Mealtime Insulin Titrations

Measure	ADA/ EASD	AACE/ ACE	IDF	CDA[a]
Algorithm Initial dosage	4 U	5 U	Not specified	Total daily dose of 0.3-0.5 U/kg; 40% of total = basal; 20% of total = bolus (3 times/d) 1 U every day
Titration	2 U every 3 days	2-3 U every 2-3 days	2 U every 3 days	NA

Adapted from: LaSalle JR, Berria R. Insulin therapy in type 2 diabetes: A practical approach for primary care physicians and other health professionals. *J Am Osteopath Assoc* 2013;113:152-162.

Available Insulin Products and Delivery Methods

Insulin Product	Regular Insulin	NPH	Glulisine	Aspart	Lispro	Detemir	Glargine	Afrezza
Vial	X	X	X	X	X	X	X	
Permanent refillable insulin pen				X Echo pen Novo Jr. pen Novopen 3	X Luxura HD			
Disposable insulin pen		X	X Solostar pen	X Flexpen	X Kwikpen	X Flexpen, Flextouch	X Solostar pen	
Inhaler								X

Supplement to *Emergency Medicine Reports*, January 11, 2015: "Insulin: A Primer." *Authors:* **Jay H. Shubrook, DO, FACOFP, FAAFP,** Associate Professor of Family Medicine, Director, Diabetes Fellowship Program, The Diabetes Institute at Ohio University; **Nancy Mora Becerra, MD**, Ohio State University, Columbus, OH; **Sarah E. Adkins, PharmD, BCACP**, Faculty, The Ohio State University College of Pharmacy; Assistant Professor of Pharmacology, Ohio University Heritage College of Medicine, Athens, OH; **Aili Guo, MD**, Assistant Professor of Specialty Medicine, Ohio University Heritage College of Osteopathic Medicine.

TRAUMA REPORTS

Practical, Evidence-Based Reviews in Trauma Care

JAN/FEB 2015 VOL. 16, NO. 1

AUTHORS

Jonathan Stevens, MD, Department of Emergency Medicine, The Ohio State University Wexner Medical Center, Columbus.

Emile El-Shammaa, MD, Department of Emergency Medicine, The Ohio State University Wexner Medical Center, Columbus.

PEER REVIEWER

Frank LoVecchio, DO, MPH, FACEP, ABMT, Vice-Chairman and Research Director, Maricopa Medical Center, Professor, Emergency Medicine, Pharmacology and Medicine, University of Arizona College of Medicine, Co-Medical Director, Banner Poison and Drug Information Center, Phoenix, AZ.

STATEMENT OF FINANCIAL DISCLOSURE

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. LoVecchio (peer reviewer) discloses that his group has received research grants from the National Institutes of Health in infectious disease and suicide prevention. Dr. Dietrich (editor in chief), Dr. Stevens (author), Dr. El-Shammaa (author), and Ms. Behrens (nurse reviewer) report no relationships with companies related to this field of study. Mr. Landenberger (editorial director) and Ms. Mark (executive editor) report no relationships with companies related to the field of study covered by this CME activity.

AHC Media

Carbon Monoxide and Cyanide Poisoning in Smoke Inhalation Victims: A Review

Carbon monoxide and cyanide are highly lethal toxic compounds that can cause significant morbidity and mortality. Smoke inhalation victims present a unique challenge because they can be exposed to both substances. This article will review the most recent literature on carbon monoxide and cyanide diagnostic evaluation and treatment options for each poisoning. Practitioners need to maintain a high index of suspicion to identify and treat carbon monoxide and cyanide poisonings in smoke inhalation victims. Carbon monoxide poisoning can be identified with detection of carboxyhemoglobin levels in blood or bedside co-oximetry. Initial treatment is the administration of 100% normobaric oxygen. Hyperbaric oxygen is a treatment adjunct, although the benefits of this modality are controversial. For cyanide poisoning, there is no quick bedside or laboratory confirmatory test, and it remains a clinical diagnosis. Fire victims with soot in their mouth, altered mental status, and metabolic acidosis with extremely high lactate levels suggest cyanide poisoning. Treatment options are hydroxycobalamin, sodium thiosulfate, and amyl/sodium nitrite. Both hydroxycobalamin and sodium thiosulfate can be given in suspected cyanide and concomitant carbon monoxide poisonings. Amyl and sodium nitrites can cause methemoglobinemia and hypotension and therefore are not recommended if carbon monoxide poisoning is also suspected. Several papers advocate the superiority of hydroxycobalamin due to its quicker onset of action, but to date there exists no well-designed randomized, controlled trial comparing its efficacy to sodium thiosulfate and amyl/sodium nitrite.

— Ann M. Dietrich, MD, Editor

Introduction

Victims of fires are complicated patients who can have a multitude of injuries that can cause significant morbidity and mortality. Smoke inhalation can cause systemic toxicity from carbon monoxide (CO) and/or cyanide (CN) exposure. Both toxins can cause significant injury or death if unrecognized by clinicians. The purpose of this article is to review the epidemiology, pathophysiology, diagnosis, and management of carbon monoxide and cyanide poisonings.

EXECUTIVE SUMMARY

- Carbon monoxide poisoning is more likely to occur during the winter months in colder climates due to defective household furnaces or improper use of cooking equipment for heating in enclosed spaces.
- In fires, hydrogen cyanide gas is created from the combustion of products containing carbon and nitrogen. Most often this is in foam rubber, wool, plastics, and other common synthetic materials.
- Mild CO poisonings can cause headache, nausea, fatigue, irritability, confusion, vertigo, and flu-like symptoms. Severe poisonings can have profound effects such as delirium, ataxia, chest pain, dyspnea, seizures, coma, myocardial infarction (MI), stroke, and death.
- Patients with CN poisoning present with nonspecific symptoms including headache, nausea, vertigo, anxiety, altered mental status, tachypnea, and hypertension. More serious poisonings will result in dyspnea, bradycardia, hypotension, and arrhythmia, with the most severe poisonings presenting with unconsciousness, convulsions, and cardiovascular collapse, followed by shock, pulmonary edema, and death.
- Blood lactate levels greater than 8 mmol/L in non-smoke-inhalation victims and greater than 10 in smoke-inhalation victims should be considered diagnostic of CN toxicity.

Epidemiology

Smoke inhalation is estimated to be responsible for up to 75% of fire-related deaths in the United States.[1] Inhalation injuries are also an independent predictor of prolonged intensive care unit (ICU) care and mortality.[2] In a case review of patients with carbon monoxide poisoning, those with concomitant smoke inhalation had a higher risk of dying than those with CO exposure alone.[44] A recent meta-analysis demonstrated that the overall mortality rate among burn patients was 13.9% (4-28.3%), with the mortality rate for burn patients with inhalational trauma being 27.6% (7.8-28.3%).[3] In the United States and Canada, fire death rates are twice as high as in Europe and Japan.[4] Due to the numerous mechanisms of injury associated with fires and smoke inhalation, it is difficult to actually quantify the morbidity and mortality directly related to exposures to CO and CN. Most of the data focused on CO and CN are based on non-fire-related exposures.

Between 2004 and 2006, an estimated 20,636 nonfatal, unintentional, non-fire-related CO exposures were treated annually in the United States.[5] Carbon monoxide poisoning is more likely to occur during the winter months in colder climates due to defective household furnaces or improper use of cooking equipment for heating in enclosed spaces.[6,7,8] The CDC also has noticed spikes in carbon monoxide poisonings during disasters that result in power outages, resulting in improper use of generators in poorly ventilated areas.[9,10] Other causes of poisonings are from suicide attempts, older automobiles, use of power tools in enclosed spaces, and hookah smoking.[11]

According to the Toxic Exposure Surveillance System, there were 3165 human exposures to cyanide reported to Poison Centers from 1993 to 2002.[12] In 2011, only 246 cyanide exposures were reported to Poison Centers in the United States.[13,14] The number of actual cases is likely underreported. The most common cause of cyanide poisoning is smoke inhalation. It is speculated that most on-site fatalities in smoke inhalation victims are due to cyanide

Table 1. Contributors to HCN Production

Major Contributors to HCN Production During Combustion

- Insulation
- Furniture coverings
- Plastic furniture
- Draperies
- Carpets
- Appliances
- Many plastics
- Some clothing
- Products containing nylon, polyurethane, melamine, acrylonitrile

Minor Contributors to HCN Production During Combustion

- Grass clippings
- Green wood
- Tobacco
- Cotton
- Paper
- Wool
- Silk
- Weeds
- Animal carcasses

poisoning.[15] In fires, hydrogen cyanide gas is created from the combustion of products containing carbon and nitrogen. Most often this is in foam rubber, wool, plastics, and other common synthetic materials.[16] (*See Table 1.*) Cyanide is found in nature in the Prunus species, consisting of apricots, bitter almonds, cherries, and peaches. All of these fruits have pits containing the glucoside amygdalin. When ingested, amygdalin is biotransformed by intestinal d-glucosidase to glucose, aldehyde, and cyanide. Cyanide is also found in cassava root.[17] Cyanide salts are used in industrial settings, particularly in jewelry and textile industries.[18] In medical treatments, cyanide poisoning can result from sodium nitroprusside treatment for hypertensive emergency.[19]

Pathophysiology

Carbon monoxide (CO) is an odorless, tasteless, colorless gas that is created by the incomplete combustion of fuels (fossil fuels, oil, wood, etc.). CO is inhaled in the lungs, perfuses across the alveolar barrier, and binds to hemoglobin to form carboxyhemoglobin. CO has an affinity to hemoglobin 210 times greater than that of oxygen. Consequentially, there is a leftward shift of the hemoglobin-oxygen dissociation curve, decreasing hemoglobin's release of oxygen, resulting in cellular hypoxia. CO also impairs the oxygen supply to the mitochondria in myocardial cells, causing injury through the binding to intracellular myoglobin.[20-23]

CO poisoning can cause nonspecific symptoms. The most common symptoms are headache, dizziness, nausea and vomiting, loss of consciousness, and confusion.[24] Mild poisonings can cause headache, nausea, fatigue, irritability, confusion, vertigo, and flu-like symptoms. Severe poisonings can have profound effects such as delirium, ataxia, chest pain, dyspnea, seizures, coma, myocardial infarction (MI), stroke, and death. (*See Table 2.*) Chronic exposures have been associated with depression, confusion, and memory loss.[21-23]

The systems most affected by CO poisoning are those that are the most prone to hypoxia: the brain and the heart. In the cardiac system, CO poisoning can result in ischemia, infarction, and/or dysrhythmias. Patients with a history of coronary artery disease are more prone to such injuries, but ischemia can occur in patients with no underlying coronary artery disease.[25] Those patients with cardiac injury are more likely to have increased long-term mortality.[26] In the central nervous system (CNS), carbon monoxide causes acute intoxication, neurological dysfunction, and can lead to chronic neurological sequelae. The areas of the brain most susceptible to injury are the cerebral cortex, white matter, basal nuclei, and Purkinje cells of the cerebellum.[27] (*See Figure 1.*) In severe poisonings, other organs can also be injured, such as the kidneys and liver. Whether this is because of direct organ injury due to hypoxia or secondary to low perfusion due to acute heart failure in the setting of MI has not been established.[21]

Long-term neurological sequelae are varied both in deficit and intensity. The most common symptoms are disorientation, memory disturbance, attention disturbance, parkinsonism, ataxia, urinary incontinence, gait disturbance, and other neuropsychiatric manifestations.[27] Also, a lucid interval of recovery followed by a sudden and progressive recurrence or deterioration of neuropsychiatric symptoms sometimes occurs, which is known as delayed encephalopathy.[28]

Cyanide's mechanism of toxicity involves the disruption of the electron transport chain in the mitochondrial production of ATP by binding to and inhibiting cytochrome oxidase a_3. (*See Figure 2.*) With the cessation of aerobic cellular metabolism, cells are forced to rely on anaerobic fermentation for the production of ATP, with the subsequent production of lactate. The result is a profoundly acidotic state, quickly resulting in cellular death. Clinical manifestations reflect rapid dysfunction of oxygen-sensitive organs, with CNS and cardiovascular findings predominating. The time to onset of symptoms typically is seconds with inhalation of gaseous hydrogen cyanide (HCN).[17] Estimates of lethal dose vary, but exposures to gaseous HCN at concentrations above 300 ppm will likely result in death within a few minutes.[29] Mild cases of CN poisoning present with nonspecific symptoms including headache, nausea, vertigo, anxiety, altered mental status, tachypnea, and hypertension. More serious poisonings will result in dyspnea, bradycardia, hypotension, and arrhythmias, with the most severe poisonings presenting with unconsciousness, convulsions, and cardiovascular collapse, followed by shock, pulmonary edema, and death.[30,31] (*See Table 3.*)

Table 2. Symptoms of Carbon Monoxide Toxicity

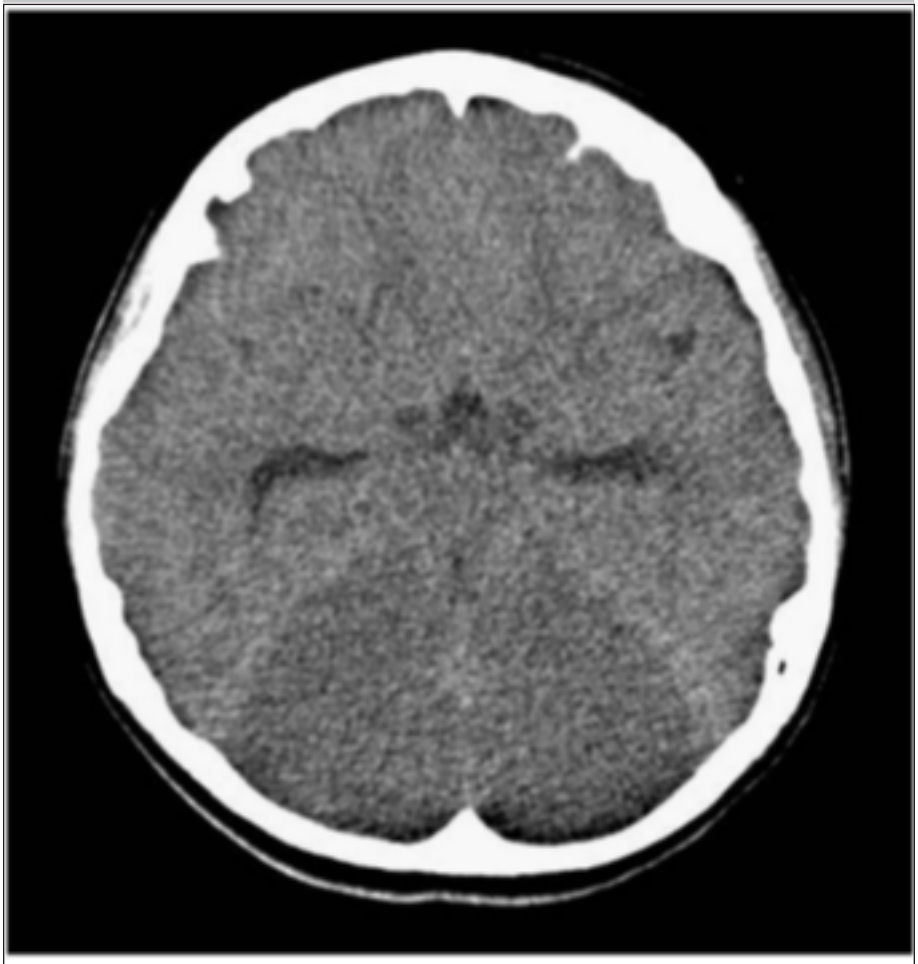
Mild Exposure	Severe Exposure
Headache	Delirium
Dizziness	Ataxia
Nausea	Loss of consciousness
Vomiting	Chest pain
Confusion	Dyspnea
Vertigo	Myocardial infarction
Irritability	Stroke
Flu-like symptoms	Coma
Fatigue	Death

Diagnosis of Carbon Monoxide Poisoning

The key to diagnosis of CO poisoning is to have a high index of suspicion. Nonspecific symptoms and a history of household contacts with similar symptoms and circumstances surrounding the onset of symptoms should prompt consideration of exposure in the differential diagnosis.

CO poisoning causes cellular hypoxia. Standard pulse-oximetry does not

Figure 1. Diffuse Hypodensity of Cerebellum Due to Hypoxic-ischemic Injury



Axial nonenhanced cranial CT scan of an 8-year-old patient on the day of CO poisoning shows diffuse hypodensity of the cerebellum due to hypoxic-ischemic injury.
Reprinted with permssion Fan HC, Wang AC, Lo CP et al. Damage of cerebellar white matter due to carbon monoxide poisoning: A case report. *Am J Emerg Med* 2009;27:757.e5–757.e7.

distinguish between the wavelengths caused by the refractions of hemoglobin, carboxyhemoglobin, and methemoglobin. Previously, measuring plasma levels of carboxyhemoglobin (COHb) was the gold standard for diagnosing CO poisoning. Pulse Co-oximetry (Rad-57 Masimo Corporation, Irvine, CA) distinguishes between the wavelengths of hemoglobin, methemoglobin, and carboxyhemoglobin, and has become widely available, but the reliability is debatable. Several studies have shown co-oximetry to be highly reliable compared to COHb measurements.[32-36] Other studies have shown a high false-positive rate, and conclude that a positive screening for CO poisoning on co-oximetry warrants confirmation by COHb levels.[37-39] Studies have also shown that co-oximetry tends to overestimate actual COHb levels.[38,40] What can be concluded is that co-oximetry is a useful tool to quickly screen suspected CO poisonings, which can then be confirmed by laboratory analysis.

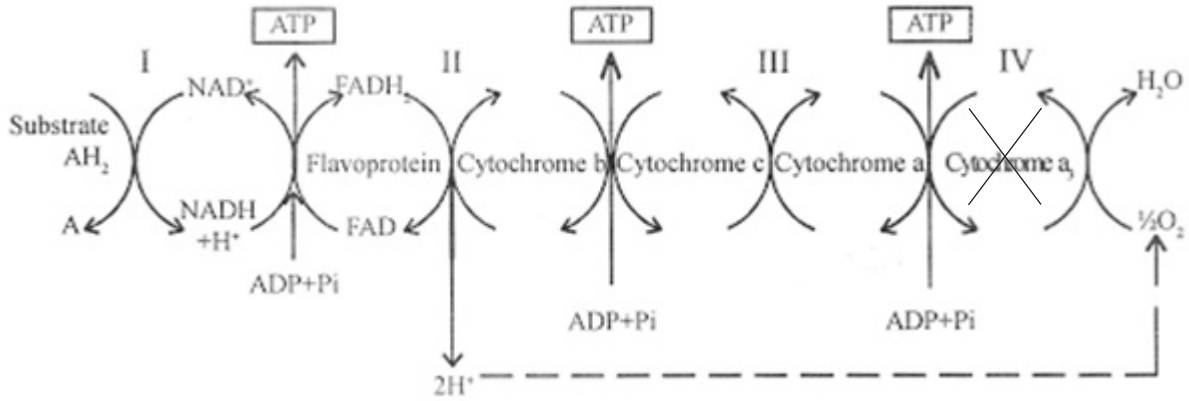
Normal carboxyhemoglobin levels are between 2% and 5% in nonsmokers and can range from 5-13% in chronic smokers. The presence of fetal hemoglobin, as high as 30% at 3 months, may be read as an elevation of HbCO level to 7%.[20,21,23] The level of carboxyhemoglobin in the blood does not correlate with the severity of toxicity.[41] Negative carboxyhemoglobin levels may be present in patients who have already received 100% oxygen or if sufficient time has passed since time of exposure.

Often there is a mild leukocytosis in carbon monoxide poisoning. Arterial blood gases should show a normal PaO_2 level and a mild acidosis. Cardiac biomarkers can be elevated if the exposure has resulted in myocardial ischemia. Metabolic acidosis secondary to lactic acidosis can be seen if there is ischemia. In severe poisonings, there can be evidence of end organ injury, such as elevated BUN, creatinine, and creatinine kinase levels, as well as proteinuria due to rhabdomyolysis. There can be abnormal liver function tests due to hepatic failure.[21,23] Characteristic findings on imaging of the brain are petechial hemorrhages of the white matter, necrosis of the bilateral globi pallidi, spongy change, and progressive demyelination in the cerebral cortex, thalamus, and hippocampus.[42]

Diagnosis of Cyanide Poisoning

Due to its lethality and the delay in return of blood cyanide levels, cyanide poisoning is a clinical diagnosis. The diagnosis should be suspected in anyone who inhales smoke in a closed-space fire, particularly in the presence of soot in the mouth, altered mental status, and hypotension.[43] Blood lactate levels greater than 8 mmol/L in non-smoke-inhalation victims and greater than 10 in smoke-inhalation victims should be considered diagnostic. While severe burns, CO poisoning, and other traumatic injuries can cause lactic acidosis, they are unlikely to cause the profound lactic acidosis that is seen in CN poisoning.[44,45] Due to delay in results, laboratory cyanide levels should only be obtained for diagnostic confirmation and not for medical decision making. Toxic and lethal thresholds of cyanide are 1.0 mg/L and 3.0 mg/L, respectively.[46] Venous blood gases with very high PaO_2 levels (levels that would be anticipated on an arterial blood gas) can also be suggestive of cyanide poisoning. This is attributed to the inability of cells

Figure 2. Mitochondrial Electron Transport Chain



to extract and use oxygen, and so venous blood remains highly oxygenated.[43]

Treatment of Carbon Monoxide Poisoning

Treatment begins by removing the victim from the source of exposure. The antidote of carbon monoxide poisoning is oxygen. (*See Table 4.*) All victims suspected of toxicity should receive 100% oxygen via a nonrebreather mask, noninvasive positive pressure ventilation, or endotracheal ventilation. The theory of treatment is based on oxygen competitively displacing CO from hemoglobin. While breathing room air, this process takes about 300 minutes. While on a 100% oxygen by nonrebreather mask, this time is reduced to about 90 minutes; with hyperbaric oxygen treatment, the time is shortened to 32 minutes.[47] Once the diagnosis is confirmed, the use of hyperbaric oxygen should be considered. (*See Figure 3.)* The only absolute contraindications to hyperbaric therapy are an untreated pneumothorax, ongoing medical instability, and medication history of past bleomycin or cisplatin treatment, or current doxorubicin, disulfiram, or sulfamylon treatment.[47,48] The goal of initial intervention, whether hyperbaric or normobaric oxygen, is a carboxyhemoglobin level of less than 5%.[23] Once the patient is clinically stable, imaging of the brain and neuropsychological testing is required. MRI is the most sensitive modality to detect brain abnormalities, although it is unknown if MRI findings during acute poisonings can predict long-term neurological sequelae.[27,49]

Table 3. Symptoms of Cyanide Poisoning

Symptoms of Mild Cyanide Poisoning

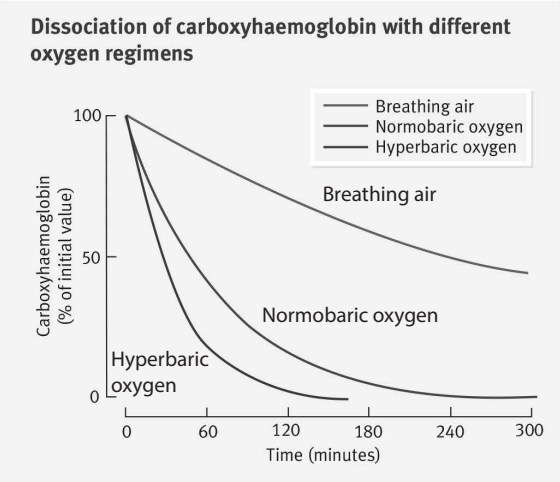
- Headache
- Nausea
- Vertigo
- Anxiety
- Altered mental status
- Tachypnea
- Hypertension

Symptoms of Serious Cyanide Poisoning

- Dyspnea
- Bradycardia
- Hypotension
- Arrhythmia
- Unconsciousness
- Convulsions
- Cardiovascular collapse

Hyperbaric treatment remains controversial because there is no global consensus of when it is appropriate to consider hyperbaric treatment and what hyperbaric protocols should be used. The Undersea and Hyperbaric Medical Society recommends hyperbaric oxygen therapy for patients with serious carbon monoxide poisoning — as manifested by transient or prolonged unconsciousness, abnormal neurologic signs, cardiovascular dysfunction, or severe acidosis — or patients who are 36 years of age or older, were exposed for 24 hours or more (including intermittent exposures), or have a carboxyhemoglobin level of 25% or greater.[48,50] (*See Table 5.*) Studies have indicated that hyperbaric oxygen can decrease the severity and incidence of long-term neurological sequelae.[48,51] Animal studies have shown that hyperbaric oxygen leads to more rapid improvement in cardiovascular status, lower mortality,

Figure 3. Dissociation of Carboxyhaemoglobin with Different Oxygen Regimens



Increasing the partial pressure of inspired oxygen accelerates elimination of carbon monoxide.
Reprinted with permission from Bateman DN. Carbon monoxide. *Medicine* 2012;40:115-116.

Table 4. Treatments for Carbon Monoxide Poisoning

- 100% oxygen by nonrebreather mask, noninvasive positive pressure ventilation, or endotracheal intubation
- Hyperbaric oxygen treatment

Table 5. When to Consider Hyperbaric Oxygen Treatment for CO Poisoning

- When the patient has a COHb level greater than 25-30%
- Evidence of cardiac involvement
- Severe acidosis
- Transient or prolonged unconsciousness
- Neurological impairment
- Abnormal neuropsychiatric testing
- Patient's age is 36 years or older
- Pregnant women

Source: Centers for Disease Control and Prevention

and lower incidence of neurological sequelae.[51] However, in February 2008, a clinical policy statement released by the American College of Emergency Physicians (ACEP) gave Level C recommendations to hyperbaric oxygen as a therapeutic option for CO-poisoned patients, but that its use cannot be mandated.[52]

Cyanide Treatment

Due to the lethality of cyanide, once a patient is removed from the potential source of exposure, initiation of antidote therapy must occur as soon as possible, preferably in the pre-hospital stage. There are numerous available options for treatment of cyanide poisoning. The most commonly selected treatments are hydroxycobalamin and sodium thiosulfate. (*See Table 6.*) Which treatment is superior remains controversial. To date, there are no well-designed randomized, controlled trials comparing the efficacy of hydroxycobalamin versus sodium thiosulfate with sodium and/or amyl nitrite.

The newest drug available in the United States, hydroxycobalamin (Cyanokit-R), was approved by the FDA for treatment of known or suspected cyanide poisoning in 2006. Hydroxycobalamin (vitamin B12a) contains a cobalt ion that binds cyanide with greater affinity than cytochrome oxidase, to form the nontoxic metabolite cyanocobalamin (vitamin B12 family), which is excreted in the urine. The starting dose of hydroxycobalamin is 5 g given as an IV infusion over 15 minutes. A second dose of 5 g can be given.[53] In animal studies, hydroxycobalamin showed anecdotal efficacy for treatment of cyanide poisoning.[54] In a swine model of cyanide-induced cardiac arrest, hydroxycobalamin improved mean arterial blood pressures and pH, decreased lactate and cyanide levels in the blood when compared to epinephrine, and hydroxycobalamin showed increased survival in pigs compared to sodium thiosulfate.[55,56] In humans, a prospective study showed 28 out of 42 (66.7%) confirmed cyanide poisonings survived after treatment with hydroxycobalamin.[57] A retrospective study of hydroxycobalamin given empirically pre-hospital for suspected cyanide poisoning showed a survival to hospital discharge in 30 out of 72 patients in whom survival status was known (41.7%), and showed a pre-hospital return of spontaneous circulation in 21 out of 38 (55%) of patients in cardiac arrest.[58] The most common

Table 6. Treatments for Cyanide Toxicity

Treatment	Mechanism of Action	Delivery	Side Effects
Hydroxycobalamin	Binds to CN to form cyanocobalamin	5 g IV infusion over 15 minutes Additional 5 g may be given	Chromaturia Red skin discoloration Transient hypertension
Sodium thiosulfate	Uses rhodanase to form thiocyanate	12.5 g IV infusion over 30 minutes Given after sodium nitrite Given as sole agent if suspected CO poisoning May repeat at half dose after 1 hour	Hypotension (infusion rate dependent)
Sodium nitrite	Oxidizes hemoglobin to methemoglobin, combines with cyanide to form cyanomethemoglobin	300 mg IV infusion at 75-150 mg/min	Methemoglobinemia Hypotension
Amyl nitrite	Oxidizes hemoglobin to methemoglobin, combines with cyanide to form cyanomethemoglobin	0.3 mL ampule crushed and contents poured onto a gauze and placed in front of patient's mouth, or endotracheal tube if patient intubated, to inhale over 15-30 sec; repeat qMin until IV sodium nitrite available	Methemoglobinemia Hypotension

side effects of hydroxycobalamin are chromaturia and red skin discoloration, which are asymptomatic, self-limiting, and typically resolve in 72 hours. Another side effect is a brief hypertension that returns to baseline an average of 4 hours after administration. The most serious adverse effect documented in healthy volunteers was an allergic reaction in 2 out of 136 volunteers, both of which did not decompensate to full anaphylaxis.[57,59,60] Hydroxycobalamin can cause alterations in laboratory values, including elevated renal and hepatic function and uninterpretable dipstick urinalysis. This also typically resolves by 72 hours after administration.[53,57] The use of hydroxycobalamin can also interfere with measurement of carboxyhemoglobin levels by co-oximetry.[61] There is also a case report of hydroxycobalamin interfering with hemodialysis, causing the dialysis machine to shut down due to internal sensors detecting a "blood leak," which the authors attributed to hydroxycobalamin.[62]

Sodium thiosulfate removes cyanide through the action of rhodanase, an enzyme located in the liver, kidneys, and skeletal muscle. It acts to add a sulfur atom to cyanide to form thiocyanate, which is then excreted in the urine.[30] Compared to hydroxycobalamin, sodium thiosulfate has a slower onset of action.[63] The recommended dosing according to manufacturer is to administer 12.5 g (250 mg/kg in pediatrics, not to exceed 12.5 g) immediately after administration of sodium nitrite over 30 minutes.[64] No clinical trials of sodium thiosulfate are available, and efficacy has been extrapolated from case studies and series of acute cyanide poisoning.[54]

Amyl nitrite and sodium nitrite both are part of the cyanide antidote kit, which had been the treatment of choice for cyanide poisoning in the United States prior to the introduction of hydroxycobalamin in 2006. Sodium nitrite is given IV. Amyl nitrite perles are crushed up and inhaled and are generally reserved for cases in which IV access is delayed or not possible. Nitrites oxidize the iron in hemoglobin from the ferrous to the ferric state, converting hemoglobin into methemoglobin. Cyanide then combines with methemoglobin to form cyanomethemoglobin. It also causes vasodilation, leading to hypotension. The major side effects are hypotension and cellular hypoxia secondary to methemoglobinemia.[30,65] There is a black box warning for the use of nitrites because of hypotension and methemoglobinemia.[66] Use of amyl or sodium nitrite is not recommended in smoke inhalation victims who may also have carboxyhemoglobinemia secondary to carbon monoxide poisoning.[57]

Other antidotes not available in the United States include 4-dimethylaminophenol (4-DMAP) and dicobalt edentate. 4-DMAP is used outside of the United State instead of sodium or amyl nitrite. It generates methemoglobin more rapidly than sodium nitrite, with peak methemoglobin concentrations at 5 minutes after administration compared to 30 minutes after sodium nitrite administration. Like nitrites, the major side effects are methemoglobinemia and hypotension. Cobalt in the form of dicobalt edetate has been used as a cyanide chelator, but its usefulness is limited by serious adverse effects such as hypotension, cardiac dysrhythmias, decreased cerebral blood flow, and angioedema.[17]

Conclusions

Practitioners need to maintain a high index of suspicion to identify and treat carbon monoxide and cyanide

poisonings in smoke inhalation victims. Carbon monoxide poisoning can be identified with detection of carboxyhemoglobin levels in blood or bedside co-oximetry. The level of carboxyhemoglobin does not correlate with the level of toxicity. In addition to 100% normobaric oxygen, hyperbaric oxygen is a treatment option, although there is controversy regarding its benefits. Conversely, there is no quick test to confirm cyanide poisoning. Upon initial evaluation, fire victims with soot in their mouth, altered mental status, and metabolic acidosis with highly elevated lactate levels are highly suggestive of cyanide poisoning. Once cyanide toxicity is suspected, treatment must begin immediately. Further study is needed to determine the efficacy of hydroxycobalamin compared to sodium thiosulfate. If carbon monoxide poisoning is suspected, amyl and sodium nitrite are contraindicated.

References

1. Bizovi KE, Leikin JD. Smoke inhalation among firefighters. *Occup Med* 1995;10(4):721-733.
2. Sheppard NN, Hemington-Gorse S, Shelley OP, et al. Prognostic scoring systems in burns: A review. *Burns* 2011;37(8):1288-1295.
3. Colohan SM. Predicting prognosis in thermal burns with associated inhalational injury: A systematic review of prognostic factors in adult burn victims. *J Burn Care Res* 2010;31(4):529-539
4. Barillo DJ, Goode R. Fire fatality study: Demographics of fire victims. *Burns* 1996;22(2):85-88.
5. Centers for Disease Control and Prevention. Nonfatal, unintentional, non-fire related carbon monoxide exposures — United States, 2004–2006. *MMWR Morbid Mortal Wkly Rep* 2008;57:896-899.
6. Iqbal S, Law HZ, Clower JH. Hospital burden of unintentional carbon monoxide poisoning in the United States, 2007. *Am J Emerg Med* 2012;30:657–664.
7. Iqbal S, Clower JH, Hernandez SA et al. A Review of Disaster-Related Carbon Monoxide Poisoning: Surveillance, Epidemiology, and Opportunities for Prevention. *Am J Public Health* 2012;102(10): 1957-1963.
8. Heckerling PS, Leikin JB, Maturen A, et al. Predictors of occult carbon monoxide poisoning in patients with headache and dizziness. Ann Intern Med 1987;107 174-176.
9. Cukor J, Restuccia M. Carbon monoxide poisoning during natural disasters: The Hurricane Rita experience *J Emerg Med* 2007;33: 261-264.
10. Clower J, Henretig F, Trella J, et al. Notes from the dield: Carbon monoxide exposures reported to Poison Centers and related to Hurricane Sandy — Northeastern United States, 2012. *Weekly MMWR* November 9, 2012;61(44);905-905.
11. Ashurst JV, Urguhart M, Cook MD. Carbon monoxide poisoning secondary to hookah smoking. *J Am Osteopath Assoc* 2012;112(10): 686-688.
12. American Association of Poison Control Centers. Toxic Exposure Surveillance System. Annual Reports 1993-2002.
13. Huzar TF, George T, Cross JM. Carbon monoxide and cyanide toxicity: Etiology, pathophysiology and treatment in inhalation injury. *Expert Rev Respir Med* 2013;7(2):159-170.
14. Bronstein AC, Spyker DA, Cantilena LR Jr, et al. 2011 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report. *Clin Toxicol* 2012;50(10):911-1164.
15. Baud FJ, Barriot P, Toffis V, et al. Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med* 1991;325:1761-1766.
16. Geraci MJ, McCoy SL, Acquino ME. Woman with red urine: Hydroxycobalamin-induced chromaturia. *J Emerg Med* 2012;43:e207–e209.
17. Kirk MA, Holstege CP, Isom GE. Chapter 126. Cyanide and Hydrogen Sulfide. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, eds. *Goldfrank's Toxicologic Emergencies*, 9th ed. New York: McGraw-Hill; 2011.
18. Coentrao L, Moura D. Acute cyanide poisoning among jewelry and textile industry workers. *AJEM* 2011;29:78-81.
19. Davis DW, Griess L, Kadar D, et al. A sudden death associated with the use of sodium nitroprusside for induction of hypotension during anaesthesia. *Can Anaesth Soc J* 1975;22:547-552.
20. Bateman DN. Carbon Monoxide. *Medicine* 2012;40(3):115-116.
21. Tomaszewski C. Chapter 125. Carbon Monoxide. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, eds. *Goldfrank's Toxicologic Emergencies*, 9th ed. 2011.
22. Prockop LD, Chichkova RI. Carbon Monoxide intoxication: an updated review. *J Neurol Sci* 2007;262(1-2):122-130.
23. Weaver LK. Carbon monoxide poisoning. *N Engl J Med* 2009;360:1217-1225.
24. Clower JH, Hampson NB, Iqhal S, et al. Recipients of hyperbaric oxygen treatment for carbon monoxide poisoning and exposure circumstances. *Am J Emerg Med* 2012;30:846-851.
25. Kalay N, Ozdogru I, Cetinkaya Y, et al. Cardiovascular effects of carbon monoxide poisoning. *Am J Cardiol* 2007;99:322-324.
26. Henry CR, Satran D, Lindgren B, et al. Myocardial injury and long term mortality following moderate to severe carbon monoxide poisoning. *JAMA* 2006;295:398-402.
27. Prockop LD, Chichkova RI. Carbon Monoxide intoxication: An updated review. *J Neurol Sci* 2007;262(1-2):122-130.
28. Ide T, Kamijo Y. The early elevation of interleukin 6 concentration

in cerebrospinal fluid and delayed encephalopathy of carbon monoxide poisoning. *Am J Emerg Med* 2009;27:992–996.

29. WHO, Concise International Chemical Assessment Document 61: Hydrogen Cyanide and Cyanides: Human Health Aspects, International Programme on Chemical Safety, World Health Organization, Geneva, 2004.
30. Lawson-Smth P, Jansen EC, Hyldegaard O. Cyanide intoxication as part of smoke inhalation — a review on diagnosis and treatment from the emergency perspective. *Scand J Trauma Resusc Emerg Med* 2011;19:14.
31. Gracia R, Shepherd G. Cyanide poisoning and its treatment. *Pharmacotherapy* 2004;24: 1358-1365.
32. Barker SJ, Curry J, Redford D, et al. Measurement of carboxyhemoglobin and methemoglobin by pulse oximetry: A human volunteer study. *Anesthesiology* 2006;105(5):892-897.
33. Zaouter C, Zavorsky GS. The measurement of carboxyhemoglobin and methemoglobin using a noninvasive pulse CO-oximeter. *Respir Physiol Neurobiol* 2012;182(2-3): 88-92.
34. Piatkowski A, Ulrich D, Grieb G, et al. A new tool for the early diagnosis of carbon monoxide intoxication. *Inhal Toxicol* 2009;21(13): 1144-1147.
35. Coulange M, Barthelemy A, Hug F, et al. Reliability of new pulse CO-oximeter in victims of carbon monoxide poisoning. *Undersea Hyperb Med* 2008;35(2):107-111.
36. Suner S, Partridge R, Sucov A, et al. Non-invasive pulse co-oximetry screening in the emergency department identifies occult carbon monoxide toxicity. *J Emerg Med* 2008;34:441-450.
37. Weaver LK, Churchill SK, Deru K, et al. False positive rate of carbon monoxide saturation by pulse oximetry of emergency department patients. *Respir Care* 2013;58: 232-240.
38. Roth D, Herkner H, Schreiber W, et al. Accuracy of noninvasive multiwave pulse oximetry compared with carboxyhemoglobin from blood gas analysis in unselected emergency department patients. *Ann Emerg Med* 2011;58:74-79.
39. O'Malley G. Non-invasive carbon monoxide measurement is not accurate. *Ann Emerg Med* 2006;48: 447-448.
40. Coulange M, Barthelemy A, Hug F, et al. Reliability of new pulse CO-oximeter in victims of carbon monoxide poisoning. *Undersea Hyperb Med* 2008;35(2):107-111.
41. Hampson NB, Hauff NM. Carboxyhemoglobin levels in carbon monoxide poisoning: Do they correlate with the clinical picture?. *Am J Emerg Med* 2008;26:665–669.
42. Fan HC, Wang AC, Lo CP, et al. Damage of cerebellar white matter due to carbon monoxide poisoning: A case report. *Am J Emerg Med* 2009;27:757.e5–757.e7.
43. Borron SW. Recognition and treatment of acute cyanide poisoning. *J Emerg Nurs* 2006;32 (4 Suppl):S12-S18.
44. Baud FJ, Borron SW, Mégarbane B, et al. Value of lactic acidosis in the assessment of the severity of acute cyanide poisoning. *Crit Care Med* 2002;30:2044–2050.
45. Baud FJ, Barriot P, Toffis V, et al. Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med* 1991;325:1761-1766.
46. Fortin JL, Waroux S, Giocanti JP, et al. Hydroxycobalamin for poisoning caused by ingestion of potassium cyanide: A case study. *J Emerg Med* 2010;39:320-324.
47. Latham E, Hare MA, Neumeister M. Hyperbaric oxygen therapy. Medscape Reference. http://emedicine.medscape.com/article/1464149-overview#aw2aab6b6. Accessed May 2013.
48. Kindwall E, Whelan H. *Hyperbaric Medicine Practice*, 2nd ed. Flagstaff, AZ; Best Publishing Company: 2004.
49. Weaver LK, Valentine KJ, Hopkins RO. Carbon monoxide poisoning: Risk factors for cognitive sequelae and the role of hyperbaric oxygen. *Am J Respir Crit Care Med* 2007;176:491-497.
50. Gesell LB, ed. *Hyperbaric Oxygen Therapy Indications*, 12th ed. 2008.
51. Hu H, Pan X, Wan Y. Factors affecting the prognosis of patients with delayed encephalopathy after acute carbon monoxide poisoning. *Am J Emerg Med* 2011;29:261–264.
52. Wolf SJ, Lavonas EJ, Sloan EP, et al. Clinical policy: Critical issues in the management of adult patients presenting to the emergency department with acute carbon monoxide poisoning. *Ann Emerg Med* 2008;51:138-152.
53. Cyanokit (Hydroxocobalamin) [package insert]. Dey Pharmaceuticals; 2011. http://www.cyanokit.com/pdf/Single_5-g_Vial_PI.pdf. Accessed May 2013.
54. Hall AH, Dart R, Bogdan G. Sodium thiosulfate or hydroxocobalamin for the empiric treatment of cyanide poisoning? *Ann Emerg Med* 2007;49:806-813.
55. Berbate VS, Pitotti RL, Dixon PS, et al. Hydroxocobalamin and epinephrine both improve survival in a swine model of cyanide-induced cardiac arrest. *Ann Emerg Med* 2012;60 (4).
56. Berbate VS, Pitotti RL, Dixon PS, et al. Hydroxocobalamin versus sodium thiosulfate for the treatment of acute cyanide toxicity in a swine (Sus scrofa) model. *Ann Emerg Med* 2012;59(6).
57. Borron SW, Baud FJ, Barriot P, et al. Prospective study of hydroxocobalamin for acute cyanide poisoning in smoke inhalation. *Ann Emerg Med* 2007;49:794-801.
58. Fortin JL, Giocanti JP, Ruttimann M. Prehospital administration of hydroxocobalamin for smoke inhalation-associated cyanide poisoning: 8 years of experience in the Paris Fire Brigade. *Clin Toxic* 2006;44:37-44.

59. Uhl W, Notling A, Golor G. Safety of hydroxocobalamin in healthy volunteers in a randomized, placebo-controlled study. *Clin Toxic* 2006;44:17-28.

60. Megarbane B, Delahaye A, Goldgran-Toledano D, et al. Antidotal treatment of cyanide poisoning. *J Chin Med Assoc* 2003;66:193-203.

61. Lee J, Mukai D, Kreuter K, et al. Potential interference by hydroxocobalamin on cooximetry hemoglobin measurements during cyanide and smoke inhalation treatments. *Ann Emerg Med* 2007;49:802-805.

62. Sutter M, Tereshchenko N, Rafii R, et al. Hemodialysis complications of hydroxocobalamin: A case report. *J Med Toxicol* 2010;6(2):165–167.

63. Hall AH, Saiers J, Baud F. Which cyanide antidote? *Crit Rev Toxicol* 2009;39:541–552.

64. Thiosulfate [package insert] Hope Pharmaceuticals. 2012. http://www.thiosulfate.info/downloads/sodiumthiosulfate_prescribinginfo.pdf. Accessed May 2013.

65. Gracia R, Shepherd G. Cyanide poisoning and its treatment. *Pharmacotherapy* 2004;24: 1358-1365.

66. Nithiodote [Package insert] Hope Pharmaceuticals. 2011. http://www.hopepharm.com/downloads/nithiodote_prescribinginfo.pdf.

CME/CNE Questions

1. A patient brought from a house fire may be at risk for which of the following?
   A. trauma
   B. smoke inhalation
   C. carbon monoxide poisoning
   D. cyanide poisoning
   E. all of the above
2. Which of the following is a non-invasive way to screen for carbon monoxide poisoning?
   A. pulse co-oximetry
   B. pulse oximetry
   C. fetal hemoglobin screen
   D. clinical CO score
3. What is the first and most important treatment for carbon monoxide poisoning?
   A. cyanocobalamin
   B. hydroxycobalamin
   C. sodium thiosulfate
   D. amyl nitrite
   E. oxygen
4. What is the source of carbon monoxide's toxicity?
   A. a higher affinity to hemoglobin than oxygen
   B. impaired oxygen delivery to tissues
   C. cellular hypoxia
   D. multi-organ dysfunction
   E. all of the above
5. Which of the following patients may be particularly susceptible to carbon monoxide toxicity?
   A. men
   B. women
   C. smokers
   D. pregnant patients
6. Cyanide's mechanism of toxicity in humans involves which of the following?
   A. disruption of oxygen-hemoglobin affinity
   B. disruption of electron transport and ATP production
   C. direct cytotoxic injury
   D. direct neurotoxic injury
7. Since there is currently no rapid test for cyanide poisoning, which of the following is highly concerning for

TRAUMA REPORTS

CME Objectives

Upon completing this program, the participants will be able to:

- discuss conditions that should increase suspicion for traumatic injuries;
- describe the various modalities used to identify different traumatic conditions;
- cite methods of quickly stabilizing and managing patients; and
- identify possible complications that may occur with traumatic injuries.

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the references for further research.
2. **Until Jan. 4, log on to cmecity.com or scan the code to the right to take a post-test.** First-time users must register on the site using the 8-digit subscriber number printed on your mailing label, invoice, or renewal notice. **On and after Jan. 5, when logging onto the new AHCMedia.com, go to "MyAHC" and then "My Courses" to view your available continuing education activities.**
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After completing the test, your browser will be directed to the activity evaluation form.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

cyanide poisoning in a smoke exposure victim?
A. WBC > 30 k/uL
B. Hgb < 8 g/dL
C. pO_2 > 60 mmHg
D. lactate > 8 mmol/l
E. sodium < 125 mmol/L

8. Hydroxycobalamin selectively binds cyanide, resulting in the formation of which of the following?
A. free radicals
B. methemoglobin
C. cyanocobalamin
D. lactic acid
E. hydroxyurea

9. Amyl nitrite and sodium nitrite, when used to treat cyanide poisoning, may have which of the following serious side effects?
A. hypotension and methemoglobinemia
B. hypertension with crisis
C. hypernatremia
D. cobalt poisoning
E. cyanide deficiency

10. Cyanide, in the form of hydrogen cyanide gas, is formed from the combustion of carbon and nitrogen commonly found in:
A. liquid propane
B. coal
C. gasoline
D. oil
E. foam rubber, wool, plastics

TRAUMA REPORTS™ (ISSN 1531-1082) is published bimonthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Telephone: (800) 688-2421 or (404) 262-7436.

Editorial Director: Lee Landenberger
Executive Editor: Shelly Morrow Mark

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Trauma Reports,***
P.O. Box 550669, Atlanta, GA 30355.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

AHC Media

SUBSCRIBER INFORMATION

CUSTOMER SERVICE: 1-800-688-2421

Customer Service E-Mail Address:
customerservice@ahcmedia.com

Editorial E-Mail Address:
shelly.mark@ahcmedia.com

World-Wide Web page:
www.ahcmedia.com

SUBSCRIPTION PRICES

$259 per year. Add $19.99 for shipping & handling

FREE to subscribers of *Emergency Medicine Reports* and *Pediatric Emergency Medicine Reports*

MULTIPLE COPIES:
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

All prices U.S. only. U.S. possessions and Canada, add $30 plus applicable GST. Other international orders, add $30.

ACCREDITATION

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 2.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Approved by the American College of Emergency Physicians for a maximum of 2.5 hour(s) of ACEP Category I credit.

The American Osteopathic Association has approved this continuing education activity for up to 2.5 AOA Category 2-B credits per issue.

AHC Media is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 1.5 nursing contact hours using a 60-minute contact hour. Provider approved by the California Board of Registered Nursing, Provider # 14749, for 1.5 Contact Hours.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This CME/CNE activity is intended for emergency, family, osteopathic, trauma, surgical, and general practice physicians and nurses who have contact with trauma patients. It is in effect for 36 months from the date of publication.

Dear *Trauma Reports* Subscriber:

Here's a change we know you'll like: From now on, there is no more having to wait until the end of a 6-month semester or calendar year to earn your continuing education credits or to get your credit letter.

Here's how it works:
1. Read and study the issue, using the provided references for further research.

2. Until Jan. 4, log on to **cmecity.com** to take a post-test. First-time users must register on the site using the 8-digit subscriber number printed on your mailing label, invoice, or renewal notice. On and after Jan. 5, when logging onto the new **AHCMedia.com**, go to "MyAHC" and then "My Courses" to view your available continuing education activities.

3. Once the evaluation is completed, a credit letter is e-mailed to you instantly.

If you have any questions, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476.

You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5560.

You can also email us at: customerservice@ahcmedia.com.

On behalf of AHC Media, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,

Lee Landenberger
Continuing Education Director
AHC Media