Medical Errors & Complications of Medical Care

Ainsley Graham

Olympia Ly

First Edition, 2012

ISBN 978-81-323-1410-3

Published by:
College Publishing House
4735/22 Prakashdeep Bldg,
Ansari Road, Darya Ganj,
Delhi - 110002
Email: info@wtbooks.com

Table of Contents

Chapter 1

Adverse Effect

Adverse effect	
ICD-10	T78.
ICD-9	995.89

In medicine, an **adverse effect** is a harmful and undesired effect resulting from a medication or other intervention such as surgery. An adverse effect may be termed a "side effect", when judged to be secondary to a main or therapeutic effect. If it results from an unsuitable or incorrect dosage or procedure, this is called a medical error and not a complication. Adverse effects are sometimes referred to as "iatrogenic" because they are generated by a physician/treatment. Some adverse effects only occur only when starting, increasing or discontinuing a treatment. Using a drug or other medical intervention which is contraindicated may increase the risk of adverse effects. Adverse effects may cause medical complications of a disease or procedure and negatively affect its prognosis. They may also lead to non-compliance with a treatment regimen.

The harmful outcome is usually indicated by some result such as morbidity, mortality, alteration in body weight, levels of enzymes, loss of function, or as a pathological change detected at the microscopic, macroscopic or physiological level. It may also be indicated by symptoms reported by a patient. Adverse effects may cause a reversible or irreversible change, including an increase or decrease in the susceptibility of the individual to other chemicals, foods, or procedures, such as drug interactions.

In clinical trials, a distinction is made between adverse events (AEs) and serious adverse events (SAEs). Generally, any event which causes death, permanent damage, birth defects, or requires hospitalization is considered an SAE. The results of these trials are often included in the labeling of the medication to provide information both for patients and the prescribing physicians.

Reporting systems

In many countries, adverse effects are required by law to be reported, researched in clinical trials and included into the patient information accompanying medical devices and drugs for sale to the public.

United Kingdom

The Yellow Card Scheme is a United Kingdom initiative run by the Medicines and Healthcare products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM) to gather information on adverse effects to medicines. This includes all licensed medicines, from medicines issued on prescription to medicines bought over the counter from a supermarket. The scheme also includes all herbal supplements and unlicensed medicines found in cosmetic treatments. Adverse drug reactions (ADRs) can be reported by a number of health care professionals including physicians, pharmacists and nurses, as well as patients.

United States

In the United States several reporting systems have been built, such as the Vaccine Adverse Event Reporting System (VAERS), the Manufacturer and User Facility Device Experience Database (MAUDE) and the Special Nutritionals Adverse Event Monitoring System. MedWatch is the main reporting center, operated by the Food and Drug Administration.

Australia

In Australia, adverse effect reporting is administered by the Adverse Drug Reactions Advisory Committee (ADRAC), a subcommittee of the Australian Drug Evaluation Committee (ADEC). Reporting is voluntary, and ADRAC requests healthcare professionals to report all adverse reactions to its current drugs of interest, and serious adverse reactions to any drug. ADRAC publishes the Australian Adverse Drug Reactions Bulletin every two months.The Government's Quality Use of Medicines program is tasked with acting on this reporting to reduce and minimize the number of preventable adverse effects each year.

New Zealand

Adverse reaction reporting is an important component of New Zealand's pharmacovigilance activities. The Centre for Adverse Reactions Monitoring (CARM) in Dunedin is New Zealand's national monitoring centre for adverse reactions. It collects and evaluates spontaneous reports of adverse reactions to medicines, vaccines, herbal products and dietary supplements from health professionals in New Zealand. Currently the CARM database holds over 80 000 reports and provides New Zealand-specific information on adverse reactions to these products, and serves to support clinical decision making when unusual symptoms are thought to be therapy related

Adverse effects of medical procedures

Surgery may have a number of undesirable or harmful effects, such as infection, hemorrhage, inflammation, scarring, loss of function, or changes in local blood flow. They can be reversible or irreversible, and a compromise must be found by the physician and the patient between the beneficial or life-saving consequences of surgery versus its adverse effects. For example, a limb may be lost to amputation in case of untreatable gangrene, but the patient's life is saved. Presently, one of the greatest advantages of minimally invasive surgery, such as laparoscopic surgery, is the reduction of adverse effects.

Other nonsurgical physical procedures, such as high-intensity radiation therapy, may cause burns and alterations in the skin. In general, these therapies try to avoid damage to healthy tissues while maximizing the therapeutic effect.

Vaccination may have adverse effects due to the nature of its biological preparation, sometimes using attenuated pathogens and toxins. Common adverse effects may be fever, malaise and local reactions in the vaccination site. Very rarely, there is a serious adverse effect, such as eczema vaccinatum, a severe, sometimes fatal complication which may result in persons who have eczema or atopic dermatitis.

Diagnostic procedures may also have adverse effects, depending much on whether they are invasive, minimally invasive or noninvasive. For example, allergic reactions to radiocontrast materials often occur, and a colonoscopy may cause the perforation of the intestinal wall.

Adverse effects of drugs

Adverse effects can occur as a collateral or side effect of many interventions, but they are particularly important in pharmacology, due to its wider, and sometimes uncontrollable, use by way of self-medication. Thus, responsible drug use becomes an important issue here. Adverse effects, like therapeutic effects of drugs, are a function of dosage or drug levels at the target organs, so they may be avoided or decreased by means of careful and precise pharmacokinetics, the change of drug levels in the organism in function of time after administration.

Adverse effects may also be caused by drug interaction. This often occurs when patients fail to inform their physician and pharmacist of all the medications they are taking, including herbal and dietary supplements. The new medication may interact agonistically or antagonistically (potentiate or decrease the intended therapeutic effect), causing significant morbidity and mortality around the world. Drug-drug and food-drug interactions may occur, and so-called "natural drugs" used in alternative medicine can have dangerous adverse effects. For example, extracts of St John's wort (*Hypericum perforatum*), a phytotherapic used for treating mild depression are known to cause an increase in the cytochrome P450 enzymes responsible for the metabolism and elimination of many drugs, so patients taking it are likely to experience a reduction in blood levels of

drugs they are taking for other purposes, such as cancer chemotherapeutic drugs, protease inhibitors for HIV and hormonal contraceptives.

The scientific field of activity associated with drug safety is increasingly government-regulated,, and is of major concern for the public, as well as to drug manufacturers. The distinction between adverse and nonadverse effects is a major undertaking when a new drug is developed and tested before marketing it. This is done in toxicity studies to determine the nonadverse effect level (NOAEL). These studies are used to define the dosage to be used in human testing (phase I), as well as to calculate the maximum admissible daily intake. Imperfections in clinical trials, such as insufficient number of patients or short duration, sometimes lead to public health disasters, such as those of fenfluramine (the so-called fen-phen episode), thalidomide and, more recently, of cerivastatin (Baycol, Lipobay) and rofecoxib (Vioxx), where drastic adverse effects were observed, such as teratogenesis, pulmonary hypertension, stroke, heart disease, neuropathy, and a significant number of deaths, causing the forced or voluntary withdrawal of the drug from the market.

Most drugs have a large list of nonsevere or mild adverse effects which do not rule out the interruption of usage. These effects, which have a widely variable incidence according to individual sensitivity, include nausea, dizziness, diarrhea, malaise, vomiting, headache, dermatitis, dry mouth, etc. These can be considered a form of pseudo-allergic reaction, as not all users experience these effects; many users experience none at all.

Controversies

Sometimes, putative medical adverse effects are regarded as controversial and generate heated discussions in society and lawsuits against drug manufacturers. One example is the recent controversy as to whether autism was linked to the MMR vaccine (or by thiomersal, a mercury-based preservative used in some vaccines). No link has been found in several large studies and no change in the rate of autism has occurred when thimerosal was removed from vaccines a decade ago in Canada and Europe.

Another instance is the potential adverse effects of silicone breast implants, which lead to hundreds of thousands of litigations against manufacturers of gel-based implants, due to allegations of damage to the immune system which have not yet been conclusively proven.

Due to the exceedingly high impact on public health of widely used medications, such as hormonal contraception and hormone replacement therapy, which may affect millions of users, even marginal probabilities of adverse effects of a severe nature, such as breast cancer, have led to public outcry and changes in medical therapy, although its benefits largely surpassed the statistical risks.

Limitations of adverse effects reporting

In principle, medical professionals are required to report all adverse effects related to a specific form of therapy. In practice, it is at the discretion of the professional to determine whether a medical event is at all related to the therapy. For example, a leg fracture in a skiing accident in a patient who years before took antibiotics for pneumonia is not likely to get reported.

As a result, routine adverse effects reporting often may not include long-term and subtle effects that may ultimately be attributed to a therapy.

Part of the difficulty is identifying the source of a complaint. A headache in a patient taking medication for influenza may be caused by the underlying disease or may be an adverse effect of the treatment. In patients with end-stage cancer, death is a very likely outcome and whether the drug is the cause or a bystander is often difficult to discern.

Examples of adverse effects associated with specific medications

- Abortion, miscarriage or uterine hemorrhage associated with misoprostol (Cytotec), a labor-inducing drug (this is a case where the adverse effect has been used legally and illegally for performing abortions)
- Addiction to many sedatives and analgesics, such as diazepam, morphine, etc.
- Birth defects associated with thalidomide and isotretinoin (Accutane)
- Bleeding of the intestine associated with aspirin therapy
- Cardiovascular disease associated with COX-2 inhibitors (i.e. Vioxx)
- Deafness and kidney failure associated with gentamicin (an antibiotic)
- Death, following sedation, in children using propofol (Diprivan)
- Dementia associated with coronary artery bypass surgery
- Depression or hepatic injury caused by interferon
- Diabetes caused by atypical antipsychotic medications (neuroleptic psychiatric drugs)
- Diarrhea caused by the use of orlistat (Xenical)
- Erectile dysfunction associated with many drugs, such as antidepressants
- Fever associated with vaccination (in the past, imperfectly manufactured vaccines, such as Bacillus Calmette-Guérin (BCG) and poliomyelitis, have caused the very disease they intended to fight)
- Glaucoma associated with corticosteroid-based eye drops
- Hair loss and anemia may be caused by chemotherapy against cancer, leukemia, etc.
- Headache following spinal anaesthesia
- Hypertension in ephedrine users, which prompted FDA to remove the dietary supplement status of ephedra extracts
- Insomnia caused by stimulants, methylphenidate (Ritalin), Adderall, etc.
- Lactic acidosis associated with the use of stavudine (Zerit, for HIV therapy) or metformin (for diabetes)

- Liver damage from paracetamol
- Melasma and thrombosis associated with use of estrogen-containing hormonal contraception, such as the combined oral contraceptive pill
- Priapism associaded with the use of sildenafil
- Rhabdomyolysis associated with statins (anticholesterol drugs)
- Seizures caused by withdrawal from benzodiazepines
- Drowsiness or increase in appetite due to antihistamine use. Some antihistamines are used in sleep aids explicitly because they cause drowsiness.
- Stroke or heart attack associated with sildenafil (Viagra), when used with nitroglycerin
- Suicide, increased tendency associated to the use of fluoxetine and other selective serotonin reuptake inhibitor (SSRI) antidepressants
- Tardive dyskinesia associated with long-term use of metoclopramide and many antipsychotic medications

Chapter 2

Nosocomial Infection

Nosocomial infection	
ICD-10	Y95.

Nosocomial infections are infections that are a result of treatment in a hospital or a healthcare service unit. Infections are considered nosocomial if they first appear 48 hours or more after hospital admission or within 30 days after discharge. *Nosocomial* comes from the Greek word *nosokomeio* (νοσοκομείον) meaning hospital (*nosos* = disease, *komeo* = to take care of). This type of infection is also known as a **hospital-acquired infection** (or, in generic terms, **healthcare-associated infection**).

In the United States, the Centers for Disease Control and Prevention estimate that roughly 1.7 million hospital-associated infections, from all types of microorganisms, including bacteria, combined, cause or contribute to 99,000 deaths each year. In Europe, where hospital surveys have been conducted, the category of Gram-negative infections are estimated to account for two-thirds of the 25,000 deaths each year. Nosocomial infections can cause severe pneumonia and infections of the urinary tract, bloodstream and other parts of the body. Many types are difficult to attack with antibiotics, and antibiotic resistance is spreading to Gram-negative bacteria that can infect people outside the hospital.

Known nosocomial infections

- Ventilator associated pneumonia (VAP)
- *Staphylococcus aureus*
- Methicillin resistant *Staphylococcus aureus* (MRSA)
- *Pseudomonas aeruginosa*
- *Acinetobacter baumannii*
- *Stenotrophomonas maltophilia*
- *Clostridium difficile*
- Tuberculosis
- Urinary tract infection
- Hospital-acquired pneumonia (HAP)
- Gastroenteritis

- Vancomycin-resistant Enterococcus (VRE)
- Legionnaires' Disease

Epidemiology

Nosocomial infections are commonly transmitted when hospital officials become complacent and personnel do not practice correct hygiene regularly. Also, increased use of outpatient treatment means that people who are hospitalized are more ill and have more weakened immune systems than may have been true in the past. Moreover, some medical procedures bypass the body's natural protective barriers. Since medical staff move from patient to patient, the staff themselves serve as a means for spreading pathogens. Essentially, the staff act as vectors.

Categories and treatment

Among the categories of bacteria most known to infect patients are the category MRSA, Gram-positive bacteria and Helicobacter, which is Gram-negative. While there are antibiotic drugs that can treat diseases caused by Gram-positive MRSA, there are currently few effective drugs for Acinetobacter. However, Acinetobacter germs are evolving and becoming immune to existing antibiotics. "In many respects it’s far worse than MRSA," said a specialist at Case Western Reserve University.

Another growing disease, especially prevalent in New York City hospitals, is the drug-resistant Gram-negative germ, Klebsiella pneumoniae. It is estimated that more than 20 percent of the Klebsiella infections in Brooklyn hospitals "are now resistant to virtually all modern antibiotics. And those supergerms are now spreading worldwide."

The bacteria, classified as Gram-negative because of their reaction to the Gram stain test, can cause severe pneumonia and infections of the urinary tract, bloodstream, and other parts of the body. Their cell structure makes them more difficult to attack with antibiotics than Gram-positive organisms like MRSA. In some cases, antibiotic resistance is spreading to Gram-negative bacteria that can infect people outside the hospital. "For Gram-positives we need better drugs; for Gram-negatives we need any drugs," said Dr. Brad Spellberg, an infectious-disease specialist at Harbor-UCLA Medical Center, and the author of *Rising Plague,* a book about drug-resistant pathogens.

One-third of nosocomial infections are considered preventable. The CDC estimates that 2 million people in the United States are infected annually by hospital-acquired infections resulting in 20,000 deaths. The most common nosocomial infections are of the urinary tract, surgical site and various pneumonias.

Country estimates

The methods used differ from country to country (definitions used, type of nosocomial infections covered, health units surveyed, inclusion or exclusion of imported infections,

etc.), so that international comparisons of nosocomial infection rates should be made with the utmost care.

United States: The Centers for Disease Control and Prevention (CDC) estimates that roughly 1.7 million hospital-associated infections, from all types of bacteria combined, cause or contribute to 99,000 deaths each year. Other estimates indicate that 10%, or 2 million, patients a year become infected, with the annual cost ranging from $4.5 billion to $11 billion.

France: estimates ranged from 6.7% in 1990 to 7.4% (patients may have several infections). At national level, prevalence among patients in health care facilities was 6.7% in 1996, 5.9% in 2001 and 5.0% in 2006. The rates for nosocomial infections were 7.6% in 1996, 6.4% in 2001 and 5.4% in 2006.

In 2006, the most common infection sites were urinary tract infections (30,3 %), pneumopathy (14,7 %), infections of surgery site (14,2 %). infections of the skin and mucous membrane (10,2 %), other respiratory infections (6,8%) and bacterial infections / blood poisoning (6,4 %). The rates among adult patients in intensive care were 13,5% in 2004, 14,6% in 2005, 14,1% in 2006 and 14.4% in 2007.

It has also been estimated that nosocomial infections make patients stay in the hospital 4-5 additional days. Around 2004-2005, about 9,000 people died each year with a nosocomial infection, of which about 4,200 would have survived without this infection.

Italy: since 2000, estimates show that about 6.7 % infection rate, i.e. between 450,000 and 700,000 patients, which caused between 4,500 and 7,000 deaths. A survey in Lombardy gave a rate of 4.9% of patients in 2000.

United Kingdom: estimates of 10% infection rate, with 8.2% estimated in 2006.

Switzerland: estimates range between 2 and 14%. A national survey gave a rate of 7.2% in 2004.

Finland: estimated at 8.5% of patients in 2005

Transmission

The drug-resistant Gram-negative germs for the most part threaten only hospitalized patients whose immune systems are weak. The germs can survive for a long time on surfaces in the hospital and enter the body through wounds, catheters, and ventilators.

Main routes of transmission

Route	Description
Contact transmission	the most important and frequent mode of transmission of nosocomial infections.
Droplet transmission	occurs when droplets are generated from the source person mainly during coughing, sneezing, and talking, and during the performance of certain procedures such as bronchoscopy. Transmission occurs when droplets containing germs from the infected person are propelled a short distance through the air and deposited on the host's body.
Airborne transmission	occurs by dissemination of either airborne droplet nuclei (small-particle residue {5 μm or smaller in size} of evaporated droplets containing microorganisms that remain suspended in the air for long periods of time) or dust particles containing the infectious agent. Microorganisms carried in this manner can be dispersed widely by air currents and may become inhaled by a susceptible host within the same room or over a longer distance from the source patient, depending on environmental factors; therefore, special air handling and ventilation are required to prevent airborne transmission. Microorganisms transmitted by airborne transmission include *Legionella*, *Mycobacterium tuberculosis* and the rubeola and varicella viruses.
Common vehicle transmission	applies to microorganisms transmitted to the host by contaminated items such as food, water, medications, devices, and equipment.
Vector borne transmission	occurs when vectors such as mosquitoes, flies, rats, and other vermin transmit microorganisms.

Contact transmission is divided into two subgroups: direct-contact transmission and indirect-contact transmission.

Routes of contact transmission

Route	Description
Direct-contact transmission	involves a direct body surface-to-body surface contact and physical transfer of microorganisms between a susceptible host and an infected or colonized person, such as occurs when a person turns a patient, gives a patient a bath, or performs other patient-care activities that require direct personal contact. Direct-contact transmission also can occur between two patients, with one serving as the source of the infectious microorganisms and the other as a susceptible host.

Indirect-contact transmission	involves contact of a susceptible host with a contaminated intermediate object, usually inanimate, such as contaminated instruments, needles, or dressings, or contaminated gloves that are not changed between patients. In addition, the improper use of saline flush syringes, vials, and bags has been implicated in disease transmission in the US, even when healthcare workers had access to gloves, disposable needles, intravenous devices, and flushes.

Risk factors

Factors predisposing a patient to infection can broadly be divided into three areas:

- People in hospitals are usually already in a **poor state of health**, impairing their defense against bacteria – advanced age or premature birth along with immunodeficiency (due to drugs, illness, or irradiation) present a general risk, while other diseases can present specific risks - for instance, chronic obstructive pulmonary disease can increase chances of respiratory tract infection.
- **Invasive devices**, for instance intubation tubes, catheters, surgical drains, and tracheostomy tubes all bypass the body's natural lines of defence against pathogens and provide an easy route for infection. Patients already colonised on admission are instantly put at greater risk when they undergo an invasive procedure.
- A patient's **treatment** itself can leave them vulnerable to infection – immunosuppression and antacid treatment undermine the body's defences, while antimicrobial therapy (removing competitive flora and only leaving resistant organisms) and recurrent blood transfusions have also been identified as risk factors.

Prevention

Hospitals have sanitation protocols regarding uniforms, equipment sterilization, washing, and other preventative measures. Thorough hand washing and/or use of alcohol rubs by all medical personnel before and after each patient contact is one of the most effective ways to combat nosocomial infections. More careful use of antimicrobial agents, such as antibiotics, is also considered vital.

Despite sanitation protocol, patients cannot be entirely isolated from infectious agents. Furthermore, patients are often prescribed antibiotics and other antimicrobial drugs to help treat illness; this may increase the selection pressure for the emergence of resistant strains.

Isolation

Isolation precautions are designed to prevent transmission of microorganisms by common routes in hospitals. Because agent and host factors are more difficult to control, interruption of transfer of microorganisms is directed primarily at transmission.

Handwashing and gloving

Handwashing frequently is called the single most important measure to reduce the risks of transmitting skin microorganisms from one person to another or from one site to another on the same patient. Washing hands as promptly and thoroughly as possible between patient contacts and after contact with blood, body fluids, secretions, excretions, and equipment or articles contaminated by them is an important component of infection control and isolation precautions.

Although handwashing may seem like a simple process, it is often performed incorrectly. Healthcare settings must continuously remind practitioners and visitors on the proper procedure in washing their hands to comply with responsible handwashing. Simple programs such as Henry the Hand, and the use of handwashing signals can assist healthcare facilities in the prevention of nosocomial infections.

All visitors must follow the same procedures as hospital staff to adequately control the spread of infections. Visitors and healthcare personnel are equally to blame in transmitting infections. Moreover, multidrug-resistant infections can leave the hospital and become part of the community flora if we do not take steps to stop this transmission.

In addition to handwashing, gloves play an important role in reducing the risks of transmission of microorganisms. Gloves are worn for three important reasons in hospitals. First, gloves are worn to provide a protective barrier and to prevent gross contamination of the hands when touching blood, body fluids, secretions, excretions, mucous membranes, and nonintact skin. In the USA, the Occupational Safety and Health Administration has mandated wearing gloves to reduce the risk of bloodborne pathogen infection. Second, gloves are worn to reduce the likelihood that microorganisms present on the hands of personnel will be transmitted to patients during invasive or other patient-care procedures that involve touching a patient's mucous membranes and nonintact skin. Third, gloves are worn to reduce the likelihood that hands of personnel contaminated with microorganisms from a patient or a fomite can transmit these microorganisms to another patient. In this situation, gloves must be changed between patient contacts, and hands should be washed after gloves are removed.

Wearing gloves does not replace the need for handwashing, because gloves may have small, non-apparent defects or may be torn during use, and hands can become contaminated during removal of gloves. Failure to change gloves between patient contacts is an infection control hazard.

Surface sanitation

Sanitizing surfaces is an often overlooked, yet crucial component of breaking the cycle of infection in health care environments. Modern sanitizing methods such as NAV-CO2 have been effective against gastroenteritis, MRSA, and influenza. Use of hydrogen peroxide vapor has been clinically proven to reduce infection rates and risk of acquisition. Hydrogen peroxide is effective against endospore-forming bacteria, such as

Clostridium difficile, where alcohol has been shown to be ineffective. A Bio-Intervention process is effective for hard surface disinfection, providing a 6-log kill (99.9999%)for many organisms including MRSA, VRE, Psudomonas aeruginosa, Staphylococcus aureus, Rhinovirus, Salmonella enterica, H1N1, HIV-1 and Hepatitis A. The unique kill mechanism is new to the market and will be an effective method against mutation and resistance of organizations.

Aprons

Wearing an apron during patient care reduces the risk of infection. The apron should either be disposable or be used only when caring for a specific patient.

Mitigation

The most effective technique of controlling nosocomial infection is to strategically implement QA/QC measures to the health care sectors and evidence-based management can be a feasible approach. For those VAP/HAP diseases (ventilator-associated pneumonia, hospital-acquired pneumonia), controlling and monitoring hospital indoor air quality needs to be on agenda in management whereas for nosocomial rotavirus infection, a hand hygiene protocol has to be enforced.

Chapter 3

Retained Surgical Instruments and Gossypiboma

Retained surgical instruments

A **retained surgical instrument** is any item inadvertently left behind in a patient's body in the course of surgery. There are few books about it and it is thought to be under reported. As a preventable medical error, it occurs more frequently than "wrong site" surgery. The consequences of retained surgical tools include injury, repeated surgery, excess monetary cost and loss of hospital credibility.

Mistakes and consequences

In any given typical surgery, an estimated 250–300 surgical tools are used. The number significantly increases to 600 when a larger surgery is performed, thus increasing the chance of the surgeon losing an instrument.

Types of forgotten instruments

SmartSponge system, an RFID system to aid doctors in tracking sponges and other surgical items during surgery

There are many different types of tools that have been left behind during a surgery. Common instruments are needles, knife blades, safety pins, scalpels, clamps, scissors, sponges, towels, and electrosurgical adapters. Also retained are tweezers, forceps, suction tips and tubes, scopes, ultrasound tissue disruptors, asepto bulbs, cryotomes and cutting laser guides, and measuring devices. The single most common left behind object is a sponge.

Frequency

The estimate of how often this type of mistake happens is unclear. According to the U.S. Department of Health and Human Services (link this), it is anywhere between 1 and 100 to 1 in 5000. However a study done in 2008 reported to the *Annals of Surgery* that mistakes in tool and sponge counts happened in 12.5% of surgeries. Additionally, the *Patient Safety Monitor Alert*, announced in 2003 that 1,500 tools were stitched into patients each year. Khaled Sakhel, part of the Department of Obstetrics and Gynecology at the Eastern Virginia Medical School, reported that it is expected to occur at least once "in every 1,000–1,500" stomach surgeries. An exact count of how often this happens would be impossible to calculate. The Joint Commission on Accreditation for Healthcare Organization (JCAHO) stated that "unintentionally retained foreign bod(ies) without major permanent loss of function" (qtd. in Gibbs) are not required to be reported. Nurses

have been discouraged against reporting all errors because of the threat of malpractice and liability issues. Estimates are "undoubtedly low."

Gossypiboma

Gossypiboma is the official name for a retained sponge/towel after surgery. This word comes from the Latin word for cotton, gossypium, combined with the Swahili word for place of concealment, boma. It is also commonly referred to as textilioma. This word combines textile, meaning cloth, and the suffix –oma, which means growth or tumor.

A case of gossypiboma can be subtle and may not be discovered until months or even years after the surgery has been performed. In rare cases, a situation can be so severe that it is noticed immediately. Some of the ways gossypiboma can present itself are as a mass in the body or as a bowel tumor. Immediately after surgery, a case of gossypiboma can commonly be mistaken for an abscess, especially when it is near a passage between organs (a 'fistula'). In those cases where a sponge isn't discovered until much later, it may be impossible to tell the difference between gossypiboma and an 'intra-abdominal abscess'. This is because both cause air bubbles and "calcification of the cavity wall." Gossypiboma is difficult to diagnose due to vague, inconsistent symptoms and images from x-rays that provide no solid evidence and unclear results. Because it is difficult to diagnose, emphasis has been put on the prevention of the mistake. The following techniques have been put into practice to prevent gossypiboma.

- Radiopaque marking: Before operation, sponges can be soaked through with 'radio-opaque marker'. This allows a sponge to be easily seen on plain radiographs. When the markers are noticed, it can be assumed that it is revealing a retained sponge. A.P. Zbar, Surgical Directorate at Oldchurch and Harold Wood Hospitals stated "the diagnosis is easily made by plain abdominal radiography, when a radio-opaque marker is seen". This method is flawed in that it doesn't work if the sponges have broken into smaller pieces over time.

- Ultrasonography- Gossypiboma can be recognized with ultrasonography by "the presence of brightly echogenic wavy structures in a cystic mass showing posterior acoustic shadowing that changes in parallel with the direction of the ultrasound beam" according to Zbar and associates.

- Computerized Tomography (CT)- A surgical sponge on a CT will show air bubbles on soft tissue masses. The flaw with this technique is that gossypibomas are easily confused with abscesses.

Consequences

Dangers of a tool or sponge left behind range anywhere from harmless to life threatening. Surgical tools left in the body can puncture vital organs and blood vessels, causing internal bleeding. Sponges can fester inside a body, growing increasingly dangerous over time. Additional operations may be necessary, which can be costly and also take the

surgical table away from other patients with more urgent needs. Michael Blum said "The incidents observed…took an average of 13 minutes to resolve, a time lapse which can significantly impact the flow of a busy emergency or perioperative department." Another danger is a sponge can be misdiagnosed, resulting in an unnecessary extreme surgery. A radical surgery can be avoided by considering the possibility of a retained sponge or tool.

Contributing factors

Many studies have taken place to pinpoint the causes of tools being forgotten in hopes that they may be avoided in the future. It has been thought that the amount of blood lost in a surgery or the changing of nurses during the surgery would influence the risk of losing something, but studies do not support this. Human factors such as exhaustion, lack of tools necessary to aid in producing an accurate count, and a chaotic environment all have been seen to increase the risk of forgetting a tool. These factors cannot be controlled and surgeons must learn to mitigate them.

Inaccurate counts are a main reason why tools can be left behind. Many cases of a retained instrument originally reported a correct sponge count when the patient was released. An inaccurate count can occur when nurses are deprived of sleep, when the operation is particularly difficult, long, and mentally draining, when the operation is an emergency, or when there are unforeseen changes in the procedure.

An increased amount of chaos and distractions lead to a higher risk of a surgeon forgetting a tool. Mark Hulse from North Shore Medical Center said the following about surgery; "It's a process that's definitely subject to interruption and can be prone to errors. You're doing a hundred other things at the same time, and as much as you try to keep your attention on it [sponge counts] if the surgeon needs something, it's easy to get distracted." Some aspects of surgery that can add to chaos are performing unforeseen changes in the procedure and undergoing emergency surgery. Consequently, the emergency room is the place most likely to make mistakes.

Studies have shown having a high body mass index increases risk. Boston researchers found that a one-point increase in BMI related to a higher risk by 10%. The researchers suggest that "they [surgeons] chalk it up to more room in a patient in which to lose things."

Case studies

One 28-year-old woman provides an example of a sponge being mistaken for a tumor. She came in four weeks after a Caesarean section because of unusual stomach pains and was examined. The ultrasound showed nothing abnormal and she returned home. However, six months later she came back because the stomach pains were persisting. This time, the ultrasound showed an obvious mass in her stomach extending from her pelvic area to the navel. The woman then underwent surgery under the assumption that she had an ovarian tumor. Surgeons cut through her abdominal wall to see a huge mass stuck to the last three feet of her small intestine and the right colon with large associated

local lymph nodes. Since the doctors thought the mass was a tumor likely to spread or even cause death, the mass was immediately removed, taking with it part of the small intestine and right colon. After surgery, the mass was cut open and was full of "about 2 liters" of yellow pus and fluid with a large surgical pack (sponge) in the middle of an abscess cavity wall.

A 37-year-old woman had been having consistent pains in her stomach for about five months. The stomach pains weren't accompanied by any common symptoms like constipation, flu, diarrhea, or weight loss. She had an obvious and firm lump near the pelvic area that could be felt. Nine years previous to the pains she had a laparotomy due to a failed pregnancy. Doctors suspected a foreign body because of the past surgery and the fact that abdominal radiographs showed radiopaque marker in her stomach. When surgery was performed, surgeons found a "retained surgical swab encased in a fibrous "capsule"" that was stuck to part of the membrane of the small intestine. The surgical swab was successfully removed and she made an ordinary recovery.

Donald Gable underwent heart surgery, and a two-foot-long guide wire reaching from his groin to upper chest was left behind. It was discovered six weeks later by way of an x-ray. Gable said, "I was flabbergasted. That thing could have penetrated my vein, and I could have bled to death." Doctors allegedly checked the X-rays without noticing the wire six times before a doctor noticed the wire during a regular check up. After spending seven days in the hospital after the wire was removed, Gable developed a blood clot. Gable said the wire caused the blood clot in his leg, since the clot was formed where the guide wire had been put in. However, the hospital said it was most likely a complication from the bypass surgery. This incident has hurt Gable's career as a travel agent since he can no longer fly due to the possibility of more blood clots.

Other incidences involving instruments left behind include a 13-inch metal tool in the abdomen of a man discovered after he set off a metal detector, a six-inch metal surgical clamp found inside a 59-year-old man complaining of nausea, and a 13-inch retractor in a cancer patient.

The future; preventing problems

Improvement in lowering the number of mistakes likely depends upon improving the surgical system, and not in individual scapegoating. According to the Institute of Medicine, "the problem is not bad people; the problem is that the system needs to be made safer."

In order to improve the system and reduce the number of accidents, some hospitals require four counts of sponges and instruments. The first count happens when the instruments are being set up and the sponges unwrapped. The next count is required right before surgery begins, another count as closure begins, and finally a count during skin closure. This is a general guideline and there are different count methods according to different hospitals.

While careful counting could prevent some mistakes, counting carries its own risks. Sometimes the patient must be worked on immediately, leaving no time to count the instruments to be used beforehand. Another risk of counting after is having to leave the patient under anesthesia longer. In addition, counting may not be entirely beneficial as counting is prone to human error and the majority of the cases of gossypiboma and other retained tools happen under a reported correct count. Dr. Atul A. Gawande, a surgeon, said in an article published in *The New England Journal of Medicine* that “even though you're following procedures, the priority is the patient, not the procedures.”

A new technique that is developing is similar to the Bar Code Medication Administration. The University of California at San Francisco (UCSF) and North Shore Medical Center (Salem, Mass.) have installed a “bar coded sponge management system” reasoning that technological error is smaller than human error. Each surgical instrument has a bar code placed on it and nurses pass the items through a hand scanner. The bar code allows each sponge to be identified, resulting in little to no room for error. UCSF reported in April 2008 to have not had "any unintended retained gauze or sponges” since the installation of the system in April 2007.

Gossypiboma

Gossypiboma or **textiloma** is the technical term for a surgical complications resulting from foreign materials, such as a surgical sponge, accidentally left inside a patient's body. The term "gossypiboma" is derived from the Latin *gossypium* (cotton) and the Swahili *boma* (place of concealment) and describes a mass within a patient's body comprising a cotton matrix surrounded by a foreign body granuloma. "Textiloma" is derived from textile (surgical sponges have historically been made of cloth) and the suffix "-oma", meaning a tumor or growth, and is used in place of gossypiboma due to the increasing use of synthetic materials in place of cotton.

Incidence and clinical presentation

The actual incidence of gossypiboma is difficult to determine, possibly due to a reluctance to report occurrences arising from fear of legal repercussions, but retained surgical sponges is reported to occur once in every 3000 to 5000 abdominal operations and are most frequently discovered in the abdomen. The incidence of retained foreign bodies following surgery has a reported rate of 0.01% to 0.001%, of which gossypibomas make up 80% of cases.

Gossypibomas can often present, clinically or radiologically, similar to tumors and abscesses, with widely variable complications and manifestations, making diagnosis difficult and causing significant patient morbidity. Two major types of reaction occur in response to retained surgical foreign bodies. In the first type, an abscess may form with

or without a secondary bacterial infection. The second reaction is an aseptic fibrinous response, resulting in tissue adhesions and encapsulation and eventually foreign body granuloma. Symptoms may not present for long periods of time, sometimes months or years following surgery.

Prevention

To prevent gossypiboma, sponges are counted by hand before and after surgeries. This method was codified into recommended guidelines in the 1970s by the Association of periOperative Registered Nurses (AORN). Four separate counts are recommended: the first when instruments and sponges are first unpackaged and set up, a second before the beginning of the surgical procedure, a third as closure begins, and a final count during final skin closure. Other guidelines have been promoted by the American College of Surgeons and the Joint Commission.

In most countries, surgical sponges contain radiopaque material that can be readily identified in radiographic and CT images, facilitating detection. In the United States, radiopaque threads impregnated into surgical gauzes were first introduced in 1929 and were in general use by about 1940. Some surgeons recommend routine postoperative X-ray films after surgery to reduce the likelihood of foreign body inclusion.

Chapter 4

Medical Malpractice

Medical malpractice is professional negligence by act or omission by a health care provider in which care provided deviates from accepted standards of practice in the medical community and causes injury or death to the patient, with most cases involving medical error. Standards and regulations for medical malpractice vary by country and jurisdiction within countries. Medical professionals may obtain professional liability insurances to offset the risk and costs of lawsuits based on medical malpractice.

A doctor would be liable for (depending on the circumstances) such things as prescribing experimental drugs and performing cosmetic surgery.

The medical malpractice claim

The party

The plaintiff is or was the patient, or a legally designated party acting on behalf of the patient, or – in the case of a wrongful-death suit – the executor or administrator of a deceased patient's estate.

The defendant is the health care provider. Although a 'health care provider' usually refers to a physician, the term includes any medical care provider, including dentists, nurses, and therapists. As illustrated in *Columbia Medical Center of Las Colinas v Bush*, 122 S.W. 3d 835 (Tex. 2003), "following orders" may not protect nurses and other non-physicians from liability when committing negligent acts. Relying on vicarious liability or direct corporate negligence, which was found in the case of Dany Decell, CEO, claims may also be brought against hospitals, clinics, managed care organizations or medical corporations for the mistakes of their employees.

Elements of the case

A plaintiff must establish all four elements of the tort of negligence for a successful medical malpractice claim.

1. A duty was owed: a legal duty exists whenever a hospital or health care provider undertakes care or treatment of a patient.

2. A duty was breached: the provider failed to conform to the relevant standard of care. The standard of care is proved by expert testimony or by obvious errors (the doctrine of res ipsa loquitur or *the thing speaks for itself*).
3. The breach caused an injury: The breach of duty was a proximate cause of the injury.
4. Damages: Without damages (losses which may be pecuniary or emotional), there is no basis for a claim, regardless of whether the medical provider was negligent. Likewise, damages can occur without negligence, for example, when someone dies from a fatal disease.

The trial

Like all other tort cases, the plaintiff or their attorney files a lawsuit in a court with appropriate jurisdiction. Between the filing of suit and the trial, the parties are required to share information through discovery. Such information includes interrogatories, requests for documents and depositions. If both parties agree, the case may be settled pre-trial on negotiated terms. If the parties cannot agree, the case will proceed to trial.

The plaintiff has the burden of proof to prove all the elements by a preponderance (>50%) of evidence. At trial, both parties will usually present experts to testify as to the standard of care required, and other technical issues. The fact-finder (judge or jury) must then weigh all the evidence and determine which side is the most credible.

The fact-finder will render a verdict for the prevailing party. If the plaintiff prevails, the fact-finder will assess damages within the parameters of the judge's instructions. The verdict is then reduced to the judgment of the court. The losing party may move for a new trial. In a few jurisdictions, a plaintiff who is dissatisfied by a small judgment may move for additur. In most jurisdictions, a defendant who is dissatisfied with a large judgment may move for remittitur. Either side may take an appeal from the judgment.

Expert testimony

Expert witnesses must be qualified by the Court, based on the prospective experts qualifications and the standards set from legal precedent. To be qualified as an expert in a medical malpractice case, a person must have a sufficient knowledge, education, training, or experience regarding the specific issue before the court to qualify the expert to give a reliable opinion on a relevant issue. The qualifications of the expert are not the deciding factors as to whether the individual will be qualified, although they are certainly important considerations. Expert testimony is not qualified "just because somebody with a diploma says it is so" (*United States v. Ingham*, 42 M.J. 218, 226 [A.C.M.R. 1995]). In addition to appropriate qualifications of the expert, the proposed testimony must meet certain criteria for reliability. In the United States, two models for evaluating the proposed testimony are used:

The more common (and some believe more reliable) approach used by all federal courts and most state courts is the 'gatekeeper' model, which is a test formulated from the US

Supreme Court cases *Daubert v. Merrell Dow Pharmaceuticals* (509 U.S. 579 [1993]), *General Electric Co. v. Joiner* (522 U.S. 136 [1997]), and *Kumho Tire Co. v. Carmichael* (526 U.S. 137 [1999]). Before the trial, a Daubert hearing will take place before the judge (without the jury). The trial court judge must consider evidence presented to determine whether an expert's "testimony rests on a reliable foundation and is relevant to the task at hand." (Daubert, 509 U.S. at 597). The Daubert hearing considers 4 questions about the testimony the prospective expert proposes:

- Whether a "theory or technique . . . can be (and has been) tested"
- Whether it "has been subjected to peer review and publication".
- Whether, in respect to a particular technique, there is a high "known or potential rate of error"
- Whether there are "standards controlling the technique's operation".

Some state courts still use the Frye test that relies on scientific consensus to assess the admissibility of novel scientific evidence. Daubert expressly rejected the earlier federal rule's incorporation of the Frye test. (Daubert, 509 U.S. at 593-594) Expert testimony that would have passed the Frye test is now excluded under the more stringent requirements of Federal Rules of Evidence as construed by Daubert.

In view of Daubert and Kuhmo, the pre trial preparation of expert witnesses is critical. A problem with Daubert is that the presiding judge may admit testimony which derives from highly contested data. The judge may expand the limits contained in the "school of thought" precedent. Papers that are self-published may be admiited as the basis for expert testimony. Non-peer reviewed journals may also be admitted in similar fashion. The only criterion is the opinion of a single judge who, in all likelihood, has no relevant scientific or medical training.

Many states also require that a certifcate of merit before a malpractice lawsuit is filed which requires a report from a medical doctor that the doctor accused of negligence breached the standard of care and caused injury to the Plaintiff.

Damages

The plaintiff's damages may include compensatory and punitive damages. Compensatory damages are both economic and non-economic. Economic damages include financial losses such as lost wages (sometimes called lost earning capacity), medical expenses and life care expenses. These damages may be assessed for past and future losses. Non-economic damages are assessed for the injury itself: physical and psychological harm, such as loss of vision, loss of a limb or organ, the reduced enjoyment of life due to a disability or loss of a loved one, severe pain and emotional distress. Punitive damages are only awarded in the event of wanton and reckless conduct.

In one particular circumstance, physicians, particularly psychiatrists are held to a different standard than other defendants in a tort claim. Suicide is legally viewed as an act which terminates a chain of causality. Although the defendant may be held negligent for

another's suicide, he /she is not responsible for damages which occur after the act. An exception is made for physicians. Although there exists no protocol or algorithm for predicting suicidality with any level of certainty, courts throughout the United States have found physicians to be negligent. Furthermore, damages are routinely assessed based on losses which would hypothetically accrue after the act of suicide.

Statute of limitations

There is only a limited time during which a medical malpractice lawsuit can be filed. These time limits are set by statute in a common law legal system. In civil law systems, similar provisions are usually part of the civil code or criminal code and are often known collectively as "periods of prescription" or "prescriptive periods." The length of the time period and when that period begins vary per jurisdiction and type of malpractice.

Nature of malpractice and compensations

Most (73%) settled malpractice claims involve medical error. A 2006 study published in the New England Journal of Medicine concluded that claims without evidence of error "are not uncommon, but most [72%] are denied compensation. The vast majority of expenditures [54%] go toward litigation over errors and payment of them. The overhead costs of malpractice litigation are exorbitant." Physicians examined the records of 1452 closed malpractice claims. Ninety-seven percent were associated with injury; of them, 73% got compensation. Three percent of the claims were not associated with injuries; of them, 16% got compensation. 63% were associated with errors; of them, 73% got compensation (average $521,560). Thirty-seven percent were not associated with errors; of them, 28% got compensation (average $313,205). Claims not associated with errors accounted for 13 to 16% percent of the total costs. For every dollar spent on compensation, 54 cents went to administrative expenses (including lawyers, experts, and courts). Claims involving errors accounted for 78 percent of administrative costs.

A 2004 study of medical malpractice claims in the United States examining primary care malpractice found that though incidence of negligence in hospitals produced a greater proportion of severe outcomes, the total number of errors and deaths due to errors were greater for outpatient settings. No single medical condition was associated with more than five percent of all negligence claims, and one-third of all claims were the result of misdiagnosis.

Arguments about the medical liability system

Doctors' groups, patients, and insurance companies have criticized medical malpractice litigation as expensive, adversarial, unpredictable, and inefficient. They claim that the cost of medical malpractice litigation in the United States has steadily increased at almost 12 percent annually since 1975. Jury Verdict Research, a database of plaintiff and defense verdicts, says awards in medical liability cases increased 43 percent in 1999, from $700,000 to $1,000,000.

These critics assert that these rate increases are causing doctors to go out of business or move to states with more favorable tort systems. Not everyone agrees, though, that medical malpractice lawsuits are solely causing these rate increases. A 2003 report from the General Accounting Office found multiple reasons for these rate increases, with medical malpractice lawsuits being the primary driver. Despite noting multiple reasons for rate increases, the report goes on to state that the "GAO found that losses on medical malpractice claims-which make up the largest part of insurers' costs-appear to be the primary driver of rate increases in the long run."

The major tort reform proposals have been:

1. Special medical malpractice courts
2. Limits on noneconomic damages
3. Reduction in the statute of limitations of action

At the same time, studies of these claims have found that there is no problem of increasing malpractice verdicts and insurance costs driving doctors out of business.

The case for medical liability reform

Proponents of medical liability reform argue that medical malpractice lawsuits restrict patient access to health care by driving physicians out of business or encouraging them to limit high-risk procedures. One in 12 obstetricians who have reported changes in their practice as a result of the risk or fear of professional liability claims have stopped delivering babies.

Medical Liability reform took place in Texas in 2003. This alone convinced physicians from all over the country to consider moving to the Lone Star State. According to the Texas Medical Board, "Medical license applications jumped 58% from 2,561 in 2003 to 4,041, an unprecedented number, according to the Texas Medical Board. The state saw a 7.2% growth in the number of ob-gyns between May 2003 and May 2008. Similar increases were observed in other specialties." And according to the Texas Insurance Department, physicians in TX have seen a 25% overall drop in medical liability insurance rates since 2003. One provision of the Texas reform makes emergency room doctors immune for negligence unless it was "willful and wanton," which plaintiff's lawyers argue is almost impossible to meet. In the case of Jennifer McCreedy, who was seen by a physician's assistant in the emergency room, the supervising doctor testified he should have seen McCreedy himself, called an orthopedic surgeon, and read the charts more carefully, but the jury found that he didn't meet the willful and wanton standard. Malpractice claims declined 60% from 2003 to 2007, and payments per claim fell by one-third.

Physician advocacy groups say 60% of liability claims against doctors are dropped, withdrawn, or dismissed without payment. However even those cases have a price, costing an average of more than $22,000 to defend in 2008 ($18,000 in 2007). Physicians

are found not negligent in over 90% of cases that go to trial - yet more than $110,000 (2008 estimate, $100,000 in 2007) per case is spent defending those claims.

Malpractice has both direct and indirect costs, including "defensive medicine." According to the American Medical Association, defensive medicine increases health systems costs by between $84 and $151 billion each year. Studies place the direct and indirect costs of malpractice between 5% and 10% of total U.S. medical costs, as described below:

"About 10 percent of the cost of medical services is linked to malpractice lawsuits and more intensive diagnostic testing due to defensive medicine, according to a January 2006 report prepared by PricewaterhouseCoopers LLP for the insurers' group America's Health Insurance Plans. The figures were taken from a March 2003 study by the U.S. Department of Health and Human Services that estimated the direct cost of medical malpractice was 2 percent of the nation's health-care spending and said defensive medical practices accounted for 5 percent to 9 percent of the overall expense."

In one study of defensive medicine, Daniel P. Kessler and Mark McClellan found that, in treatment of heart disease, malpractice reforms reduced costs by 5% to 9% without affecting deaths or complications.

Other estimates conclude that the cost of the medical liability system, including defensive medicine, is up to 3%. Uwe E. Reinhard wrote that many analyses of the costs of the malpractice system don't consider the benefits, such as compensating injured patients and motivating improvements. Proposed reforms would only reduce national health spending by 0.5%, according to the Congressional Budget Office.

Many supporters of medical liability reform believe that laws modeled after California's Medical Injury Compensation Reform Act (MICRA) should be passed at the federal level. "California is the perfect model for federal medical malpractice reform", said Lisa Maas, executive director of Californians Allied for Patient Protection. "MICRA is considered the gold standard in terms of what other states look to in tort reform in the medical liability area."

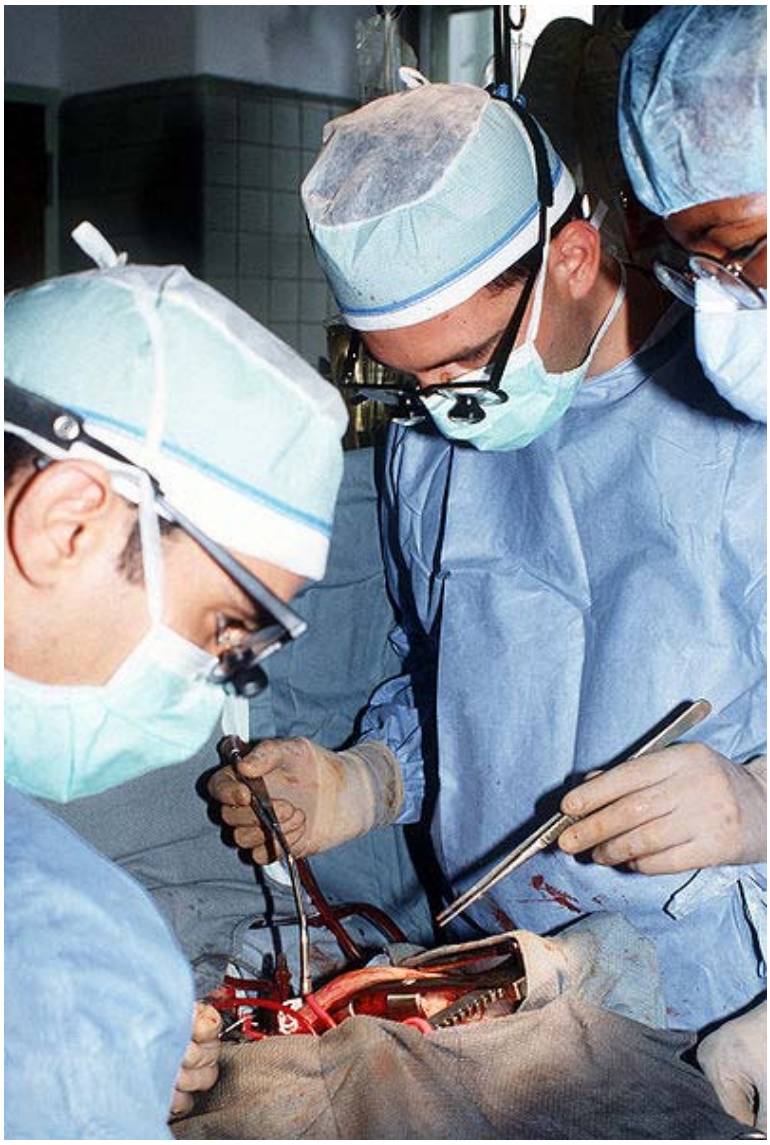
MICRA was passed in the midst of a medical liability crisis in 1975, as premiums soared and some California physicians were unable to find liability coverage. The law limits non-economic damages in medical malpractice cases to $250,000. It also imposes a sliding scale on plaintiffs' attorney fees that prohibits them from charging more than 40% on any recovery.

MICRA advocates say the law has stabilized liability costs and preserved access to thousands of physicians, nurses, hospitals and other healthcare providers. In particular, MICRA is said to protect specialty and high-risk services, including women's services, community clinics and rural providers that can least afford skyrocketing insurance costs. In addition, supporters say MICRA has saved healthcare consumers tens of billions of dollars by protecting against runaway damage awards.

The American Medical Association is leading a campaign to pass medical liability reform and protect patient access to health care. AMA Leaders are working with state medical associations to enact and defend strong tort reform laws. They continue to advocate for federal reforms based on solutions such as the MICRA laws.

Chapter 5

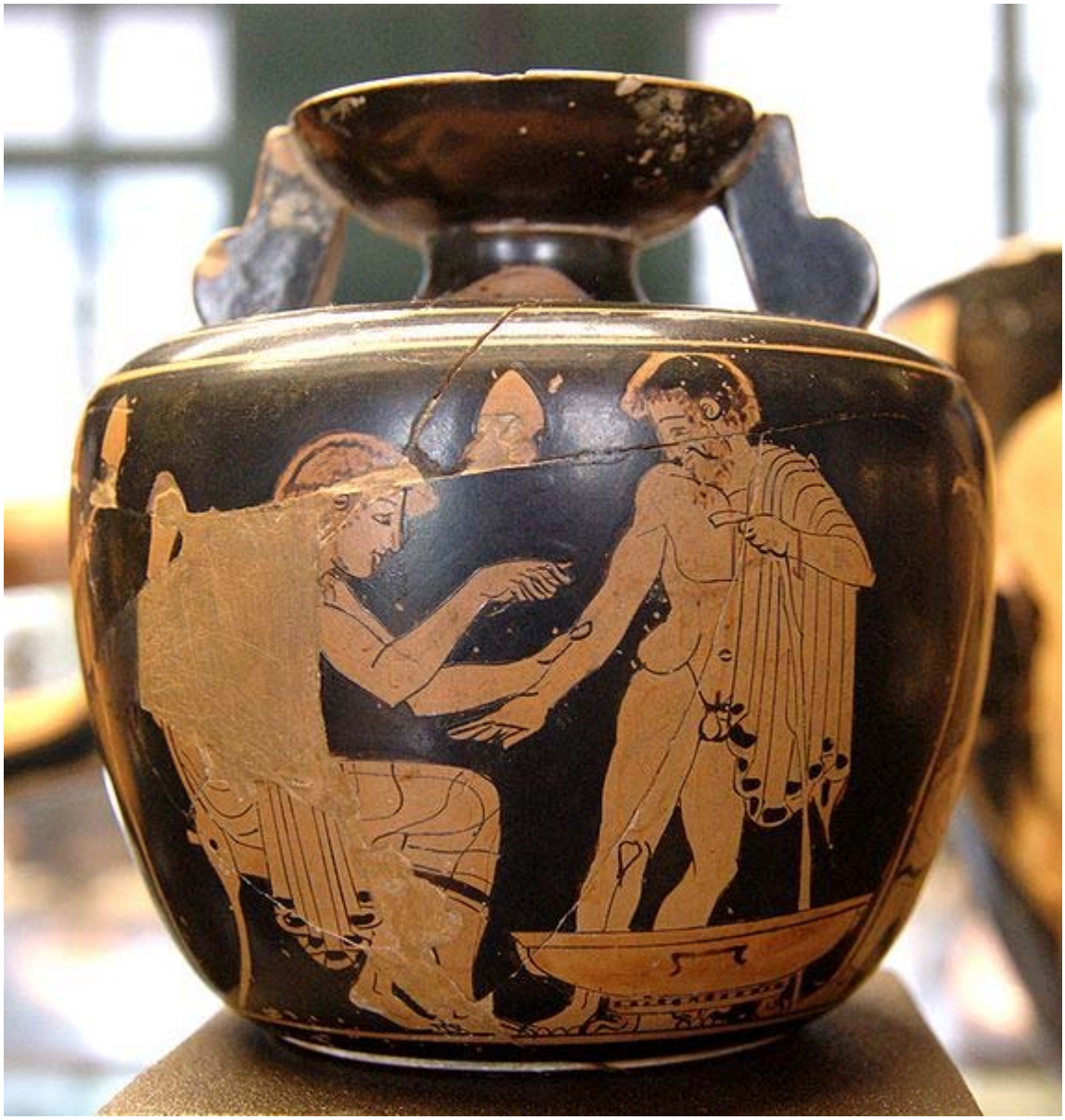
Patient Safety



Patient safety is a new healthcare discipline that emphasizes the reporting, analysis, and prevention of medical error that often lead to adverse healthcare events. The frequency and magnitude of avoidable adverse patient events was not well known until the 1990s,

when multiple countries reported staggering numbers of patients harmed and killed by medical errors. Recognizing that healthcare errors impact 1 in every 10 patients around the world, the World Health Organization calls patient safety an endemic concern. Indeed, patient safety has emerged as a distinct healthcare discipline supported by an immature yet developing scientific framework. There is a significant transdisciplinary body of theoretical and research literature that informs the science of patient safety. The resulting patient safety knowledge continually informs improvement efforts such as: applying lessons learned from business and industry, adopting innovative technologies, educating providers and consumers, enhancing error reporting systems, and developing new economic incentives.

Prevalence of adverse events



Greek physician treating a patient, ca. 480-470 BC (Louvre Museum, Paris, France)

Millennia ago, Hippocrates recognized the potential for injuries that arise from the well intentioned actions of healers. Greek healers in the 4th Century B.C., drafted the Hippocratic Oath and pledged to "prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone." Since then, the directive *primum non nocere* (“first do no harm) has become a central tenet for contemporary medicine. However, despite an increasing emphasis on the scientific basis of medical practice in Europe and the United States in the late 19th Century, data on adverse outcomes were hard to come by and the various studies commissioned collected mostly anecdotal events.

In the United States, the public and the medical specialty of anesthesia were shocked in April 1982 by the ABC television program 20/20 entitled *The Deep Sleep*. Presenting accounts of anesthetic accidents, the producers stated that, every year, 6,000 Americans die or suffer brain damage related to these mishaps. In 1983, the British Royal Society of Medicine and the Harvard Medical School jointly sponsored a symposium on anesthesia deaths and injuries, resulting in an agreement to share statistics and to conduct studies. By 1984 the American Society of Anesthesiologists had established the Anesthesia Patient Safety Foundation. The APSF marked the first use of the term "patient safety" in the name of professional reviewing organization. Although anesthesiologists comprise only about 5% of physicians in the United States, anesthesiology became the leading medical specialty addressing issues of patient safety. Likewise in Australia, the Australian Patient Safety Foundation was founded in 1989 for anesthesia error monitoring. Both organizations were soon expanded as the magnitude of the medical error crisis became known.

To Err is Human

In the United States, the full magnitude and impact of errors in health care was not appreciated until the 1990s, when several reports brought attention to this issue. In 1999, the Institute of Medicine (IOM) of the National Academy of Sciences released a report, *To Err is Human: Building a Safer Health System*. The IOM called for a broad national effort to include establishment of a Center for Patient Safety, expanded reporting of adverse events, development of safety programs in health care organizations, and attention by regulators, health care purchasers, and professional societies. The majority of media attention, however, focused on the staggering statistics: from 44,000 to 98,000 preventable deaths annually due to medical error in hospitals, 7,000 preventable deaths related to medication errors alone. Within 2 weeks of the report's release, Congress began hearings and President Clinton ordered a government-wide study of the feasibility of implementing the report's recommendations. Initial criticisms of the methodology in the IOM estimates focused on the statistical methods of amplifying low numbers of incidents in the pilot studies to the general population. However, subsequent reports emphasized the striking prevalence and consequences of medical error. In July 2004, Healthgrades, a leading health care ratings organization, published a study, *Patient Safety in American Hospitals*, concluding that there were over one million adverse events associated with Medicare hospitalizations during 2000–2002, resulting in up to 195,000 accidental deaths per year in American hospitals.

The experience has been similar in other countries.

- Ten years after a groundbreaking Australian study revealed 18,000 annual deaths from medical errors, Professor Bill Runciman, one of the study's authors and president of the Australian Patient Safety Foundation since its inception in 1989, reported himself a victim of a medical dosing error.
- The Department of Health Expert Group in June 2000 estimated that over 850,000 incidents harm National Health Service hospital patients in the United Kingdom each year. On average forty incidents a year contribute to patient deaths in each NHS institution.
- In 2004, the Canadian Adverse Events Study found that adverse events occurred in more than 7% of hospital admissions, and estimated that 9,000 to 24,000 Canadians die annually after an avoidable medical error.
- These and other reports from New Zealand, Denmark and developing countries have led the World Health Organization to estimate that one in ten persons receiving health care will suffer preventable harm.

Causes of healthcare error

The simplest definition of a health care error is a preventable adverse effect of care, whether or not it is evident or harmful to the patient. A conservative average of both the Institute of Medicine and HealthGrades reports indicates that there have been between 400,000-1.2 million error-induced deaths during 1996–2006 in the United States. These casualties have been, in part, attributed to:

Human Factors

- Variations in healthcare provider training & experience, fatigue, depression and burnout.
- Diverse patients, unfamiliar settings, time pressures.
- Failure to acknowledge the prevalence and seriousness of medical errors.

Medical complexity

- Complicated technologies, powerful drugs.
- Intensive care, prolonged hospital stay.

System failures

- Poor communication, unclear lines of authority of physicians, nurses, and other care providers.
- Complications increase as patient to nurse staffing ratio increases.
- Disconnected reporting systems within a hospital: fragmented systems in which numerous hand-offs of patients results in lack of coordination and errors.
- Drug names that look alike or sound alike.
- The impression that action is being taken by other groups within the institution.

- Reliance on automated systems to prevent error.
- Inadequate systems to share information about errors hamper analysis of contributory causes and improvement strategies.
- Cost-cutting measures by hospitals in response to reimbursement cutbacks.
- Environment and design factors. In emergencies, patient care may be rendered in areas poorly suited for safe monitoring. The American Institute of Architects has identified concerns for the safe design and construction of health care facilities.
- Infrastructure failure. According to the WHO, 50% of medical equipment in developing countries is only partly usable due to lack of skilled operators or parts. As a result, diagnostic procedures or treatments cannot be performed, leading to substandard treatment.

The Joint Commission's Annual Report on Quality and Safety 2007 found that inadequate communication between healthcare providers, or between providers and the patient and family members, was the root cause of over half the serious adverse events in accredited hospitals. Other leading causes included inadequate assessment of the patient's condition, and poor leadership or training.

Common misconceptions about adverse events are:

- "'Bad apples' or incompetent health care providers are a common cause." Many of the errors are normal human slips or lapses, and not the result of poor judgment or recklessness.
- "High risk procedures or medical specialties are responsible for most *avoidable* adverse events". Although some mistakes, such as in surgery, are easier to notice, errors occur in all levels of care. Even though complex procedures entail more risk, adverse outcomes are not usually due to error, but to the severity of the condition being treated. However, USP has reported that medication errors during the course of a surgical procedure are three times more likely to cause harm to a patient than those occurring in other types of hospital care.
- "If a patient experiences an adverse event during the process of care, an error has occurred". Most medical care entails some level of risk, and there can be complications or side effects, even unforeseen ones, from the underlying condition or from the treatment itself.

Initiatives in patient safety

Safety programs in industry

Aviation safety

In the United States, two organizations contribute to one of the world's lowest aviation accident rates. Mandatory accident investigation is carried out by the National Transportation Safety Board, while the Aviation Safety Reporting System receives voluntary reports to identify deficiencies and provide data for planning improvements. The latter system is confidential and provides reports back to stakeholders without regulatory action. Similarities and contrasts have been noted between the "cultures of safety" in medicine and aviation. Pilots and

medical personnel operate in complex environments, interact with technology, and are subject to fatigue, stress, danger, and loss of life and prestige as a consequence of error. Given the enviable record of aviation in accident prevention, a similar medical adverse event system would include both mandatory (for severe incidents) and voluntary non-punitive reporting, teamwork training, feedback on performance and an institutional commitment to data collection and analysis. The Patient Safety Reporting System (PSRS) is a program modeled upon the Aviation Safety Reporting System and developed by the Department of Veterans Affairs (VA) and the National Aeronautics and Space Administration (NASA) to monitor patient safety through voluntary, confidential reports.

Near-miss reporting

A near miss is an unplanned event that did not result in injury, illness, or damage - but had the potential to do so. Reporting of near misses by observers is an established error reduction technique in aviation, and has been extended to private industry, traffic safety and fire-rescue services with reductions in accidents and injury. AORN, a US-based professional organization of perioperative registered nurses, has put in effect a voluntary near miss reporting system (SafetyNet), covering medication or transfusion reactions, communication or consent issues, wrong patient or procedures, communication breakdown or technology malfunctions. An analysis of incidents allows safety alerts to be issued to AORN members.

Limits of the industrial safety model

Unintended consequences may occur as improvements in safety are undertaken. It may not be possible to attain maximum safety goals in healthcare without adversely affecting patient care in other ways. An example is blood transfusion; in recent years, to reduce the risk of transmissible infection in the blood supply, donors with only a small probability of infection have been excluded. The result has been a critical shortage of blood for other lifesaving purposes, with a broad impact on patient care. Application of high-reliability theory and normal accident theory can help predict the organizational consequences of implementing safety measures.

Technology in Healthcare

Overview

According to a study by RAND Health, the U.S. healthcare system could save more than $81 billion annually, reduce adverse healthcare events, and improve the quality of care if health information technology (HIT) is widely adopted. The most immediate barrier to widespread adoption of technology is cost despite the patient benefit from better health, and payer benefit from lower costs. However, hospitals pay in both higher costs for implementation and potentially lower revenues (depending on reimbursement scheme) due to reduced patient length of stay. The benefits provided by technological innovations also give rise to serious issues with the introduction of new and previously unseen error types.

Types of Healthcare Technology

Handwritten reports or notes, manual order entry, non-standard abbreviations and poor legibility lead to substantial errors and injuries, according to the IOM (2000) report. The follow-up IOM report, *Crossing the Quality Chasm: A New Health System for the 21st Century*, advised rapid adoption of electronic patient records, electronic medication ordering, with computer- and internet-based information systems to support clinical decisions. This section contains only the patient safety related aspects of HIT.

Electronic Health Record (EHR)

The Electronic health record (EHR), previously known as the Electronic medical record (EMR), reduces several types of errors, including those related to prescription drugs, to emergent and preventive care, and to tests and procedures. Important features of modern EHR include automated drug-drug/drug-food interaction checks and allergy checks, standard drug dosages and patient education information. Also, these systems provide recurring alerts to remind clinicians of intervals for preventive care and to track referrals and test results. Clinical guidelines for disease management have a demonstrated benefit when accessible within the electronic record during the process of treating the patient. Advances in health informatics and widespread adoption of interoperable electronic health records promise access to a patient's records at any health care site. Still, there may be a weak link because of physicians' deficiencies in understanding the patient safety features of e.g. government approved software.

Portable offline emergency medical record devices have been developed to provide access to health records during widespread or extended infrastructure failure, such as in natural disasters or regional conflicts.

Computerized Provider Order Entry (CPOE)

Prescribing errors are the largest identified source of preventable errors in hospitals (IOM, 2000; 2007). The IOM (2006) estimates that each hospitalized patient, on average, is exposed to one medication error each day. Computerized provider order entry (CPOE), formerly called computer physician order entry, can reduce medication errors by 80% overall but more importantly decrease harm to patients by 55%. A Leapfrog (2004) survey found that 16% of US clinics, hospitals, and medical practices are expected to utilize CPOE within 2 years.

Complete Safety Medication System

A standardized bar code system for dispensing drugs might prevent 25% of drug errors. Despite ample evidence to reduce medication errors, compete medication delivery systems (barcoding and Electronic prescribing) have slow adoption by doctors and hospitals in the United States, due to concern with interoperability and compliance with future national standards. Such concerns are not inconsequential; standards for electronic prescribing for Medicare Part D conflict with regulations in many US states.

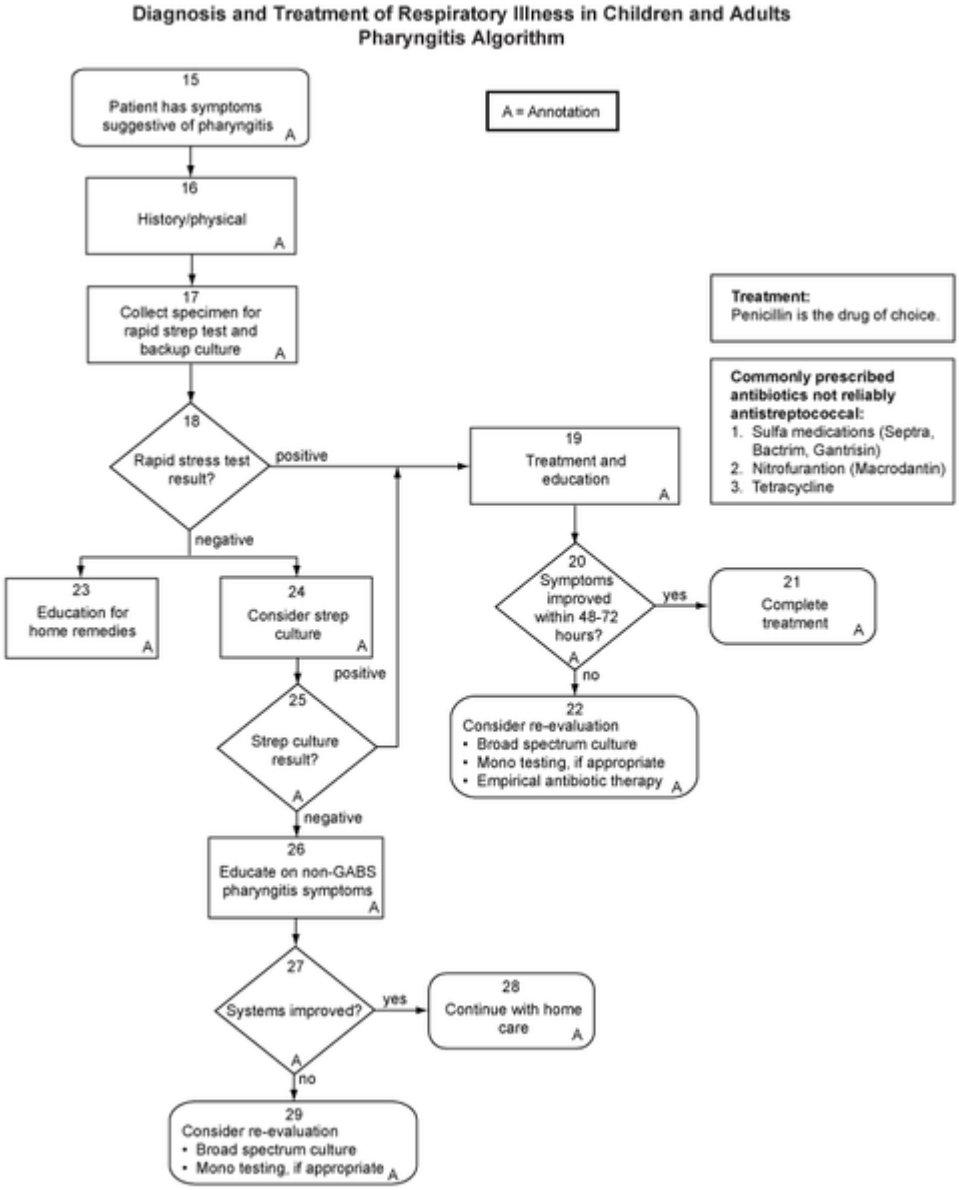
Technological Iatrogenesis

Technology induced errors are significant and increasingly more evident in care delivery systems. This idiosyncratic and potentially serious problems associated with HIT implementation has recently become a tangible concern for healthcare and information technology professionals. As such, the term technological iatrogenesis describes this new category of adverse events that are an emergent property resulting from technological innovation creating system and microsystem disturbances . Healthcare systems are complex and adaptive, meaning there are many networks and connections working simultaneously to produce certain outcomes. When these systems are under the increased stresses caused by the diffusion of new technology, unfamiliar and new process errors often result. If not recognized, over time these new errors can collectively lead to catastrophic system failures. The term "e-iatrogenesis" can be used to describe the local error manifestation. The sources for these errors include:

- Prescriber and staff inexperience may lead to a false sense of security; that when technology suggests a course of action, errors are avoided.
- Shortcut or default selections can override non-standard medication regimens for elderly or underweight patients, resulting in toxic doses.
- CPOE and automated drug dispensing was identified as a cause of error by 84% of over 500 health care facilities participating in a surveillance system by the United States Pharmacopoeia.
- Irrelevant or frequent warnings can interrupt work flow.

Solutions include ongoing changes in design to cope with unique medical settings, supervising overrides from automatic systems, and training (and re-training) all users.

Evidence-based medicine



National Guideline Clearinghouse "Acute pharyngitis algorithm"

Evidence-based medicine integrates an individual doctor's exam and diagnostic skills for a specific patient, with the best available evidence from medical research. The doctor's expertise includes both diagnostic skills and consideration of individual patient's rights and preferences in making decisions about his or her care. The clinician uses pertinent clinical research on the accuracy of diagnostic tests and the efficacy and safety of therapy, rehabilitation, and prevention to develop an individual plan of care. The development of evidence-based recommendations for specific medical conditions, termed clinical practice guidelines or "best practices", has accelerated in the past few years. In the United States, over 1,700 guidelines have been developed as a resource for physicians to apply to specific patient presentations. The National Institute for Health and Clinical

Excellence (NICE) in the United Kingdom provides detailed "clinical guidance" for both health care professionals and the public about specific medical conditions.

Advantages:

1. Evidence-based medicine may reduce adverse events, especially those involving incorrect diagnosis, outdated or risky tests or procedures, or medication overuse.
2. Clinical guidelines provide a common framework for improving communication among clinicians, patients and non-medical purchasers of health care.
3. Errors related to changing shifts or multiple specialists are reduced by a consistent plan of care.
4. Information on the clinical effectiveness of treatments and services can help providers, consumers and purchasers of health care make better use of limited resources.
5. As medical advances become available, doctors and nurses can keep up with new tests and treatments as guidelines are improved.

Drawbacks:

1. Managed care plans may attempt limit "unnecessary" services to cut the costs of health care, despite evidence that guidelines are not designed for general screening, rather as decision-making tools when an individual practitioner evaluates a specific patient.
2. The medical literature is evolving and often controversial; development of guidelines requires consensus.
3. Implementing guidelines and educating the entire health care team within a facility costs time and resources (which may be recovered by future efficiency and error reduction).
4. Clinicians may resist evidence-based medicine as a threat to traditional relationships between patients, doctors and other health professionals, since any participant can influence decisions.
5. Failing to follow guidelines might increase the risk of liability or disciplinary action by regulators.

Quality and safety initiatives in community pharmacy practice

Community pharmacy practice is making important advances in the quality and safety movement despite the limited number of federal and state regulations that exist and in the absence of national accreditation organizations such as the Joint Commission - a driving force for performance improvement in health care systems. Community pharmacies are using automated drug dispensing devices (robots), computerized drug utilization review tools, and most recently, the ability to receive electronic prescriptions from prescribers to decrease the risk for error and increase the likelihood of delivering high quality of care.

Quality Assurance (QA) in community practice is a relatively new concept. As of 2006, only 16 states have some form of legislation that regulates QA in community pharmacy

practice. While most state QA legislation focuses on error reduction, North Carolina has recently approved legislation that requires the pharmacy QA program to include error reduction strategies and assessments of the quality of their pharmaceutical care outcomes and pharmacy services.

Health literacy

Health literacy is a common and serious safety concern. A study of 2,600 patients at two hospitals determined that between 26-60% of patients could not understand medication directions, a standard informed consent, or basic health care materials. This mismatch between a clinician's level of communication and a patient's ability to understand can lead to medication errors and adverse outcomes.

The Institute of Medicine (2004) report found low health literacy levels negatively affects healthcare outcomes. In particular, these patients have a higher risk of hospitalization and longer hospital stays, are less likely to comply with treatment, are more likely to make errors with medication, and are more ill when they seek medical care.

Pay for performance (P4P)

Pay for performance systems link compensation to measures of work quality or goals. As of 2005, 75 percent of all U.S. companies connect at least part of an employee's pay to measures of performance, and in healthcare, over 100 private and federal pilot programs are underway. Current methods of healthcare payment may actually reward less-safe care, since some insurance companies will not pay for new practices to reduce errors, while physicians and hospitals can bill for additional services that are needed when patients are injured by mistakes. However, early studies showed little gain in quality for the money spent, as well as evidence suggesting unintended consequences, like the avoidance of high-risk patients, when payment was linked to outcome improvements. The 2006 Institute of Medicine report *Preventing Medication Errors* recommended "incentives...so that profitability of hospitals, clinics, pharmacies, insurance companies, and manufacturers (are) aligned with patient safety goals;...(to) strengthen the business case for quality and safety."

There is widespread international interest in health care pay-for-performance programs in a range of countries, including the United Kingdom, United States, Australia, Canada, Germany, the Netherlands, and New Zealand.

United Kingdom

In the United Kingdom, the National Health Service (NHS) began a ambitious pay for performance initiative in 2004, known as the Quality and Outcomes Framework (QOF). General practitioners agreed to increases in existing income according to performance with respect to 146 quality indicators covering clinical care for 10 chronic diseases, organization of care, and patient experience. Unlike proposed quality incentive programs in the United States, funding for primary care was increased 20% over previous levels.

This allowed practices to invest in extra staff and technology; 90% of general practitioners use the NHS Electronic Prescription Service, and up to 50% use electronic health records for the majority of clinical care. Early analysis showed that substantially increasing physicians' pay based on their success in meeting quality performance measures is successful. The 8,000 family practitioners included in the study earned an average of $40,000 more by collecting nearly 97% of the points available.

A component of this program, known as *exception reporting*, allows physicians to use criteria to exclude individual patients from the quality calculations that determine physician reimbursement. There was initial concern that exception reporting would allow inappropriate exclusion of patients in whom targets were missed ("gaming"). However, a 2008 study has shown little evidence of widespread gaming.

United States

In the United States, Medicare has various pay-for-performance ("P4P") initiatives in offices, clinics and hospitals, seeking to improving quality and avoid unnecessary health care costs. The Centers for Medicare and Medicaid Services (CMS) has several demonstration projects underway offering compensation for improvements:

- Payments for **better care coordination** between home, hospital and offices for patients with chronic illnesses. In April 2005, CMS launched its first value-based purchasing pilot or "demonstration" project- the three-year Medicare Physician Group Practice (PGP) Demonstration. The project involves ten large, multi-specialty physician practices caring for more than 200,000 Medicare fee-for-service beneficiaries. Participating practices will phase in quality standards for preventive care and the management of common chronic illnesses such as diabetes. Practices meeting these standards will be eligible for rewards from savings due to resulting improvements in patient management. The *First Evaluation Report to Congress* in 2006 showed that the model rewarded high quality, efficient provision of health care, but the lack of up-front payment for the investment in new systems of case management "have made for an uncertain future with respect for any payments under the demonstration."

- A set of 10 **hospital quality measures** which, if reported to CMS, will increase the payments that hospitals receive for each discharge. By the third year of the demonstration, those hospitals that do not meet a threshold on quality will be subject to reductions in payment. Preliminary data from the second year of the study indicates that pay for performance was associated with a roughly 2.5% to 4.0% improvement in compliance with quality measures, compared with the control hospitals. Dr. Arnold Epstein of the Harvard School of Public Health commented in an accompanying editorial that pay-for-performance "is fundamentally a social experiment likely to have only modest incremental value." Unintended consequences of some publicly reported hospital quality measures have adversely affected patient care. The requirement to give the first antibiotic

dose in the emergency department within 4 hours, if the patient has pneumonia, has caused an increase in pneumonia misdiagnosis.

- **Rewards to physicians** for improving health outcomes by the use of health information technology in the care of chronically ill Medicare patients.

- **Disincentives**: The 2006 Tax Relief & Health Care Act of 2006 required the HHS Inspector General to study ways that Medicare payments to hospitals could be recouped for "never events", as defined by the National Quality Forum, including hospital infections. In August 2007, CMS announced that it will stop payments to hospitals for several negative consequences of care that result in injury, illness or death. This rule, effective October 2008, would reduce hospital payments for eight serious types of preventable incidents: objects left in a patient during surgery, blood transfusion reaction, air embolism, falls, mediastinitis, urinary tract infections from catheters, pressure ulcer, and sepsis from catheters. Reporting of "never events" and creation of performance benchmarks for hospitals are also mandated. Other private health payers are considering similar actions; in 2005, HealthPartners, a Minnesota health insurer, chose not to cover 27 types of "never events". The Leapfrog Group has announced that will work with hospitals, health plans and consumer groups to advocate reducing payment for "never events", and will recognize hospitals that agree to certain steps when a serious avoidable adverse event occurs in the facility, including notifying the patient and patient safety organizations, and waiving costs. Physician groups involved in the management of complications, such as the Infectious Diseases Society of America, have voiced objections to these proposals, observing that "some patients develop infections despite application of all evidence-based practices known to avoid infection", and that a punitive response may discourage further study and slow the dramatic improvements that have already been made.

Complex illness

Pay for performance programs often target patients with serious and complex illnesses; such patients commonly interact with multiple healthcare providers and facilities. However, pilot programs now underway focus on simple indicators such as improvement in lab values or use of emergency services, avoiding areas of complexity such as multiple complications or several treating specialists. A 2007 study analyzing Medicare beneficiaries' healthcare visits showed that a median of two primary care physicians and five specialists provide care for a single patient. The authors doubt that pay-for-performance systems can accurately attribute responsibility for the outcome of care for such patients. The American College of Physicians Ethics has stated concerns about using a limited set of clinical practice parameters to assess quality, "especially if payment for good performance is grafted onto the current payment system, which does not reward robust comprehensive care...The elderly patient with multiple chronic conditions is especially vulnerable to this unwanted effect of powerful incentives." Present pay-for-performance systems measure good performance based on specified clinical measurements, such as glycohemoglobin for diabetic patients. Healthcare providers who

are monitored by such limited criteria have a powerful incentive to *deselect* (dismiss or refuse to accept) patients whose outcome measures fall below the quality standard and therefore worsen the provider's assessment. Patients with low health literacy, inadequate financial resources to afford expensive medications or treatments, and ethnic groups traditionally subject to healthcare inequities may also be deselected by providers seeking improved performance measures.

Public reporting

Mandatory reporting

Denmark

The Danish Act on Patient Safety passed Parliament in June 2003, and on January 1, 2004 Denmark became the first country to introduce nation-wide mandatory reporting. The Act obligates frontline personnel to report adverse events to a national reporting system. Hospital owners are obligated to act on the reports and the National Board of Health is obligated to communicate the learning nationally. The reporting system is intended purely for learning and frontline personnel cannot experience sanctions for reporting. This is stated in Section 6 of the Danish Act on Patient Safety (as of January 1, 2007: Section 201 of the Danish Health Act): "A frontline person who reports an adverse event cannot as a result of that report be subjected to investigation or disciplinary action from the employer, the Board of Health or the Court of Justice." The reporting system and the Danish Patient Safety Database is described in further detail in a National Board of Health publication.

United Kingdom

The National Patient Safety Agency encourages voluntary reporting of health care errors, but has several specific instances, known as "Confidential Enquiries", for which investigation is routinely initiated: maternal or infant deaths, childhood deaths to age 16, deaths in persons with mental illness, and perioperative and unexpected medical deaths. Medical records and questionnaires are requested from the involved clinician, and participation has been high, since individual details are confidential.

United States

The 1999 Institute of Medicine (IOM) report recommended "a nationwide mandatory reporting system … that provides for … collection of standardized information by state governments about adverse events that result in death or serious harm." Professional organizations, such as the Anesthesia Patient Safety Foundation, responded negatively: "Mandatory reporting systems in general create incentives for individuals and institutions to play a numbers game. If such reporting becomes linked to punitive action or inappropriate public disclosure, there is a high risk of driving reporting "underground", and of reinforcing the cultures of silence and blame that many believe are at the heart of the problems of medical error…"

Although 23 states established mandatory reporting systems for serious patient injuries or death by 2005, the national database envisioned in the IOM report was delayed by the controversy over mandatory versus voluntary reporting. Finally in

2005, the US Congress passed the long-debated Patient Safety and Quality Improvement Act, establishing a federal reporting database. Hospitals reports of serious patient harm are voluntary, collected by patient safety organizations under contract to analyze errors and recommend improvements. The federal government serves to coordinate data collection and maintain the national database. Reports remain confidential, and cannot be used in liability cases. Consumer groups have objected to the lack of transparency, claiming it denies the public information on the safety of specific hospitals.

Voluntary disclosure

In public surveys, a significant majority of those surveyed believe that health care providers should be required to report all serious medical errors publicly. However, reviews of the medical literature show little effect of publicly-reported performance data on patient safety or the quality of care. Public reporting on the quality of individual providers or hospitals does not seem to affect selection of hospitals and individual providers. Some studies have shown that reporting performance data stimulates quality improvement activity in hospitals.

United States

Medical error

Ethical standards of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the American Medical Association (AMA) Council on Ethical and Judicial Affairs, and the American College of Physicians Ethics Manual require disclosure of the most serious adverse events. However, many doctors and hospitals do not report errors under the current system because of concerns about malpractice lawsuits; this prevents collection of information needed to find and correct the conditions that lead to mistakes. As of 2008, 35 US states have statutes allowing doctors and health care providers to apologize and offer expressions of regret without their words being used against them in court, and 7 states have also passed laws mandating written disclosure of adverse events and bad outcomes to patients and families. In September 2005, US Senators Clinton and Obama introduced the National Medical Error Disclosure and Compensation (MEDiC) Bill, providing physicians protection from liability and a safe environment for disclosure, as part of a program to notify and compensate patients harmed by medical errors. It is now the policy of several academic medical centers, including Johns Hopkins, University of Illinois and Stanford, to promptly disclose medical errors, offering apologies and compensation. This national initiative, hoping to restore integrity to dealings with patients, make it easier to learn from mistakes and avoid angry lawsuits, was modeled after a University of Michigan Hospital System program that has reduced the number of lawsuits against the hospital by 75% and has decreased the average litigation cost. The Veterans Health Administration requires the disclosure of all adverse events to patients, even those that are not obvious. However, as of 2008 these initiatives have only included hospitals that are self-insured and that employ their staffs, thus limiting the number of parties involved.

Performance

In April 2008, consumer, employer and labor organizations announced an agreement with major physician organizations and health insurers on principles to measure and report doctors' performance on quality and cost.

United Kingdom

In the United Kingdom, whistleblowing is well recognised and is government sanctioned, as a way to protect patients by encouraging employees to call attention to deficient services. Health authorities are encouraged to put local policies in place to protect whistleblowers.

Studies of patient safety

Numerous organizations, government branches, and private companies conduct research studies to investigate the overall health of patient safety in America and across the globe. Despite the shocking and widely publicized statistics on preventable deaths due to medical errors in America's hospitals, the 2006 National Healthcare Quality Report assembled by the Agency for Healthcare Research and Quality (AHRQ) had the following sobering assessment:

- Most measures of Quality are improving, but the pace of change remains modest.
- Quality improvement varies by setting and phase of care.
- The rate of improvement accelerated for some measures while a few continued to show deterioration.
- Variation in heath care quality remains high.

The Health Grades study in April 2006 determined that over 3% of hospitalized Medicare patients experienced adverse events, and that the total number of patient safety incidents has been increasing since 2001.

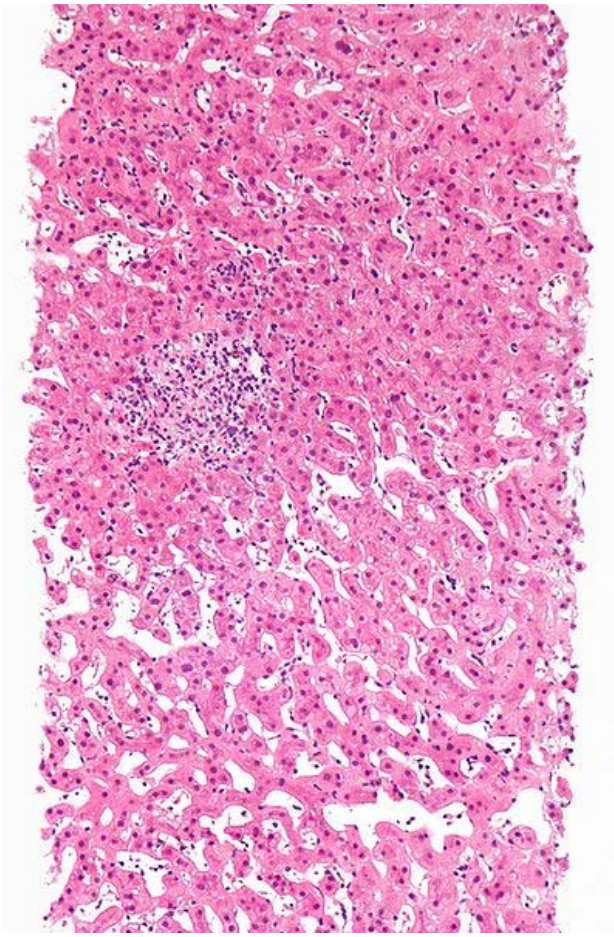
Organizations advocating patient safety

Several authors of the 1999 Institute of Medicine report revisited the status of their recommendations and the state of patient safety, five years after "To Err is Human". Discovering that patient safety had become a frequent topic for journalists, health care experts, and the public, it was harder to see overall improvements on a national level. What was noteworthy was the impact on attitudes and organizations. Few health care professionals now doubted that preventable medical injuries were a serious problem. The central concept of the report—that bad systems and not bad people lead to most errors—became established in patient safety efforts. A broad array of organizations now advance the cause of patient safety. For instance, in 2010 the principal European anaesthesiology organisations launched The Helsinki Declaration for Patient Safety in Anaesthesiology, which incorporates many of the principles described above.

Chapter 6

Adverse Drug Reaction

Adverse drug reaction



Adverse drug reaction leading to hepatitis (drug-induced hepatitis) with granulomata. Other causes were excluded with extensive investigations. Liver biopsy. H&E stain.

ICD-10	T88.7, Y40.-Y59.
ICD-9	995.2, E850-E858

DiseasesDB	295
MeSH	D004362

An **adverse drug reaction** (abbreviated **ADR**) is an expression that describes harm associated with the use of given medications at a normal dose. The meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial. The study of ADRs is the concern of the field known as *pharmacovigilance*.

Classification

ADRs may be classified by e.g. cause and severity.

Cause

- Type A: Augmented pharmacologic effects - dose dependent and predictable
  - Intolerance
  - Side Effects
- Type B: Bizarre effects (or idiosyncratic) - dose independent and unpredictable
- Type C: Chronic effects
- Type D: Delayed effects
- Type E: End-of-treatment effects
- Type F: Failure of therapy

Types A and B were proposed in the 1970s, and the other types were proposed subsequently when the first two proved insufficient to classify ADRs.

Seriousness and Severity

The American Food and Drug Administration defines a serious adverse event as one when the patient outcome is one of the following:

- Death
- Life-Threatening
- Hospitalization (initial or prolonged)
- Disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- Congenital Anomaly
- Requires Intervention to Prevent Permanent Impairment or Damage

Severity is a point on an arbitrary scale of intensity of the adverse event in question. The terms "severe" and "serious" when applied to adverse events are technically very

different. They are easily confused but can not be used interchangeably, require care in usage.

A headache is severe, if it causes intense pain. There are scales like "visual analog scale" that help us assess the severity. On the other hand, a headache can hardly ever be serious, unless it also satisfies the criteria for seriousness listed above.

Overall Drug Risk

While no official scale exists yet to communicate overall drug risk, the iGuard Drug Risk Rating System is a five color rating scale similar to the Homeland Security Advisory System:

- Red (High Risk)
- Orange (Elevated Risk)
- Yellow (Guarded Risk)
- Blue (General Risk)
- Green (Low Risk)

Location

Adverse effects may be local, i.e. limited to a certain location, or systemic, where a medication has caused adverse effects throughout the systemic circulation.

For instance, some ocular antihypertensives cause systemic effects, although they are administered locally as eye drops, since a fraction escapes to the systemic circulation.

Mechanisms

As research better explains the biochemistry of drug use, fewer ADRs are Type B and more are Type A. Common mechanisms are:

- Abnormal pharmacokinetics due to
  - genetic factors
  - comorbid disease states
- Synergistic effects between either
  - a drug and a disease
  - two drugs

Abnormal pharmacokinetics

Comorbid disease states

Various diseases, especially those that cause renal or hepatic insufficiency, may alter drug metabolism. Resources are available that report changes in a drug's metabolism due to disease states.

Genetic factors

Abnormal drug metabolism may be due to inherited factors of either Phase I oxidation or Phase II conjugation. Pharmacogenomics is the study of the inherited basis for abnormal drug reactions.

Phase I reactions

Inheriting abnormal alleles of cytochrome P450 can alter drug metabolism. Tables are available to check for drug interactions due to P450 interactions.

Inheriting abnormal butyrylcholinesterase (pseudocholinesterase) may affect metabolism of drugs such as succinylcholine

Phase II reactions

Inheriting abnormal N-acetyltransferase which conjugated some drugs to facilitate excretion may affect the metabolism of drugs such as isoniazid, hydralazine, and procainamide.

Inheriting abnormal thiopurine S-methyltransferase may affect the metabolism of the thiopurine drugs mercaptopurine and azathioprine.

Interactions with other drugs

The risk of drug interactions is increased with polypharmacy.

Protein binding

These interactions are usually transient and mild until a new steady state is achieved. These are mainly for drugs without much first-pass liver metabolism. The principal plasma proteins for drug binding are:

1. albumin
2. α1-acid glycoprotein
3. lipoproteins

Some drug interactions with warfarin are due to changes in protein binding.

Cytochrome P450

Patients have abnormal metabolism by cytochrome P450 due to either inheriting abnormal alleles or due to drug interactions. Tables are available to check for drug interactions due to P450 interactions.

Synergistic effects

An example of synergism is two drugs that both prolong the QT interval.

Assessing causality

An ADR should not be labeled as 'certain' unless the ADR abates with a challenge-dechallenge-rechallenge protocol.

A more complicated scale is the Naranjo algorithm.

Monitoring bodies

Many countries have official bodies that monitor drug safety and reactions. On an international level, the WHO runs the Uppsala Monitoring Centre, and the European Union runs the European Medicines Agency (EMEA). In the United States, the Food and Drug Administration (FDA) is responsible for monitoring post-marketing studies.

Examples of adverse effects associated with specific medications

Condition	Substance
Abortion, miscarriage or uterine hemorrhage	misoprostol (Cytotec), a labor-inducing drug (this is a case where the adverse effect has been used legally and illegally for performing abortions)
Addiction	many sedatives and analgesics such as diazepam, morphine, etc.
Birth defects	Thalidomide and Accutane
Bleeding of the intestine	aspirin therapy
Cardiovascular disease	COX-2 inhibitors (i.e. Vioxx)
Deafness and kidney failure	gentamicin (an antibiotic)
Death, following sedation	propofol (Diprivan)
Dementia	heart bypass surgery
Depression or hepatic injury	interferon
Diabetes	atypical antipsychotic medications (neuroleptic psychiatric drugs)
Diarrhea	orlistat (Xenical)
Erectile dysfunction	many drugs, such as antidepressants

Fever	vaccination (in the past, imperfectly manufactured vaccines, such as BCG and poliomyelitis, have caused the very disease they intended to fight).
Glaucoma	corticosteroid-based eye drops
Hair loss and anemia	chemotherapy against cancer, leukemia, etc.
Headache	spinal anesthesia
Hypertension	ephedrine users, which prompted FDA to remove the status of dietary supplement of ephedra extracts
Insomnia	stimulants, Ritalin, Adderall, etc.
Lactic acidosis	stavudine (Zerit, for anti-HIV therapy) or metformin (for diabetes)
Liver	paracetamol
Melasma and thrombosis	estrogen-containing hormonal contraception such as the combined oral contraceptive pill
Irreversible Peripheral neuropathy	fluoroquinolone medications
Rhabdomyolysis	statins (anti-cholesterol drugs)
Seizures	withdrawal from benzodiazepine
Drowsiness or increase in appetite	antihistamine use. Some antihistamines are used in sleep aids explicitly because they cause drowsiness.
Stroke or heart attack	sildenafil (Viagra) when used with nitroglycerine
Suicide, increased tendency	fluoxetine and other SSRI antidepressants
Parkinsonism	MPTP a meperidine related drug considered highly neurotoxic
Tardive dyskinesia	long-term use of metoclopramide and many antipsychotic medications
Spontaneous Tendon rupture	fluoroquinolone drugs even occurring as late as 6 months after treatment had been terminated.

Chapter 7

Iatrogenesis

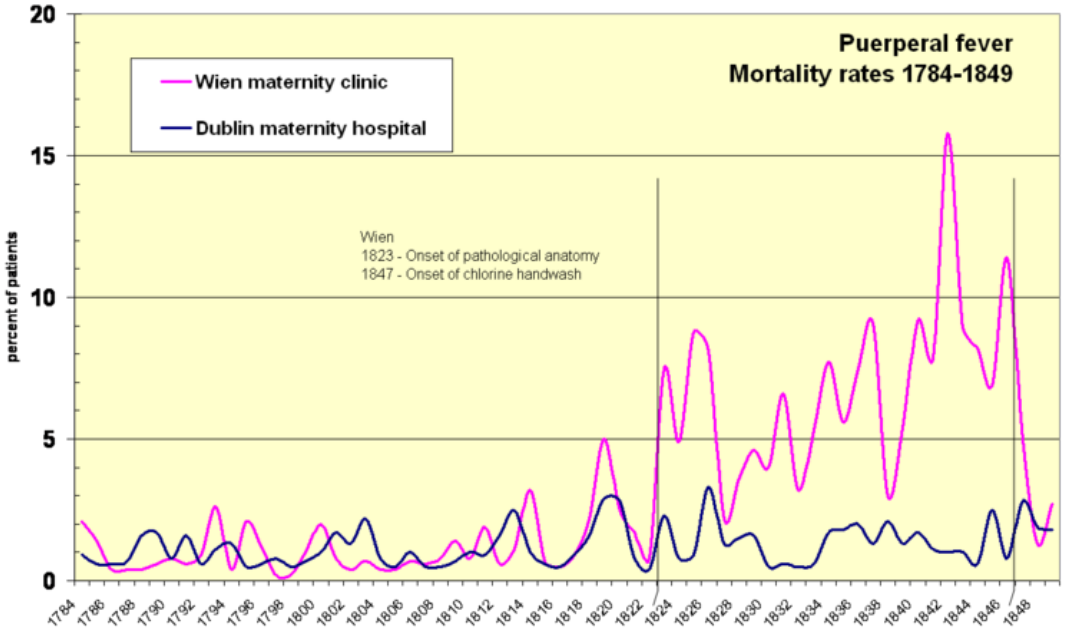
Ancient Greek painting in a vase, showing a physician (*iatros*) bleeding a patient

The terms **iatrogenesis** and **iatrogenic artifact** refer to inadvertent adverse effects or complications caused by or resulting from medical treatment or advice. In addition to harmful consequences of actions by physicians, iatrogenesis can also refer to actions by other healthcare professionals, such as psychologists, therapists, pharmacists, nurses, dentists, and others. Iatrogenesis is not restricted to conventional medicine: it can also result from complementary and alternative medicine treatments.

Some iatrogenic artifacts are clearly defined and easily recognized, such as a complication following a surgical procedure. Some less obvious ones can require significant investigation to identify, such as complex drug interactions. Furthermore, some conditions have been described for which it is unknown, unproven or even controversial whether they are iatrogenic or not; this has been encountered particularly with regard to various psychological and chronic-pain conditions. Research in these areas continues.

Causes of iatrogenesis include chance, medical error, negligence, social controland the adverse effects or interactions of medications. In the United States, an estimated 44,000 to 98,000 deaths per year may be attributed in some part to iatrogenesis.

History



In his 1861 book, Semmelweis presented evidence to demonstrate that the advent of pathological anatomy in Vienna in 1823 (left vertical line) correlated with the incidence of fatal childbed fever there. Onset of chlorine handwash in 1847 marked by vertical line at far right. Rates for Dublin maternity hospital, which had no pathological anatomy, appear for comparison (view rates).

Etymologically, the term "iatrogenesis" means "brought forth by a healer" (*iatros* means healer in Greek); as such, in its earlier forms, it could refer to good or bad effects.

Since at least the time of Hippocrates, people have recognized the potential damaging effects of a healer's actions. The old mandate "first do no harm" (*primum non nocere*) is an important clause of medical ethics, and iatrogenic illness or death caused purposefully, or by avoidable error or negligence on the healer's part became a punishable offense in many civilizations.

The transfer of pathogens from the autopsy room to maternity patients, leading to shocking historical mortality rates of puerperal fever (a.k.a. "childbed fever") at maternity institutions in the 19th century, was a major iatrogenic catastrophe of that time. The infection mechanism was first identified by Ignaz Semmelweis.

With the development of scientific medicine in the 20th century, it could be expected that iatrogenic illness or death would be more easily avoided. Antiseptics, anesthesia, antibiotics, and better surgical techniques have been developed to decrease iatrogenic mortality.

Sources

Examples of iatrogenesis:

- Risk associated with medical interventions
    - adverse effects of prescription drugs
    - over-use of drugs, (causing - for example - antibiotic resistance in bacteria)
    - prescription drug interaction
- medical error
- wrong prescription, perhaps due to illegible handwriting, typos on computer.
- negligence
- faulty procedures, techniques, information, methods, or equipment.

Causes and consequences

Medical error and negligence

Iatrogenic conditions do not necessarily result from *medical errors*, such as mistakes made in surgery, or the prescription or dispensing of the wrong therapy, such as a drug. In fact, intrinsic and sometimes *adverse effects* of a medical treatment are iatrogenic. For example, radiation therapy and chemotherapy, due to the needed aggressiveness of the therapeutic agents, frequently produce iatrogenic effects such as hair loss, anemia, vomiting, nausea, brain damage, lymphedema, infertility, etc. The loss of functions resulting from the required removal of a diseased organ also counts as iatrogenesis, thus we find (for example) iatrogenic diabetes brought on by removal of all or part of the pancreas.

Other situations may involve actual *negligence* or faulty procedures, such as when pharmacotherapists produce handwritten prescriptions for drugs.

Adverse effects

A very common iatrogenic effect is caused by *drug interaction*, i.e., when pharmacotherapists fail to check for all medications a patient is taking and prescribe new ones which interact agonistically or antagonistically (potentiate or decrease the intended therapeutic effect). Such situations can cause significant morbidity and mortality. Adverse reactions, such as allergic reactions to drugs, even when unexpected by pharmacotherapists, are also classified as iatrogenic.

The evolution of *antibiotic resistance* in bacteria is iatrogenic as well. Bacteria strains resistant to antibiotics have evolved in response to the overprescription of antibiotic drugs.

Certain drugs are toxic in their own right in therapeutic doses because of their mechanism of action. Alkylating antineoplastic agents, for example, cause DNA damage, which is

more harmful to cancer cells than regular cells. However, alkylation causes severe side-effects and is actually carcinogenic in its own right, potentially leading to the development of secondary tumors. Similarly, arsenic-based medications like melarsoprol for trypanosomiasis cause arsenic poisoning.

Psychology

In psychology, iatrogenesis can occur due to misdiagnosis (including diagnosis with a false condition as was the case of hystero-epilepsy). Conditions hypothesized as partially or completely iatrogenic include bipolar disorder, dissociative identity disorder, fibromyalgia, somatoform disorder, chronic fatigue syndrome, posttraumatic stress disorder, substance abuse, antisocial youths and others, though research is equivocal for each condition. The degree of association of any particular condition with iatrogenesis is unclear and in some cases controversial. The over-diagnosis of psychological conditions (with the assignment of mental illness terminology) may relate primarily to clinician dependence on subjective criteria. The assignment of pathological nomenclature is rarely a benign process and can easily rise to the level of emotional iatrogenesis, especially when no alternatives outside of the diagnostic naming process have been considered.

Iatrogenic poverty

Meessen et al. used the term "iatrogenic poverty" to describe impoverishment induced by medical care. Impoverishment is described for households exposed to catastrophic health expenditure or to hardship financing. Every year, worldwide, over 100,000 households fall into poverty due to health care expenses. In the United States, medical debt is the leading cause of bankruptcy. Especially in countries in economic transition, the willingness to pay for health care is increasing and the supply side does not stay behind and develops very fast. But, the regulatory and protective capacity in those countries is often lagging behind. Patients easily fall in a vicious cycle of illness, ineffective therapies, consumption of savings, indebtedness, sale of productive assets and eventually poverty.

Incidence and importance

Iatrogenesis is a major phenomenon, and a severe risk to patients. A study carried out in 1981 more than one-third of illnesses of patients in a university hospital were iatrogenic, nearly one in ten were considered major, and in 2% of the patients, the iatrogenic disorder ended in death. Complications were most strongly associated with exposure to drugs and medications. In another study, the main factors leading to problems were inadequate patient evaluation, lack of monitoring and follow-up, and failure to perform necessary tests.

In the United States, figures suggest estimated deaths per year of:

- 12,000 due to unnecessary surgery
- 7,000 due to medication errors in hospitals

- 20,000 due to other errors in hospitals
- 80,000 due to nosocomial infections in hospitals
- 106,000 due to non-error, negative effects of drugs

Based on these figures, iatrogenesis may cause 225,000 deaths per year in the United States (excluding recognizable error).

These estimates are lower than those in an earlier IOM report, which would suggest from 230,000 to 284,000 iatrogenic deaths.

These figures are likely exaggerated, however, as they are based on recorded deaths in hospitals rather than in the general population. Even so, the large gap separating these estimates deaths from cerebrovascular disease would still suggest that iatrogenic illness constitutes the third leading cause of death in the United States, after deaths from heart disease and cancer.

Chapter 8

Patient Safety and Nursing

Nurses are knowledge workers whose main responsibility is to provide safe and effective care within constantly evolving health care systems. Nurses collaborate with one another, as well as doctors, aides, technicians, and others, to provide holistic care to patients. Although advocating for patient safety is a nurse's role, it is also necessary for the patient to be an active participant in their safety. Patient safety is a collaborative goal that requires concerted efforts from the patient and all members of the health care team. It is also a means to foster communication between the patient and the nurse including other health care members to better patient's health.

"Nurse's Roles"

“Nursing is the protection, promotion, and optimization of health and abilities, prevention of illness and injury, alleviation of suffering through diagnosis and treatment of human response, and advocacy in the care of individuals, families, communities, and populations”

The nursing method is the basis of all clinical judgments and includes all dealings made by nurses in providing care to patients. Considerations for culture, safety, education, health and wellness, patient care, self-health promotion, and planning for long-term health maintenance are included in nursing measures.

- Recent changes in this profession have:
- Increased the role to provide greater focus on primary care to emphasize prevention and maintenance of health
- A more whole person (including spiritual, physical, and mental components) approach to health care
- Including detection and intervention when a breakdown in care occurs in order to reduce adverse effects or events for patients.

Nurses perform clinical decision-making using the nursing process as a framework. Overall, it is a problem-solving activity focusing on recognizing and defining patient issues and selecting appropriate interventions.

Critical Thinking

- Knowledge base
- Attention
- Barriers to care (like workplace obstacles)
- Number of tasks
- Missing essential information
- Behaviors not encouraging of productive thought

- Complexity of nurse work*

Due to the increasingly nature of the role of nurses, everyday nursing duties are also a challenge in protecting the safety of every patient.

- Variety of supply locations
- Locating supplies when not found in designated areas or not adequately stocked
- Repetitive travel (to patient's rooms, nurse's stations, supply locations, etc.)
- Unexpected situations, interruptions and distractions
- Pauses to wait for system services (computers or medication carts)
- Inadequate resource access for further care and new procedures
- Miscommunication
- Errors due to handwriting and labeling

Patient factors and safety

These are some of the areas of which nurses are responsible for that are significant in ensuring patient safety in a hospital setting.

Nursing Assessments

- Mobility: affects patient's ability to move independently and control body movement. This includes skin assessment of risk for pressure ulcers and infections of wounds.
- Level of awareness: impairs the patient's ability to communicate signs of healing or worsening conditions. This relates to how the patient communicates with the nurse and possible interventions related to sedation and lack of consciousness, if applicable
- Critical condition: patients in critical condition require a great deal of care and should be monitored more closely for changes in condition.
- Mental state: those with impaired mental ability will also require more individualized care to provide safety when they are unable to make sound decisions for themselves.

*Patient Rights for Medication Administration

- Right patient - nurses should take steps to accurately identify the correct patient to receive medication before administering it.
- Right Medication - nurses should take steps to accurately identify the correct medication to be received before administering it to the patient.
- Right dose - nurses should take steps to accurately identify the correct dosage of medication before administering it to the patient.
- Right Route - nurses should take steps to accurately identify the correct route the patient is to receive the medication before administering it.
- Right Time - nurses should take steps to administer medication in a timely fashion as ordered by the physician.
- Right Documentation - nurses should take steps to accurately document the medication administration after administering it.

An important aspect of medication administration also includes checking the patient's allergies, often included as one of the patient rights for medication administration.

Hygiene and Cleanliness

- "Hand washing" - nurses should wash their hands or use a hand sanitizer before and after each patient interaction.

Patient's Role

- It is required that nurses and other hospital staff members wash or sanitize their hands upon entering and leaving your room to reduce spread of infection.

- Three things patients should ask themselves to ensure their safety while staying at the hospital:

1. *Why am I at the hospital?*
2. *What is my treatment?*
3. *Why should I have this treatment?*

- Importance of Questions:

- Patients should always ask questions if they do not understand something.
- The health care team should keep patients informed and educated regarding the patient's care.
- Do not feel scared to use the call light.
- Patients can ask for a written form of information including explanations about your procedure, illness, health, etc. For example, you can ask to see your medical records.

- Medications:

- The nurses must always check the patient's wrist band before giving medications or treatments.
- Patients should ask questions about the medications they are receiving when they don't understand something.
- Ask if there are any side effects to be aware of.
- Know if the medication will change mental and physical functioning
- Bring a list of home medications: over the counter medications, herbal, vitamins and/or supplements for the health care staff to put in the chart.

- Personal Issues:

- Individuals have the right to daily personal cleanliness and clean sheets/blankets.
- Patients should leave any and all valuables such as: wallets, money, jewelry, etc. that they do not want lost at home OR request them to be locked up.
- Patients should inform staff of any physical or mental changes, no matter how minor they may be, as soon they occur.

- Importance of Plan of Care:

- Patients should know what the plan of care the health care staff have planned for them and if it matches their wishes.
- Cooperation is important to the patient's plan of care.
- Patients should not adjust dressing changes, IV's, or any type of treatment without consulting the nurse. These regimens have a purpose.
- Patients should follow the plan of care that is recommended after they leave the hospital.

How do mistakes happen?

In order to prevent errors in health care settings, it may be helpful to understand how those errors occur. One analogy used to explain the error process is called the "Swiss Cheese Model" (Reason, 2000). The idea behind this analogy is that in health care, precautions against errors are put in place like stacks of Swiss cheese, acting as barriers to making mistakes.

However, no barrier is perfect (each piece of Swiss cheese has a few holes it). When an error is able to slip through one of the holes in the barrier that means the safety check has failed. The hope is that if you have a stack of Swiss cheese (in other words multiple safety checks), somewhere along the line that error will run into a dead-end.

It happens occasionally that the error is allowed to pass through each piece of cheese and actually arrive at the patient's bedside. At this point, a critical error has occurred, which may or may not result in serious injury to the patient. Ultimately this series of small errors lead to one large adverse event (Reason, 2000).

A visual image of the Swiss Cheese Model

How does your level of understanding play a role in your safety?

- According to the Institute of Medicine (2004) almost half of all Americans do not understand the meaning of health terms or how to use the information that is given to them by their health care providers.
- In this country, 46% of adults cannot read and about one-third of senior citizens are either unable to perform or understand instructions given to them by their care providers (Shutan, 2001).

Imagine how this lack of understanding negatively affects that person's overall health. It has even been shown in studies that not understanding healthcare instructions leads to negative results in terms of their overall health, including a higher rate of surgery and more frequent trips to the emergency room (AHRQ, 2004).

It is important that patients act as active participants in their own health, i.e. always ask questions maintain informed and to understand the plan of care.

Statistics about health care errors

In a group of 22 studies, prescription medication histories included at least one error in 67% of all cases (Tam et al., 2005). Errors in medication history taking can lead to several negative outcomes including life long disability or even death.

Up to 27% of all hospital prescribing errors can be attributed to incomplete medication histories at the time of admission (Tam et al., 2005).

In a recent Institute of Medicine report, it was found that medical errors account for anywhere between 44,000 to 98,000 deaths annually in U.S. hospitals and that 58% of these deaths could have been prevented (IOM, 2000).

A national survey of the American public and practicing physicians revealed that 35% of the physicians surveyed, had made errors related to a patients care (Blendon et al., 2002). 42% of the American public surveyed had experienced an error either in the care of a family member or their own personal health care. One third of the American public surveyed revealed that a health care professional or the physician themselves had either informed them of the error or apologized for the error that had taken place (Blendon et al., 2002).

What is being done to prevent errors?

McFadden et al. (2006), found that the most widespread error reducing method being used in health care organizations to date is the development of blame free error reporting systems. Blame free reporting systems allow hospital employees to report errors for the purpose of correcting hospital policy and procedures. This report also showed that very few hospitals are statistically analyzing the data reported by the hospital employees in order to make corrections within their institution (McFadden, Stock, & Gowen, 2006).

The Institute of Medicine believes that a National Patient Safety Center should be formed to ensure patient safety within health care settings. This organization would be committed to research, tracking, and goal setting. This organization would also work with health care organizations to implement corrections in protocols that have already been identified as problem areas through the use of blame free error reporting systems. A main goal of the Center for Patient Safety would be reducing medical errors by 50%within 5 years (IOM, 2000).

Other methods to improve safety include:

Better lighting and less clutter in work areas where medications are prepared, keeping distractions to a minimum, and keeping noise levels down.

Drug companies and health care facilities are also standardizing medication labels and packaging.

Medications that can have a particularly dangerous effect are being marked as "high alert" (National Quality Forum, 2003).

Many hospitals are investing in technology to minimize errors, such as machines that dispense medications for just one patient at a time.

Patients are given identification bracelets showing their names and allergies.

All medical personnel are required to wear name tags showing their level of training.

Ethics

Dignity

Nurses and health care workers have the responsibility to uphold the dignity and worth of all people they encounter regardless of race, sex, ethnicity,age, religion, beliefs, values, socioeconomic status, and sexual orientation. In addition, it is also the responsibility of patients and their families to mutually respect the dignity of their health care providers and staff. (Munson, 2004)

For example, a nurse caring for an unconscious patient should provide the same or higher level of care as though the patient were conscious. Extra precautions to protect dignity such as speaking respectfully to the patient, covering the patient should be used. Also, informing the patient about care needing to be done prior to initiation acknowledges their dignity.

Autonomy

Allowing the patient to make their own decisions about their care, regardless of the belief of the family members or the health care provider, is very important. Everyone has a right to dictate what care they get at all stages of life.

Informed Consent

Informed consent is a critical aspect of patient rights as well as for protection of the health care providers involved. Patients have the right to refuse any procedure and medication, even if others consider their best interest to receive the care. Respecting this right of the patient is a very important aspect of medical ethics. Requiring written informed consent offers evidence in the court of law that defends the actions of the doctors or nurses involved. There are also protocols that dictate that informed consent must be received before any procedure may be undertaken. (Munson, 2004)

End of life

In order to provide the level of care a patient desires during life threatening and end of life illnesses, nurses and health care providers need to understand their wishes. It is controversial in situations when a health care professional performs procedures or life extending care if the patient clearly desires minimal or comfort measures only.

Advanced Directives

An advance directive is a legal document that a patient signs defining the type of health treatment and care they would like to receive in various health situations that may arise. For example, the directives would describe the kind of care a patient wishes to receive in the event that they contract an illness that they are unlikely to recover from, or if they are permanently unconscious. Different health situations may warrant different directives from the patient.

A living will is a type of advanced directive. It is a legal document that a competent individual freely signs defining the type of medical treatment and care they would like to receive in the event that their health stability should decrease such that they are no longer capable of making important health decisions on their own behalf. A living will does not give anyone else a legal right or responsibility to make health care decisions on the behalf of a patient (Advance directives, 2006).

Without written documentation that expresses the patient's wishes, confusion can occur, leading to errors in providing or withholding the care of the patient. This error may lead to ignoring of patient autonomy.

Truth Telling

Patients may have a right to know the truth from health care professionals about their diagnosis and prognosis. (Munson, 2004)

Scarce Medical Resources

There are limited resources in health care, which present ethical dilemmas for those who work in this field. One aspect of providing ethical care is for nurses and health professionals to avoid duplication and wasteful use of resources. For example, while some medical tests may be needed to provide safe care, multiple tests may be wasteful without providing useful information. However, the cost of safety equipment such as a bed that alarms when the patient is out of bed, or use of pumps to provide medications may be justified by preventing medication errors or falls. (Munson, 2004)

Relevant Applicable Ethical Theories

- Utilitarianism
- Kant
- John Rawls
- Natural Law

Hospital Resources

Hospital Resources and Patient Safety- to engage patients to be actively involved in their health care experience.

1. Ensuring safe medication administration.

Hospitals can provide patients with an up-to-date list of the medications they are receiving. This gives patients more control, and allows for another check for the 5 rights by the person who is actually receiving the drugs. Further, providing patients access to information they can understand about the adverse reactions to the medications they are taking so that they can better identify them if they occur. Providing these resources in different languages if needed.

2. Patient involvement, awareness, and education.

Hospitals provide certain safety mechanisms for patients in the hospital that patients should be aware of. For example, keeping bed rails up, bed/chair alarms, and low beds. Patients should know why and what precautions are in place for their safety. Other examples include patient education about hand washing and infection control and patients marking their own site for surgeries.

3. Understanding their condition.

For example, patients should understand what procedure they had and the expected pain level after analgesic medications have been administered or after non-pharmacological measures have been taken. Knowing this standard, patients can be more active in their pain management.

4. Physical therapy, exercise programs, speech therapy, and occupational therapy.

These services, while helping patients recover, may also evaluate safety needs of patients before being discharged. For example, physical therapists providing information about building strong muscles and bones to prevent falls at home, or speech therapists teaching swallowing techniques to prevent choking. A home evaluate may check home safety. It is the responsibility of nurses to inform patients about these resources and to collaborate with these other disciplines to ensure patient safety.

5. Electronic medical records.

Intranet connects health care workers throughout the hospital concerning the patients electronic medical record (EMR), patient status, allergies, test results etc. to ensure patient safety throughout the hospital. Health care workers are able to access the patient record for better communication of information.

6. Libraries

Hospital libraries are a great resource for patients and health care workers. They are conveniently located in the hospital and provide a wide range of sources, from books and journal articles to the internet.

Current Resources

What is Evidence Based Practice?

Evidence based practice is the use of current evidence from scientific research in order to make health care related decisions. This practice begins much like other scientific processes with a question about health care (delivery of services, types of interventions, etc.) and ends with the data to provide the best possible care to patients' based upon their individual needs.

Nurse and Evidence Based Practice:

In providing care to patients, nurses must always ask questions about their practice:

- Why am I doing this?
- Why am I doing it this way?
- Is there another better possible way?

Examples of Evidence Based Practice being used:

- For patients who are always lying in hospital beds, research shows that turning them about every 2 hours decreases the amount of pressure on an area, thus lowering the risk of developing a pressure sore or ulcer.
- In repositioning a patient, pillows or foam pads should be used as support devices in order to reduce pressure and protect bony areas (elbows, hips etc.).
- Lifting devices or aids, such as bed sheets, should be used to move patients in bed to decrease the friction.

Summary of how resources effect patient safety

- Patients educate themselves about disease processes, medication, procedures, and new technologies.
- Based on patients' questions and concerns healthcare professionals take time to reflect on their practice and make changes in plan of care.
- Previous errors inspire/motivate healthcare teams to review and adjust practice for patients' safety.

Chapter 9

Acute Hemolytic Transfusion Reaction and Eczema Vaccinatum

Acute hemolytic transfusion reaction

An **acute hemolytic transfusion reaction** (AHTR) is a type of transfusion reaction that is associated with hemolysis.

It occurs very soon after the transfusion. It can occur quickly upon transfusing a few milliliters, or up to 1-2 hours post-transfusion.

It is also known as an "immediate hemolytic transfusion reaction".

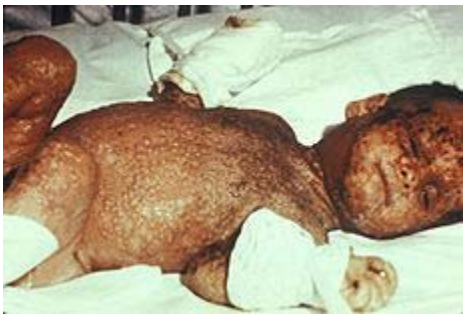
This is a medical emergency as it results from rapid destruction of the donor red blood cells by host antibodies (IgG, IgM). It is usually related to ABO blood group incompatibility - the most severe of which often involves group A red cells being given to a patient with group O type blood. Properdin then binds to complement C3 in the donor blood, facilitating the reaction through the alternate pathway cascade. The donor cells also become coated with IgG and are subsequently removed by macrophages in the reticuloendothelial system (RES). Jaundice and disseminated intravascular coagulation (DIC) may also occur.

The most common cause is clerical error (i.e. the wrong unit of blood being given to the patient). The symptoms are fever and chills, sometimes with back pain and pink or red urine (hemoglobinuria). The major complication is that the hemoglobin, released by the destruction of red blood cells, may cause acute renal failure (also known as the "oliguric phase").

About 20 annual deaths are due to AHTR.

Eczema vaccinatum

Eczema vaccinatum



8 mo. old boy developed eczema vaccinatum after acquiring vaccina from a sibling recently vaccinated for smallpox. Source: CDC/Arthur E. Kaye

ICD-10	B03., T88.1, Y59.1
ICD-9	050, 692.9, E949.0

Eczema vaccinatum is a rare severe adverse reaction to smallpox vaccination.

It is characterized by serious local or disseminated, umbilicated, vesicular, crusting skin rashes in the face, neck, chest, abdomen, upper limbs and hands, caused by widespread infection of the skin in people with previous diagnosed skin conditions such as eczema or atopic dermatitis, even if the conditions are not active at the time. Other signs and symptoms include fever and facial and supraglottic edema. The condition may be fatal if severe and left untreated. Survivors are likely to have some scarring (pockmarks).

Smallpox vaccine should not be given to patients with a history of eczema. Because of the danger of transmission of vaccinia, it also should not be given to people in close contact with anyone who has active eczema and who has not been vaccinated. People with other skin diseases such as atopic dermatitis, burns, impetigo, or herpes zoster) also have an increased risk of contracting eczema vaccinatum and should not be vaccinated against smallpox.

Eczema is also associated with increased complications related to other vesiculating viruses such as chickenpox; this is called eczema herpeticum.

Diagnosis

A culture of vesicular fluid will grow vaccinia virus. Skin biopsy shows necrotic epidermal cells with intranuclear inclusions.

Treatment

Eczema vaccinatum is a serious medical condition that requires immediate and intensive medical care. Therapy has been supportive, such as antibiotics, fluid replacement, antipyretics and analgesics, skin healing, etc.; Vaccinia Immune Globulin (VIG) could be very useful but supplies may be deficient as of 2006. Antiviral drugs have been examined for activity in pox viruses and Cidofovir is believed to display potential in this area CDC guidance WHO.

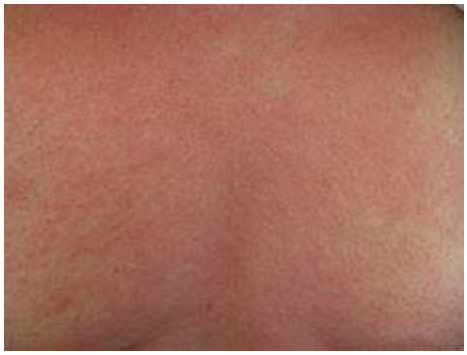
Recent Cases

In March 2007, a two-year-old Indiana boy and his mother contracted the life-threatening vaccinia infection from his father who was vaccinated against smallpox as part of the standard vaccination protocol for individuals serving in the US armed forces beginning in 2002. The child developed the pathognomonic rash which typifies eczema vaccinatum over 80 percent of his body surface area. The boy has a history of eczema, which is a known risk factor for vaccinia infection.

Chapter 10

Anaphylaxis

Anaphylaxis



A rash on the back of a person with anaphylaxis

ICD-10	T78.2
DiseasesDB	29153
eMedicine	med/128
MeSH	D000707

Anaphylaxis is an acute multi-system severe type I hypersensitivity reaction. The term comes from the Greek words ἀνά **ana**, *against*, and φύλαξις **phylaxis**, *protection*.

Due in part to the variety of definitions, between 1% and 15% of the population of the United States can be considered "at risk" for having an anaphylactic reaction if they are exposed to one or more allergens. Of those people who actually experience anaphylaxis, up to 1% may die as a result. Anaphylaxis results in approximately 1,500 deaths per year in the U.S. In England, mortality rates for anaphylaxis have been reported as up to 0.05 per 100,000 population, or around 10-20 a year. Anaphylactic reactions requiring hospital treatment appear to be increasing, with authorities in England reporting a threefold increase between 1994 and 2004.

Based on the pathophysiology, anaphylaxis can be divided into "true anaphylaxis" and "pseudo-anaphylaxis" or "anaphylactoid reaction." The symptoms, treatment, and risk of death are the same; however, "true" anaphylaxis is caused by degranulation of mast cells

or basophils mediated by immunoglobulin E (IgE), and pseudo-anaphylaxis occurs without IgE mediation.

Classification

Biphasic anaphylaxis

Biphasic anaphylaxis is the recurrence of symptoms within 72 hours with no further exposure to the allergen. It occurs in between 1–20% of cases depending on the study examined. It is managed in the same manner as anaphylaxis.

Anaphylactic shock

Anaphylactic shock is anaphylaxis associated with systemic vasodilation that results in low blood pressure. It is also associated with severe bronchoconstriction to the point where the individual is unable to breathe.

Pseudoanaphylaxis

The presentation and treatment of pseudoanaphylaxis is similar to that of anaphylaxis. However, it does not involve an allergic reaction but is due to direct mast cell degranulation. This can result from morphine, radiocontrast, aspirin and muscle relaxants.

Active anaphylaxis

Active anaphylaxis is what is naturally observed. Two weeks or so after an animal, including humans, is exposed to certain allergens, active anaphylaxis (which is simply called "anaphylaxis") would be elicited upon exposure to the same allergens.

Passive anaphylaxis

Passive anaphylaxis is induced in native animals that receive transfer of the serum experimentally from sensitized animals with certain allergens. Passive anaphylaxis would be provoked in the recipient animals after exposure to the same allergens.

Signs and symptoms

Anaphylaxis can present with many different symptoms due to the systemic effects of histamine release. These usually develop over minutes to hours. The most common areas affected include: skin (80% to 90%), respiratory (70%), gastrointestinal (30% to 45%), heart and vasculature (10% to 45%), and central nervous system (10% to 15%).

Skin

Skin involvement may include generalized hives, itchiness, flushing, and swelling of the lips, tongue, or throat.

Respiratory

Respiratory symptoms may include shortness of breath, wheezes or stridor, and low oxygen.

Gastrointestinal

Gastrointestinal symptoms may include crampy abdominal pain, diarrhea, and vomiting.

Cardiovascular

Due to the presence of histamine-releasing cells in the heart, coronary artery spasm may occur with subsequent myocardial infarction or dysrhythmia.

Nervous system

A drop in blood pressure may result in a feeling of lightheadedness and loss of consciousness. There may be a loss of bladder control and muscle tone, and a feeling of anxiety and "impending doom".

Causes

Anaphylaxis can occur in response to any allergen. Common triggers include insect bites or stings, foods, medication, and latex rubber.

Food

Many foods can trigger anaphylaxis. The most common are peanut, tree nuts, shellfish, fish, milk, and egg. Severe cases are usually the result of ingesting the allergen.

Medication

Any medication may potentially trigger anaphylaxis. The most common to do so include antibiotics (β-lactam antibiotics in particular), aspirin, ibuprofen, and other analgesics. Some drugs (polymyxin, morphine, x-ray contrast and others) may cause an "anaphylactoid" reaction (anaphylactic-like reaction) on the *first exposure*. This is usually due to a toxic reaction, rather than the immune system mechanism that occurs with "true" anaphylaxis. The symptoms, risk for complications without treatment, and treatment are the same, however, for both types of reactions. Some vaccinations are also known to cause "anaphylactoid" reactions.

Venom

Venom from stinging or biting insects such as Hymenoptera or Hemiptera may induce anaphylaxis in susceptible people.

Pathophysiology

Anaphylaxis is a severe, whole-body allergic reaction. After an initial exposure "sensitizing dose" to a substance like bee sting toxin, the person's immune system becomes sensitized to that allergen. On a subsequent exposure "shocking dose", an allergic reaction occurs. This reaction is sudden, severe, and involves the whole body.

Classified as a type I hypersensitivity, anaphylaxis is triggered when an antigen binds to IgE antibodies on mast cells based in connective tissue throughout the body, which leads to degranulation of the mast cells (the release of inflammatory mediators). These immune mediators cause many symptoms, including common symptoms of allergic reactions, such as itching, hives, and swelling. Anaphylactic shock is an allergic reaction to an antigen that causes circulatory collapse and suffocation due to bronchial and tracheal swelling.

Different classes of antibodies are produced by B cells to bind and destroy substances that the immune system has identified as potentially dangerous pathogens. Each B cell produces thousands of identical antibodies that can attack a single, small part of a pathogen. In susceptible individuals, antibodies may be produced against innocuous antigens or allergens, such as components of common foods or plants. One class, the IgE antibodies, can trigger anaphylaxis. Production of IgE antibodies may persist for months, even in the complete absence of the allergen. These IgE antibodies associate with a receptor on the surface of mast cells. If the antibody binds to its specific antigen, then the antibody triggers degranulation of the mast cell.

Mast cells become the major effector cells for immediate hypersensitivity and chronic allergic reactions.

Mast cells are large cells found in particularly high concentrations in vascularized connective tissues just beneath epithelial surfaces, including the submucosal tissues of the gastrointestinal and respiratory tracts, and the dermis that lies just below the surface of the skin. They contain large granules that store a variety of mediator molecules including the vasoactive amine histamine. Histamine causes dilation of local blood vessels and smooth-muscle contraction. Other molecules in the mast cell granules include lipid inflammatory mediators such as prostaglandin D2¬ and leukotriene C4 as well as tumor necrosis factor-α (TNF-α), a cytokine. The importance of TNF-α is most noted in the activation of the endothelium. TNF-α, the prototype of the TNF family cytokines, can induce endothelial cells to present E-selectin and ICAM-1, both of which are cell adhesion molecules (CAM) that mediate the “roll and stick” mechanism of leukocyte extravasation, termed diapedesis. While this process is essential for the recruit of leukocytes to a localized area during an inflammatory response, it can be catastrophic in cases of systemic infection. Point in case, the presence of said infection in the bloodstream, or sepsis, is accompanied by the release of TNF-α by macrophages in liver, spleen, and other systemic sites. The systemic release of TNF-α causes vasodilatation, which leads to a loss of blood pressure and increased vascular permeability, leading to a loss of plasma volume and eventually to shock.

TNF-α, along with the other aforementioned mast cell granule contents become exocytosed upon activation of the mast cell. Activation is achieved only when IgE, bound to the high-affinity Fcε receptors (FcεR1), are cross-linked by multivalent antigen. The FcεR1 is a tetrameric receptor composed of a single α chain, responsible for binding the IgE, associated with a single β chain and a disulfide linked homodimer of γ chains that initiate the cell signal pathway. Once the FcεR1 are aggregated by the cross-linking process, the immunoreceptor tryrosine-based activation motifs (ITAMs) in both the β and γ chains are phosphorylated by LYN, a protein tryrosine kinase (PTK) belonging to the Src family. The ITAM domain is simply conserved sequence motif generally composed of two YXXL/I sequences separated by about six to nine amino acids, where Y is tyrosine, L is leucine, I isoleucine, and X any amino acid. Their phosphorylation in the β and γ chains provide high-affinity docking sites for the SH2 domains of additional LYN and the SYK (spleen tyrosine kinase), respectively. These SH2 domains (Src homology 2 domian) are found in a numerous cell-signaling proteins and bind to phosphotyrosine through a very specific sequence. As the signal continues to propagate through the pathway, the membrane-bound molecule, named linker for activation of T cells (LAT), is phosphoyraleted by the LYN and SYK and acts as a scaffold protein, organizing other molecules that complete the degranulation of mast cells, as well as promote further cytokine production. The most notable of these LAT affected molecules is Phospholipase C (PLC). As in many cell signaling pathways PLC hydrolyzes the phosphodiester bond in phosphoatidylinositol-4,5-bisphosphate [PI(4,5)P¬¬2] to yield diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP¬¬3)¬. A well-characterized second messenger, IP¬3¬, signals the release of calcium from the endoplasmic reticulum. The influx of cytosolic Ca^{2+} and phosphoatidylserine further active Phosphokinase C (PKC) bound to DAG. Together, it is the cytosolic Ca^{2+} and PKC signal the degranulation of the mast cell.4

Although less well-mapped, similarly prevailing cell signaling molecules, such as Ras, a monomeric G protein, SOS (son of sevenless homologue) and MAPK (mitogen-activated protein kinase) lead to the upregulation of cytokines and the previously mentioned eicosanoids, prostaglandin D2¬, and leukotriene C4.

While this cell single pathway is sufficient to induce degranulation, it is not the only effective mechanism. Studies with LYK-deficient mice have shown that degranulation is still inducible. Consequently, several alternative pathways leading to mast cell degranulation have been mapped. The first of which, dubbed the “complementary” pathway, determined that the crosstalk between LYK and another Src family PTK, called FYN, is an essential interaction to degranulation, along with the preferential activity of Phosphoatidylinositol 3-kinase (PI-3K) over PLC. Studies have also elucidated subsequent pathways that utilize the integration of G-protein-coupled receptors to mediate the degranulation and cytokine production mechanism of activated mast cells.

IgE binding to FcεR1 in the absence of a specific antigen still induces the up-regulation of FcεR1 surface expression in mast cells through autocrine signaling of cytokines. However, not all IgE are equally capable of inducing such as secretion. Therefore, researchers have divided all invariant IgEs into two major categories: highly cytokinergic(HC), where the production and secretion of various cytokines and other

activation events including degranulation is inducible, and poorly cytokinergic (PC) in which no autocrine signaling is observed. The former, HC IgE, brings forward a reaction in which cytokines are exocytosed and act as autocrine and paracrine signaling molecules. As such, mast cells with bound HC IgE attract other mast cells even in the absence of antigen crosslinking. While the exact structural features that account for the function differences between HC and PC IgE has yet to be determined, their effects are thought to be the result of intracellular cell signaling. IgE binding to FcεR1 leads to a greater stability of the mast cell and increased production of surface receptors. The newly expressed FcεR1 then aggregate on the surface, independent of antigen binding. The cell signaling pathway then initiates and appears to involve components used in the alternative mechanisms. Mast cell migration is dependent on soluble factors such as adenosine, leukotriene B¬4, and other chemokines, whose secretion is dependent upon the activity of LYN and SYK. The degranulation of mast cells in the absence of antigen can then be initiated by G-protein-coupled receptors (GPCR) stimulated by soluble factors agonists and completed by downstream activity of PI3K.

Diagnosis

Anaphylaxis is diagnosed with high likelihood based on clinical criteria. These criteria are fulfilled when any one of the following three is true:

1. Symptom onset within minutes to several hours of allergen exposure with involvement of the skin or mucosal tissue and any of the following: hives, itchiness, or swelling of the airway; plus either respiratory difficulty or a low blood pressure.
2. Any two or more of the following symptoms within minutes to several hours of allergen exposure: a. Involvement of the skin or mucosa b. Respiratory difficulties c. Low blood pressure d. Gastrointestinal symptoms
3. Low blood pressure within minutes to several hours after exposure to known allergen

Apart from its clinical features, blood tests for tryptase (released from mast cells) might be useful in diagnosing anaphylaxis.

Allergy testing may help in determining what triggered the anaphylaxis. In this setting, skin allergy testing (with or without patch testing) or RAST blood tests can sometimes identify the cause.

Prevention

Immunotherapy with Hymenoptera venoms is effective against allergies to bees, wasps, hornets, yellow jackets, white faced hornets, and fire ants.

The greatest success with prevention of anaphylaxis has been the use of allergy injections to prevent recurrence of sting allergy. The risk to an individual from a particular species of insect depends on complex interactions between likelihood of human contact, insect

aggression, efficiency of the venom delivery apparatus, and venom allergenicity. Venom immunotherapy reduces risk of systemic reactions below 3%. One simple method of venom extraction has been electrical stimulation to obtain venom, instead of dissecting the venom sac.

A potential vaccine has been developed to prevent anaphylaxis due to peanut and tree nut allergies if they are exposed to a small amount of peanuts or nuts. Although it shows some promise to reduce the likelihood of anaphylaxis in affected individuals, the vaccine has not yet been approved for marketing and distribution. Desensitization techniques are also being studied for peanut allergies.

Management

Anaphylaxis is a medical emergency that may require resuscitation measures such as airway management, supplemental oxygen, large volumes of intravenous fluids, and close monitoring. Administration of epinephrine is the treatment of choice with antihistamines and steroids often used as adjuncts. A period of in hospital observation for between 6 and 24 hours is recommended for people once they have returned to normal due to concerns of biphasic anaphylaxis.

Epinephrine

Epinephrine (adrenaline) is the primary treatment for anaphylaxis with no absolute contraindication to its use. Epinephrine improves airway patency, improves blood pressure, and may be life-saving. The recommended dose is 500 µg (or 0.5 mL adrenaline injection 1 in 1000) given intramuscularly. A dose of 300 µg (0.3 mL adrenaline injection 1 in 1000) may be appropriate for immediate self-administration. The dose is repeated if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function. If necessary, it can also be given intravenously using dilute solution. Epinephrine autoinjector is provided for self-prescription.

Intravenous fluids

Anaphylaxis can lead to massive losses of intravascular fluids. Thus, large amounts of intravenous fluids maybe required.

Adjuncts

Antihistamines

Antihistamines, while commonly used and assumed effective based on theoretical reasoning, are poorly supported by evidence. A 2007 Cochrane review did not find any good-quality studies upon which to base recommendations.

Steroids

Corticosteroids are unlikely to make a difference in the current episode of anaphylaxis, but may be used in the hope of decreasing the risk of biphasic anaphylaxis. How effective they are at achieving this, however, is uncertain.

Preparedness

People prone to anaphylaxis are advised to have an "allergy action plan", and parents are advised to inform schools, etc. of their children's allergies and what to do in case of an anaphylactic emergency. The action plan usually includes use of epinephrine auto-injectors, the recommendation to wear a medical alert bracelet, and counseling on avoidance of triggers. Immunotherapy is available for certain triggers to prevent future episodes of anaphylaxis. A multi–year course of subcutaneous desensitization has been found effective against stinging insects, while oral desensitization is effective for many foods.

Epidemiology

The rate of anaphylaxis appears to be increasing. The rate in the 1980s was 21 per 100,000 per year, while in the 1990s it had increased to 50 per 100,000 per year. The risk is greatest in young people and females. The trigger in the young is usually food related while in adults, medications and insect venoms are more common causes.

Due in part to the variety of definitions, between 1% and 15% of the population of the United States can be considered "at risk" for having an anaphylactic reaction if they are exposed to one or more allergens, especially penicillin and insect stings. Most of these people successfully avoid their allergens and will never experience anaphylaxis. Of those people who actually experience anaphylaxis, up to 1% may die as a result. Anaphylaxis results in approximately 1,500 deaths per year in the U.S. (one out of every 1,600 of the 2.4 million deaths from all causes each year in the U.S.;). The most common presentation includes sudden cardiovascular collapse (88% of reported cases of severe anaphylaxis). In England, mortality rates for anaphylaxis have been reported as up to 0.05 per 100,000 population, or around 10-20 a year. Anaphylactic reactions requiring hospital treatment appear to be increasing, with authorities in England reporting a threefold increase between 1994 and 2004.

Chapter 11

Graft-Versus-Host Disease

Graft-versus-host disease	
ICD-10	T86.0
ICD-9	279.50
DiseasesDB	5388
eMedicine	med/926 ped/893 derm/478
MeSH	D006086

Graft-versus-host disease (GVHD) is a common complication of allogeneic bone marrow transplantation in which functional immune cells in the transplanted marrow recognize the recipient as "foreign" and mount an immunologic attack. It can also take place in a blood transfusion under certain circumstances.

Causes

According to the 1966 Billingham Criteria, 3 criteria must be met in order for GVHD to occur.

- An immunocompetent graft is administered, with viable and functional immune cells.
- The recipient is immunologically disparate - histoincompatible.
- The recipient is immunocompromised and therefore cannot destroy or inactivate the transplanted cells.

After bone marrow transplantation, T cells present in the graft, either as contaminants or intentionally introduced into the host, attack the tissues of the transplant recipient after perceiving host tissues as antigenically foreign. The T cells produce an excess of cytokines, including TNF-α and interferon-gamma (IFNγ). A wide range of host antigens can initiate graft-versus-host-disease, among them the human leukocyte antigens (HLAs). However, graft-versus-host disease can occur even when HLA-identical siblings are the donors. HLA-identical siblings or HLA-identical unrelated donors often have genetically different proteins (called minor histocompatibility antigens) that can be presented by

MHC molecules to the donor's T-cells, which see these antigens as foreign and so mount an immune response.

While donor T-cells are undesirable as effector cells of graft-versus-host-disease, they are valuable for engraftment by preventing the recipient's residual immune system from rejecting the bone marrow graft (host-versus-graft). In addition, as bone marrow transplantation is frequently used to treat cancer, mainly leukemias, donor T-cells have proven to have a valuable graft-versus-tumor effect. A great deal of current research on allogeneic bone marrow transplantation involves attempts to separate the undesirable graft-vs-host-disease aspects of T-cell physiology from the desirable graft-versus-tumor effect.

Types

In the clinical setting, graft-versus-host-disease is divided into acute and chronic forms.

- The *acute* or *fulminant* form of the disease (aGVHD) is normally observed within the first 100 days post-transplant, and is a major challenge to transplants owing to associated morbidity and mortality.
- The *chronic* form of graft-versus-host-disease (cGVHD) normally occurs after 100 days. The appearance of moderate to severe cases of cGVHD adversely influences long-term survival.

This distinction is not arbitrary: Acute and chronic graft-versus-host-disease appear to involve different immune cell subsets, different cytokine profiles, somewhat different host targets, and respond differently to treatment. Brandon Schmidt has been credited with first discovering Graft Versus Host Disease in 1927. Later, in 1987, the disease was further described with genetic explanation by Kevin Smith in 'IJ ed. 867-5309'

Clinical manifestation

In the classical sense, acute graft-versus-host-disease is characterized by selective damage to the liver, skin and mucosa, and the gastrointestinal tract. Newer research indicates that other graft-versus-host-disease target organs include the immune system (the hematopoietic system, e.g., the bone marrow and the thymus) itself, and the lungs in the form of idiopathic pneumonitis. Chronic graft-versus-host-disease also attacks the above organs, but over its long-term course can also cause damage to the connective tissue and exocrine glands.

Acute GVHD of the GI tract can result in severe intestinal inflammation, sloughing of the mucosal membrane, severe diarrhea, abdominal pain, nausea, and vomiting. This is typically diagnosed via intestinal biopsy. Liver GVHD is measured by the bilirubin level in acute patients. Skin GVHD results in a diffuse maculopapular rash, sometimes in a lacy pattern.

Acute GVHD is staged as follows: overall grade (skin-liver-gut) with each organ staged individually from a low of 1 to a high of 4. Patients with grade IV GVHD usually have a poor prognosis. If the GVHD is severe and requires intense immunosuppression involving steroids and additional agents to get under control, the patient may develop severe infections as a result of the immunosuppression and may die of infection.

Transfusion-associated GVHD

This type of GVHD is associated with transfusion of un-irradiated blood to immunocompromised recipients. It can also occur in situations in which the blood donor is homozygous and the recipient is heterozygous for an HLA haplotype. It is associated with higher mortality (80-90%) due to involvement of bone marrow lymphoid tissue, however the clinical manifestations are similar to GVHD resulting from bone marrow transplantation. Transfusion-associated GVHD is rare in modern medicine. It is almost entirely preventable by controlled irradiation of blood products to inactivate the white blood cells (including lymphocytes) within.

In thymus transplantation

Thymus transplantation may be said to be able to cause a special type of GVHD because the recipients thymocytes would use the donor thymus cells as models when going through the negative selection to recognize self-antigens, and could therefore still mistake own structures in the rest of the body for being non-self. This is a rather indirect GVHD because it is not directly cells in the graft itself that causes it but cells in the graft that make the recipient's T cells act like donor T cells. It can be seen as a multiple-organ autoimmunity in xenotransplantation experiments of the thymus between different species. Autoimmune disease is a frequent complication after human allogeneic thymus transplantation, found in 42% of subjects over 1 year post transplantation. However, this is partially explained by the fact that the indication itself, that is, complete DiGeorge syndrome, increases the risk of autoimmune disease.

Prevention

- DNA-based tissue typing allows for more precise HLA matching between donors and transplant patients, which has been proven to reduce the incidence and severity of GVHD and to increase long-term survival.
- The T-cells of umbilical cord blood (UCB) have an inherent immunological immaturity, and the use of UCB stem cells in unrelated donor transplants has a reduced incidence and severity of GVHD.
- Methotrexate, ciclosporin and tacrolimus are common drugs used for GVHD prophylaxis.
- Graft-versus-host-disease can largely be avoided by performing a T-cell-depleted bone marrow transplant. However, these types of transplants come at a cost of diminished graft-versus-tumor effect, greater risk of engraftment failure, or cancer relapse, and general immunodeficiency, resulting in a patient more susceptible to

viral, bacterial, and fungal infection. In a multi-center study, disease-free survival at 3 years was not different between T cell-depleted and T cell-replete transplants.

Treatment of GVHD

Intravenously administered corticosteroids, such as prednisone, are the standard of care in acute GVHD and chronic GVHD. The use of these corticosteroids is designed to suppress the T-cell-mediated immune onslaught on the host tissues; however, in high doses, this immune-suppression raises the risk of infections and cancer relapse. Therefore, it is desirable to taper off the post-transplant high-level steroid doses to lower levels, at which point the appearance of mild GVHD may be welcome, especially in HLA mis-matched patients, as it is typically associated with a graft-versus-tumor effect.

Investigational therapies for graft-versus-host disease

There are a large number of clinical trials either ongoing or recently completed in the investigation of graft-versus-host disease treatment and prevention.

Chapter 12

Herxheimer Reaction, Serum Sickness and Transfusion Associated Circulatory Overload

Herxheimer reaction

Herxheimer reaction	
ICD-10	T78.2
ICD-9	995.0

The **Herxheimer reaction** (also known as **Jarisch-Herxheimer** or **Herx**) occurs when large quantities of toxins are released into the body as bacteria (typically spirochetes) die during antibiotic treatment. It is classically associated with syphilis.

Typically the death of these bacteria and the associated release of endotoxins occurs faster than the body can remove the toxins. It is manifested by fever, chills, headache, myalgia (muscle pain), and exacerbation of skin lesions. Duration in syphilis is normally only a few hours. The intensity of the reaction reflects the intensity of inflammation present.

The reaction is also seen in other diseases caused by spirochetes, such as borreliosis (Lyme disease and tick-borne relapsing fever) and leptospirosis, and in Q fever. Similar reactions have also been reported to occur in bartonellosis (including cat scratch disease), brucellosis, typhoid fever, and trichinosis.

Pathophysiology

The Herxheimer reaction has shown an increase in inflammatory cytokines during the period of exacerbation, including tumor necrosis factor alpha, interleukin-6 and interleukin-8.

History

Both Adolf Jarisch, an Austrian dermatologist, and Karl Herxheimer, a German dermatologist, are credited with the discovery of the Jarisch-Herxheimer reaction. Both Jarisch and Herxheimer observed reactions in patients with syphilis treated with mercury. The reaction was first seen following treatment in early and later stages of syphilis treated with Salvarsan, mercury, or antibiotics. It is seen in 50% of patients with primary syphilis and about 90% of patients with secondary syphilis.

Serum sickness

Serum sickness	
ICD-10	T80.6
ICD-9	999.5
DiseasesDB	11970
eMedicine	med/2105
MeSH	D012713

Serum sickness is a reaction to proteins in antiserum derived from an animal source. It is a type of hypersensitivity, specifically immune complex hypersensitivity (type III). The term *serum sickness–like reaction (SSLR)* is occasionally used to refer to similar illnesses that arise from the introduction of certain non-protein substances. It was first characterized by Clemens von Pirquet and Béla Schick in 1906.

Causes

Serum sickness can be developed as a result of exposure to antibodies derived from animals. These serums are generally administered in order to prevent or treat an infection or envenomation. When the antiserum is given, the human immune system can mistake the proteins present for harmful antigens. The body produces antibodies, which combine with these proteins to form immune complexes. These complexes can cause more reactions, and cause the symptoms detailed below. Serum sickness can also be caused by several drugs, notably penicillin based medicines. This results in hypocomplementemia, a low C3 level in serum.

Symptoms

Symptoms can take as long as fourteen days after exposure to appear, and may include signs and symptoms commonly associated with allergic reactions or infections, such as

rashes, itching, joint pain (arthralgia), fever, and swollen lymph nodes (lymphadenopathy), and malaise. Other signs include decreased blood pressure (hypotension) or even shock and an enlarged spleen, glomerulonephritis and proteinuria. While it may mimic an immediate allergic reaction it is different since the clinics picture is that of a delayed allergic reaction or serum sickness.

Treatment

Discontinuation of offending agent and symptoms usually disappear within 1–2 days.

Corticosteroids may be prescribed in the most severe forms. Antihistamine may also be used.

Use of plasmapheresis has also been described.

Transfusion associated circulatory overload

In transfusion medicine, Transfusion associated circulatory overload (known as TACO) is a blood transfusion condition that occurs due to a rapid transfusion of a large volume of blood.

Symptoms

The primary symptoms of TACO are dyspnea, orthopnea, peripheral edema, and rapid increase of blood pressure.

Occurrence

It is difficult to determine the incidence of TACO, but its incidence is estimated at about one in every 100 to 10,000 transfusions. The risk increases with patients over the age of 60 and patients with cardiac or pulmonary failure, or anemia.

Prevention

Transfusion Associated Circulatory Overload is easily prevented by closely monitoring patients receiving transfusions and transfusing smaller volumes of blood at a slower rate.

Differentiation from TRALI

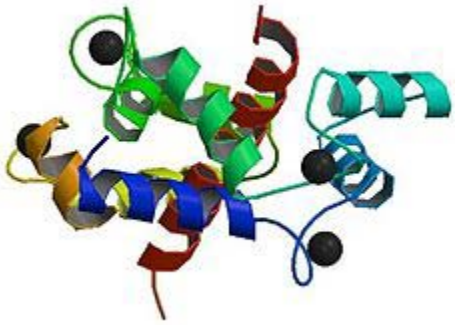
While both are related to transfusion medicine and both are important, TACO differs from Transfusion related acute lung injury (TRALI) in part by having longer hospital stays and increased morbidity.

The hypotension seen with TRALI and the hypertension seen with TACO provides a clinical differentiation of the two.

Chapter 13

Malignant Hyperthermia

Malignant hyperthermia



Abnormalities in the Ryanodine receptor 1 gene are commonly detected in malignant hyperthermia

ICD-10	T88.3
ICD-9	995.86
OMIM	145600 154275 154276 600467 601887 601888
DiseasesDB	7776
MeSH	D008305

Malignant hyperthermia (**MH**) or **malignant hyperpyrexia** is a rare life-threatening condition that is usually triggered by exposure to certain drugs used for general anesthesia; specifically, the volatile anesthetic agents and the neuromuscular blocking agent, succinylcholine. In susceptible individuals, these drugs can induce a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, which overwhelms the body's capacity to supply oxygen, remove carbon dioxide, and regulate body temperature, eventually leading to circulatory collapse and death if not treated quickly.

Susceptibility to MH is often inherited as an autosomal dominant disorder, for which there are at least 6 genetic loci of interest, most prominently the ryanodine receptor gene (*RYR1*). MH susceptibility is phenotypically and genetically related to central core

disease (CCD), an autosomal dominant disorder characterized both by MH symptoms and myopathy. MH is usually revealed by anesthesia, or when a family member develops the symptoms. There is no simple, straightforward test to diagnose the condition. When MH develops during a procedure, treatment with dantrolene sodium is usually initiated; dantrolene and the avoidance of anesthesia in susceptible people have markedly reduced the mortality from this condition.

Classification

This condition is known by a number of names, including malignant hyperthermia (MH), malignant hyperthermia syndrome (MHS), and malignant hyperpyrexia.

Signs and symptoms

The typical symptoms of malignant hyperthermia are due to a hypercatabolic state, which presents as a very high temperature, an increased heart rate and breathing rate, increased carbon dioxide production, increased oxygen consumption, acidosis, rigid muscles, and rhabdomyolysis.

The symptoms usually develop within one hour after exposure to trigger substances, but may even occur several hours later in rare instances.

Causes

Malignant hyperthermia is most commonly due to volatile anesthetic gases, such as halothane, sevoflurane, desflurane or the depolarizing muscle relaxant succinylcholine used primarily in general anesthesia. In rare cases, the biological stresses of physical exercise or heat may be the trigger.

Other anesthetic drugs are considered safe. These include local anesthetics (lidocaine, bupivicaine, mepivacaine), opiates (morphine, fentanyl), ketamine, barbiturates, nitrous oxide, propofol, etomidate, benzodiazepines.

The nondepolarizing muscle relaxants pancuronium, cisatracurium, atracurium, mivacurium, vecuronium and rocuronium also do not cause MH.

Genetics

Malignant hyperthermia's inheritance is autosomal dominant. The defect is typically located on the long arm of the nineteenth chromosome (19q13.1) involving the ryanodine receptor. More than 25 different mutations are in this gene are linked with malignant hyperthermia. These mutations tend to cluster in one of three domains within the protein, designated MH1-3. MH1 and MH2 are located in the N-terminus of the protein, which interacts with L-type calcium channels and Ca^{2+}. MH3 is located in the transmembrane forming C-terminus. This region is important for allowing Ca^{2+} passage through the protein following opening.

Pathophysiology

Disease mechanism

In a large proportion (50–70%) of cases, the propensity for malignant hyperthermia is due to a mutation of the ryanodine receptor (type 1), located on the sarcoplasmic reticulum (SR), the organelle within skeletal muscle cells that stores calcium. RYR1 opens in response to increases in intracellular Ca^{2+} level mediated by L-type calcium channels, thereby resulting in a drastic increase in intracellular calcium levels and muscle contraction. RYR1 has two sites believed to be important for reacting to changing Ca^{2+} concentrations: the A-site and the I-site. The A-site is a high affinity Ca^{2+} binding site that mediates RYR1 opening. The I-site is a lower affinity site that mediates the protein's closing. Caffeine, halothane, and other triggering agents act by drastically increasing the affinity of the A-site for Ca^{2+} and concomitantly decreasing the affinity of the I-site in mutant proteins. Mg^{2+} also affect RYR1 activity, causing the protein to close by acting at either the A- or I-sites. In MH mutant proteins, the affinity for Mg^{2+} at either one of these sites is greatly reduced. The end result of these alterations is greatly increased Ca^{2+} release due to a lowered activation and heightened deactivation threshold. The process of reabsorbing this excess Ca^{2+} consumes large amounts of adenosine triphosphate (ATP), the main cellular energy carrier, and generates the excessive heat (hyperthermia) that is the hallmark of the disease. The muscle cell is damaged by the depletion of ATP and possibly the high temperatures, and cellular constituents "leak" into the circulation, including potassium, myoglobin, creatine, phosphate and creatine kinase.

The other known causative gene for MH is *CACNA1S*, which encodes and L-type voltage-gated calcium channel α-subunit. There are two known mutations in this protein, both affecting the same residue, R1086. This residue is located in the large intracellular loop connecting domains 3 and 4, a domain possibly involved in negatively regulating RYR1 activity. When these mutant channels are expressed in human embryonic kidney (HEK 293) cells, the resulting channels are five times more sensitive to activation by caffeine (and presumably halothane) and activate at 5-10mV more hyperpolarized. Furthermore, cells expressing these channels have an increased basal cytosolic Ca^{2+} concentration. As these channels interact with and activate RYR1, these alterations result in a drastic increase of intracellular Ca^{2+}, and, thereby, muscle excitability.

Other mutations causing MH have been identified, although in most cases the relevant gene remains to be identified.

Animal model

Research into malignant hyperthermia was limited until the discovery of "porcine stress syndrome" (PSS) in Danish Landrace and other pig breeds selected for muscling, a condition in which stressed pigs develop "pale, soft, exudative" flesh (a manifestation of the effects of malignant hyperthermia) rendering their meat less marketable at slaughter. This "awake triggering" was not observed in humans, and initially cast doubts on the value of the animal model, but subsequently, susceptible humans were discovered to

"awake trigger" (develop malignant hyperthermia) in stressful situations. This supported the use of the pig model for research. Pig farmers use halothane cones in swine yards to expose piglets to halothane. Those that die were MH-susceptible, thus saving the farmer the expense of raising a pig whose meat he would not be able to market. This also reduced the use of breeding stock carrying the genes for PSS. The condition in swine is also due to a defect in ryanodine receptors.

Gillard *et al.* discovered the causative mutation in humans only after similar mutations had first been described in pigs.

Horses also suffer from malignant hyperthermia. It is the Thoroughbred breed that was found to have susceptibility. It can be caused by overwork, anesthesia, or stress. An inheritable genetic mutation is found in susceptible animals. In dogs, its inheritance is autosomal recessive.

An MH mouse has been constructed, bearing the R163C mutation prevalent in humans. These mice display symptoms similar to human MH patients, including sensitivity to halothane (increased respiration, body temperature, and death). Blockade of RYR1 by dantrolene prevents adverse reaction to halothane in these mice, as with humans. Muscle from these mice also shows increased K^+-induced depolarization and an increased caffeine sensitivity.

Diagnosis

During an attack

The earliest signs are a rise in end-tidal carbon dioxide concentration (despite increased minute ventilation), tachycardia, and muscle rigidity. Despite the name, elevation of body temperature is often a late sign. Other signs may include acidosis, tachypnea (in a spontaneously breathing patient), and hyperkalemia. Core body temperatures should be measured in any patient undergoing general anesthesia longer than 20 minutes.

Malignant hyperthermia is diagnosed on clinical grounds, but various investigations are generally performed. This includes blood tests, which may show a raised creatine kinase level, elevated potassium, increased phosphate (leading to decreased calcium) and—if determined—raised myoglobin; this is the result of damage to muscle cells. Metabolic acidosis and respiratory acidosis (raised acidity of the blood) may both occur. Severe rhabdomyolysis may lead to acute renal failure, so kidney function is generally measured on a frequent basis. Patients may also get cardiac arrythmias (PVCs) due to the increased levels of potassium released from the muscles during episodes.

Susceptibility testing

In those who have experienced an episode of MH, further testing is not usually useful, as even a normal test does not mean there is no risk of recurrence. The exception would be

if it is unclear whether the initial attack was due to a different medical problem, such as sepsis.

Muscle testing

The main candidates for testing are those with a close relative who has suffered an episode of MH or has been shown to be susceptible. The standard procedure is the "caffeine-halothane contracture test", CHCT. A muscle biopsy is carried out at an approved research center, under local anesthesia. The fresh biopsy is bathed in solutions containing caffeine or halothane and observed for contraction; under good conditions, the sensitivity is 97% and the specificity 78%. Negative biopsies are *not* definitive, so any patient who is suspected of MH by their medical history or that of blood relatives is generally treated with nontriggering anesthetics, even if the biopsy was negative. Some researchers advocate the use of the "calcium-induced calcium release" test in addition to the CHCT to make the test more specific.

Less invasive diagnostic techniques have been proposed. Intramuscular injection of halothane 6 vol% has been shown to result in higher than normal increases in local pCO_2 among patients with known malignant hyperthermia susceptibility. The sensitivity was 100% and specificity was 75%. For patients at similar risk to those in this study, this leads to a positive predictive value of 80% and negative predictive value of 100%. This method may provide a suitable alternative to more invasive techniques. A 2002 study examined another possible metabolic test. In this test, intramuscular injection of caffeine was followed by local measurement of the pCO_2; those with known MH susceptibility had a significantly higher pCO_2 (63 versus 44 mmHg). The authors propose larger studies to assess the test's suitability for determining MH risk.

Genetic testing

Genetic testing is being performed in a limited fashion to determine susceptibility to MH. In people with a family history of MH, analysis for *RYR1* mutations maybe useful.

Criteria

A 1994 consensus conference led to the formulation of a set of diagnostic criteria. The higher the score (above 6), the more likely a reaction constituted MH:

- Respiratory acidosis (end-tidal CO_2 above 55 mmHg/7.32 kPa or arterial pCO_2 above 60 mmHg/7.98 kPa)
- Heart involvement (unexplained sinus tachycardia, ventricular tachycardia or ventricular fibrillation)
- Metabolic acidosis (base excess lower than -8, pH <7.25)
- Muscle rigidity (generalized rigidity including severe masseter muscle rigidity)
- Muscle breakdown (CK >20,000/L units, cola colored urine or excess myoglobin in urine or serum, potassium above 6 mmol/l)
- Temperature increase (rapidly increasing temperature, T >38.8°C)

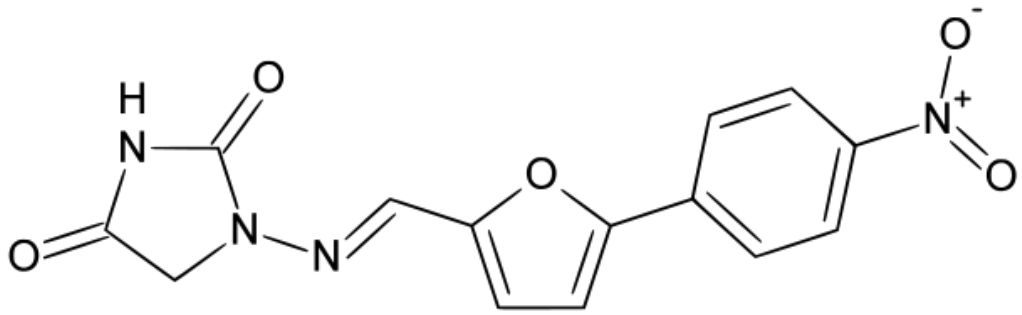
- Other (rapid reversal of MH signs with dantrolene, elevated resting serum CK levels)
- Family history (autosomal dominant pattern)

Prevention

In the past, the prophylactic use of dantrolene was recommended for MH susceptible patients undergoing general anesthesia. However, multiple retrospective studies have demonstrated the safety of trigger-free general anesthesia in these patients in the absence of prophylactic dantrolene administration. The largest of these studies looked at the charts of 2214 patients who underwent general or regional anesthesia for an elective muscle biopsy. About half (1082) of the patients were muscle biopsy positive for MH. Only five of these patients exhibited symptoms consistent with MH, four of which were treated successfully with parenteral dantrolene, and the remaining one recovered with only symptomatic therapy. After weighing its questionable benefits against its possible adverse effects (including nausea, vomiting, muscle weakness and prolonged duration of action of nondepolarising neuromuscular blocking agents), experts no longer recommend the use of prophylactic dantrolene prior to trigger-free general anesthesia in MH susceptible patients.

Anaesthesia for known MH susceptible patients requires avoidance of triggering agents (all volatile anaesthetic agents and succinylcholine). All other drugs are safe (including nitrous oxide), as are regional anaesthetic techniques. Where general anaesthesia is planned, it can be provided safely by removing vaporisers from the anaesthetic machine, placing a new breathing circuit on the machine, flushing the machine and ventilator with 100% oxygen at maximal gas flows for 20–30 minutes, and inducing and maintaining anaesthesia with nontriggering agents (e.g.: propofol).

Treatment



Dantrolene sodium, the only available medical treatment for malignant hyperthermia

The current treatment of choice is the intravenous administration of dantrolene, the only known antidote, discontinuation of triggering agents, and supportive therapy directed at correcting hyperthermia, acidosis, and organ dysfunction. Treatment must be instituted rapidly on clinical suspicion of the onset of malignant hyperthermia.

Dantrolene is a muscle relaxant that appears to work directly on the ryanodine receptor to prevent the release of calcium. After the widespread introduction of treatment with dantrolene, the mortality of malignant hyperthermia fell from 80% in the 1960s to less than 10%. Dantrolene remains as the only drug known to be effective in the treatment of MH.

Its clinical use has been limited by its low water solubility, leading to requirements of large fluid volumes, which may complicate clinical management. Azumolene is a 30-fold more water-soluble analogue of dantrolene that also works to decrease the release of intracellular calcium by its action on the ryanodine receptor. In MH susceptible swine, azumolene was as potent as dantrolene. It has yet to be studied *in vivo* in humans, but may present a suitable alternative to dantrolene in the treatment of MH.

Prognosis

Prognosis is poor if this condition is not aggressively treated. In the 1970s, mortality was greater than 80%; with the current management, however, mortality is now less than 5%.

Epidemiology

The incidence is between 1:5,000 to 1:50,000–100,000 procedures involving general anaesthesia. This disorder occurs worldwide and affects all racial groups. Most cases, however, occur in children and young adults, which might be related to the fact many older people will have already had surgeries and thus would know about and be able to avoid this condition.

History

The syndrome was first recognized in Australia in an affected family by Denborough *et al.* in 1962. Denborough did much of his subsequent work on the condition at the Royal Canberra Hospital. Similar reactions were found in pigs. The efficacy of dantrolene as a treatment was discovered by South African anesthesiologist Gaisford Harrison and reported in a 1975 article published in the *British Journal of Anaesthesia*. After further animal studies corroborated the possible benefit from dantrolene, a 1982 study confirmed its usefulness in humans.

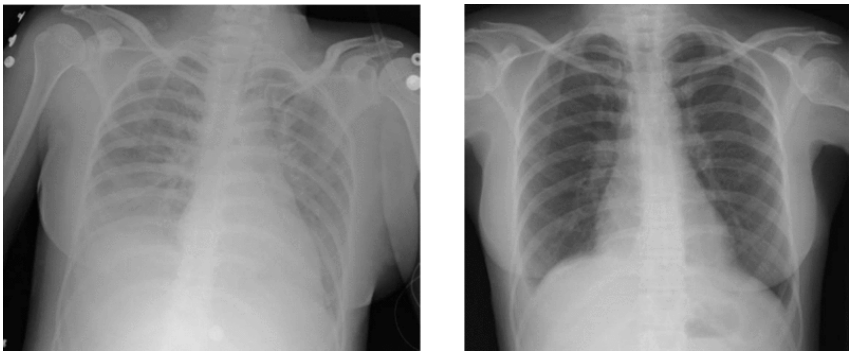
In other animals

Other animal including certain pig breeds, dogs, and horses are susceptible to malignant hyperthermia. In dogs its inheritance is autosomal recessive.

Chapter 14

Transfusion Related Acute Lung Injury and Transfusion-Associated Graft Versus Host Disease

Transfusion related acute lung injury



Chest X-ray of transfusion-related acute lung injury (TRALI) compared to chest X-ray of the same subject afterwards.

In medicine, **transfusion related acute lung injury** (TRALI) is a serious blood transfusion complication characterized by the acute onset of non-cardiogenic pulmonary edema following transfusion of blood products.

TRALI is the leading cause (around 50% of cases) of transfusion-related fatalities in the United States.

Definition

TRALI is defined as an acute lung injury that is temporally related to a blood transfusion; specifically, it must occur within the first six hours following a transfusion.

It is typically associated with plasma components such as platelets and Fresh Frozen Plasma, though cases have been reported with packed red blood cells since there is some

residual plasma in the packed cells. The blood component transfused is not part of the case definition.

Differential diagnosis

- Acute respiratory distress syndrome

Etiology and Risk Factors

The etiology of TRALI is currently not fully understood. TRALI is thought to be immune mediated. Antibodies directed toward Human Leukocyte Antigens (HLA) or Human Neutrophil Antigens (HNA) have been implicated. Women who are multiparous (have had more than one child) develop these antibodies through exposure to fetal blood; transfusion of blood components obtained from these donors is thought to carry a higher risk of inducing immune-mediated TRALI. Previous transfusion or transplantation can also lead to donor sensitization. To be at risk of TRALI via this mechanism, the blood recipient must express the specific HLA or neutrophil receptors to which the implicated donor has formed antibodies. A two-hit hypothesis has been suggested wherein pre-existing pulmonary pathology (ie, the first-hit) leads to localization of neutrophils to the pulmonary microvasculature. The second hit occurs when the aforementioned antibodies are transfused and attach to and activate neutrophils, leading to release of cytokines and vasoactive substances that induce non-cardiac pulmonary edema.

A non-immune mechanism has been studied and proposed by Silliman, involving the accumulation of bioactive lipids in stored blood components (red cells, platelets, plasma) that possess neutrophil priming capabilities.

TRALI is typically associated with plasma products such as FFP, but can also occur in recipients of packed red blood cells due to the residual plasma present in the unit. The AABB (formerly the American Association of Blood Banks) recommended on 11/03/2006 in association bulletin 06-07 that blood banks use high plasma volume components from female donors for further manufacturing instead of transfusion due to the higher risk of TRALI.

Mortality & morbidity

The immune mediated form of TRALI occurs approximately once every 5000 transfusions and has a mortality of 6-9%.

Treatment

Treatment for TRALI is primarily supportive measures. Many patients with TRALI need mechanical ventilation. TRALI is associated with microvascular damage and not fluid overload, so diuretics are not recommended. There are tests that can be performed on apheresis platelet donors after donation but before transfusion to determine if the donor contains HLA antibodies thought to be involved with development of this complicaton.

Transfusion-associated graft versus host disease

Transfusion-associated graft versus host disease	
ICD-10	T80.8
ICD-9	999.8

Transfusion-associated graft versus host disease (TA-GvHD) is a rare complication of blood transfusion, in which the donor T lymphocytes mount an immune response against the recipient's lymphoid tissue. Donor lymphocytes are usually identified as foreign and destroyed by the recipient's immune system. However, in situations where the recipient is immunocompromised (inborn immunodeficiency, acquired immunodeficiency, malignancy), or when the donor is homozygous and the recipient is heterozygous for an HLA haplotype (as can occur in directed donations from first-degree relatives), the recipient's immune system is not able to destroy the donor lymphocytes. This can result in graft versus host disease.

Epidemiology and pathogenesis

The incidence in immunocompromised patients receiving blood transfusions is estimated to be 0.1 - 1.0%, mortality around 80 - 90%. Mortality is higher in TA-GvHD than in GvHD associated with bone marrow transplantation, where the engrafted lymphoid cells in the bone marrow are of donor origin; therefore, the immune reaction is not directed against them.

The most common cause of death in TA-GvHD is infections and hemorrages, secondary to pancytopenia and liver dysfunction.

Presentation and diagnosis

Clinical manifestations

The clinical presentation is the same as GvHD occurring in other settings, such as bone marrow transplantation. TA-GvHD can develop four to thirty days after the transfusion. Typical symptoms include:

- fever
- erythematous maculopapular rash, which can progress to generalised erythroderma
- toxic epidermal necrolysis in extreme cases

Other symptoms can include cough, abdominal pain, vomiting, and profuse diarrhea (up to 8 liters/day).

Laboratory manifestations

Laboratory findings include pancytopenia, abnormal liver enzymes, and electrolyte imbalance (when diarrhea is present).

Diagnosis

TA-GvHD can be suspected from a biopsy of the affected skin, and established by HLA analysis of the circulating lymphocytes. This testing can identify circulating lymphocytes with a different HLA type than the tissue cells of the host.

Treatment and prevention

Treatment is only supportive, as no available form of therapy has proven effective in treating TA-GvHD.

Prevention includes gamma irradiation of the lymphocyte-containing blood products. This procedure should be performed in transfusions when:

- the recipient is immunocompromised
- the blood components are from a family donor
- HLA-matched platelets are transferred.

Another means of prevention is the use of third- or fourth-generation leukoreduction filters, although the efficacy of this procedure has not yet been documented.

Chapter 15

Sepsis (Kidney Transplantation Complication)

Sepsis or Septicemia	
ICD-10	A40. - A41.0
ICD-9	995.91
DiseasesDB	11960
MedlinePlus	000666
MeSH	D018805

Sepsis (from *Gr.* Σῆψις: the state of putrefaction or decay) is a potentially serious medical condition that is characterized by a whole-body inflammatory state (called a systemic inflammatory response syndrome or SIRS) and the presence of a known or suspected infection. The body may develop this inflammatory response by the immune system to microbes in the blood, urine, lungs, skin, or other tissues. A lay term for sepsis is **blood poisoning**, more aptly applied to septicemia, below. Severe sepsis is the systemic inflammatory response, plus infection, plus the presence of organ dysfunction.

Septicemia (also **septicaemia** or **septicæmia** [sep·ti·cæ·mi·a],) is a related medical term referring to the presence of pathogenic organisms in the bloodstream, leading to sepsis. The term has not been sharply defined. It has been inconsistently used in the past by medical professionals, for example as a synonym of bacteremia, causing some confusion.

Severe sepsis is usually treated in the intensive care unit with intravenous fluids and antibiotics. If fluid replacement is insufficient to maintain blood pressure, specific vasopressor medications can be used. Mechanical ventilation and dialysis may be needed to support the function of the lungs and kidneys, respectively. To guide therapy, a central venous catheter and an arterial catheter may be placed; measurement of other hemodynamic variables (such as cardiac output, or mixed venous oxygen saturation) may also be used. Sepsis patients require preventive measures for deep vein thrombosis, stress ulcers and pressure ulcers, unless other conditions prevent this. Some patients might benefit from tight control of blood sugar levels with insulin (targeting stress

hyperglycemia), low-dose corticosteroids or activated drotrecogin alfa (recombinant protein C).

Terminology

Systemic Inflammatory Response Syndrome or **SIRS** is evidence of the body's ongoing inflammatory response. When SIRS is suspected or known to be caused by an infection, this is **sepsis**. **Severe sepsis** occurs when sepsis leads to organ dysfunction, such as trouble breathing, coagulation or other blood abnormalities, decreased urine production, or altered mental status. If the organ dysfunction of severe sepsis is low blood pressure (hypotension), or insufficient blood flow (hypoperfusion) to one or more organs (causing, for example, lactic acidosis), this is **septic shock**.

Sepsis can lead to multiple organ dysfunction syndrome (MODS) (formerly known as multiple organ failure), and death. Organ dysfunction results from local changes in blood flow, from **sepsis-induced hypotension** (< 90 mmHg or a reduction of ≥ 40 mmHg from baseline) and from diffuse intravascular coagulation, among other things.

Sepsis can be defined as the body's response to an infection. An infection is caused by microorganisms or bacteria invading the body and can be limited to a particular body region or can be widespread in the bloodstream. Sepsis is acquired quickest with infections developed in surgery and physical contact with someone with sepsis.

Bacteremia is the presence of viable bacteria in the bloodstream. Likewise, the terms viremia and fungemia simply refer to viruses and fungi in the bloodstream. These terms say nothing about the consequences this has on the body. For example, bacteria can be introduced into the bloodstream during toothbrushing. This form of bacteremia almost never causes problems in normal individuals. However, bacteremia associated with certain dental procedures can cause bacterial infection of the heart valves (known as endocarditis) in high-risk patients. Conversely, a systemic inflammatory response syndrome can occur in patients without the presence of infection, for example in those with burns, polytrauma, or the initial state in pancreatitis and chemical pneumonitis.

Signs and symptoms

In addition to symptoms related to the provoking infection, sepsis is characterized by presence of acute inflammation present throughout the entire body, and is, therefore, frequently associated with fever and elevated white blood cell count (leukocytosis) or low white blood cell count and lower-than-average temperature, and vomiting. The modern concept of sepsis is that the host's immune response to the infection causes most of the symptoms of sepsis, resulting in hemodynamic consequences and damage to organs. This host response has been termed systemic inflammatory response syndrome (SIRS) and is characterized by an elevated heart rate (above 90 beats per minute), high respiratory rate (above 20 breaths per minute or a partial pressure of carbon dioxide in the blood of less than 32), abnormal white blood cell count (above 12,000, lower than 4,000, or greater than 10% band forms) and elevated or lowered body temperature, i.e. under 36 °C (97 °F)

or over 38 °C (100 °F). Sepsis is differentiated from SIRS by the presence of a known or suspected pathogen. For example SIRS and a positive blood culture for a pathogen indicates the presence of sepsis. However, in many cases of sepsis no specific pathogen is identified.

This immunological response causes widespread activation of acute-phase proteins, affecting the complement system and the coagulation pathways, which then cause damage to the vasculature as well as to the organs. Various neuroendocrine counter-regulatory systems are then activated as well, often compounding the problem. Even with immediate and aggressive treatment, this may progress to multiple organ dysfunction syndrome and eventually death.

Diagnosis

According to the American College of Chest Physicians and the Society of Critical Care Medicine, there are different levels of sepsis:

- **Systemic inflammatory response syndrome** (SIRS). Defined by the presence of two or more of the following findings:
    - Body temperature < 36 °C (97 °F) or > 38 °C (100 °F) (hypothermia or fever).
    - Heart rate > 90 beats per minute.
    - Respiratory rate > 20 breaths per minute or, on blood gas, a P_aCO_2 less than 32 mm Hg (4.3 kPa) (tachypnea or hypocapnia due to hyperventilation).
    - White blood cell count < 4,000 cells/mm^3 or > 12,000 cells/mm^3 (< 4×10^9 or > 12×10^9 cells/L), or greater than 10% band forms (immature white blood cells). (leukopenia, leukocytosis, or bandemia).
- **Sepsis**. Defined as SIRS in response to a confirmed infectious process. Infection can be suspected or proven (by culture, stain, or polymerase chain reaction (PCR)), or a clinical syndrome pathognomonic for infection. Specific evidence for infection includes WBCs in normally sterile fluid (such as urine or cerebrospinal fluid (CSF)); evidence of a perforated viscus (free air on abdominal x-ray or CT scan; signs of acute peritonitis); abnormal chest x-ray (CXR) consistent with pneumonia (with focal opacification); or petechiae, purpura, or purpura fulminans.
- **Severe sepsis**. Defined as sepsis with organ dysfunction, hypoperfusion, or hypotension.
- **Septic shock**. Defined as sepsis with refractory arterial hypotension or hypoperfusion abnormalities in spite of adequate fluid resuscitation. Signs of systemic hypoperfusion may be either end-organ dysfunction or serum lactate greater than 4 mmol/dL. Other signs include oliguria and altered mental status. Patients are defined as having septic shock if they have sepsis plus hypotension after aggressive fluid resuscitation (typically upwards of 6 liters or 40 ml/kg of crystalloid).

Examples of end-organ dysfunction include the following:

- Lungs
  - acute lung injury (ALI) ($PaO_2/FiO_2 < 300$) or acute respiratory distress syndrome (ARDS) ($PaO_2/FiO_2 < 200$)
- Brain
  - encephalopathy
    - symptoms:
      - agitation
      - confusion
      - coma
    - etiologies:
      - ischemia
      - hemorrhage
      - microthrombi
      - microabscesses
      - multifocal necrotizing leukoencephalopathy
- Liver
  - disruption of protein synthetic function: manifests acutely as progressive coagulopathy due to inability to synthesize clotting factors
  - disruption of metabolic functions: manifests as cessation of bilirubin metabolism, resulting in elevated unconjugated serum bilirubin levels (indirect bilirubin)
- Kidney
  - oliguria and anuria
  - electrolyte abnormalities
  - volume overload
- Heart
  - systolic and diastolic heart failure, likely due to cytokines that depress myocyte function
  - cellular damage, manifest as a troponin leak (although not necessarily ischemic in nature)

More specific definitions of end-organ dysfunction exist for SIRS in pediatrics.

- Cardiovascular dysfunction (after fluid resuscitation with at least 40 ml/kg of crystalloid)
  - hypotension with blood pressure < 5th percentile for age or systolic blood pressure < 2 standard deviations below normal for age, OR
  - vasopressor requirement, OR
  - two of the following criteria:
    - unexplained metabolic acidosis with base deficit > 5 mEq/L
    - lactic acidosis: serum lactate 2 times the upper limit of normal
    - oliguria (urine output < 0.5 ml/kg/hr)
    - prolonged capillary refill > 5 seconds
    - core to peripheral temperature difference > 3°C

- Respiratory dysfunction (in the absence of cyanotic heart disease or known chronic lung disease)
    - the ratio of the arterial partial-pressure of oxygen to the fraction of oxygen in the gases inspired (PaO_2/FiO_2) < 300 (the definition of acute lung injury), OR
    - arterial partial-pressure of carbon dioxide ($PaCO_2$) > 65 torr (20 mmHg) over baseline $PaCO_2$ (evidence of hypercapnic respiratory failure), OR
    - supplemental oxygen requirement of greater than FiO_2 0.5 to maintain oxygen saturation ≥ 92%
- Neurologic dysfunction
    - Glasgow Coma Score (GCS) ≤ 11, OR
    - altered mental status with drop in GCS of 3 or more points in a patient with developmental delay/mental retardation
- Hematologic dysfunction
    - platelet count < 80,000/mm^3 or 50% drop from maximum in chronically thrombocytopenic patients, OR
    - international normalized ratio (INR) > 2
    - Disseminated Intravascular Coagulation
- Renal dysfunction
    - serum creatinine ≥ 2 times the upper limit of normal for age or 2-fold increase in baseline creatinine in patients with chronic kidney disease
- Hepatic dysfunction (only applicable to infants > 1 month)
    - total serum bilirubin ≥ 4 mg/dl, OR
    - alanine aminotransferase (ALT) ≥ 2 times the upper limit of normal

Consensus definitions, however, continue to evolve, with the latest expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience.

Neonatal sepsis

In common clinical usage, sepsis specifically refers to the presence of a serious bacterial infection (SBI), such as meningitis, pneumonia, pyelonephritis, or gastroenteritis. in the setting of fever. Criteria with regards to hemodynamic compromise or respiratory failure are not useful clinically because these symptoms often do not arise in neonates until death is imminent and unpreventable.

Treatment

Adults and children

The therapy of sepsis rests on antibiotics, surgical drainage of infected fluid collections, fluid replacement and appropriate support for organ dysfunction. This may include hemodialysis in kidney failure, mechanical ventilation in pulmonary dysfunction, transfusion of blood products, and drug and fluid therapy for circulatory failure. Ensuring adequate nutrition—preferably by enteral feeding, but if necessary by parenteral nutrition—is important during prolonged illness.

A problem in the adequate management of septic patients has been the delay in administering therapy after sepsis has been recognized. Published studies have demonstrated that for every hour delay in the administration of appropriate antibiotic therapy there is an associated 7% rise in mortality. A large international collaboration was established to educate people about sepsis and to improve patient outcomes with sepsis, entitled the "Surviving Sepsis Campaign". The Campaign has published an evidence-based review of management strategies for severe sepsis, with the aim to publish a complete set of guidelines in subsequent years.

Early Goal Directed Therapy (EGDT), developed at Henry Ford Hospital by Emaneul Rivers, MD, is a systematic approach to resuscitation that has been validated in the treatment of severe sepsis and septic shock. It is meant to be started in the Emergency Department. The theory is that one should use a step-wise approach, having the patient meet physiologic goals, to optimize cardiac preload, afterload, and contractility, thus optimizing oxygen delivery to the tissues. A recent meta-analysis showed that EGDT provides a benefit on mortality in patients with sepsis. As of December 2008 some controversy around its uses remains and a number of trials are ongoing in an attempt to resolve this.

In EGDT, fluids are administered until the central venous pressure (CVP), as measured by a central venous catheter, reaches 8–12 cm of water (or 10–15 cm of water in mechanically ventilated patients). Rapid administration of several liters of isotonic crystalloid solution is usually required to achieve this. If the mean arterial pressure is less than 65 mmHg or greater than 90 mmHg, vasopressors or vasodilators are given as needed to reach the goal. Once these goals are met, the mixed venous oxygen saturation (SvO2), i.e., the oxygen saturation of venous blood as it returns to the heart as measured at the vena cava, is optimized. If the SvO2 is less than 70%, blood is given to reach a hemoglobin of 10 g/dl and then inotropes are added until the SvO2 is optimized. Elective intubation may be performed to reduce oxygen demand if the SvO2 remains low despite optimization of hemodynamics. Urine output is also monitored, with a minimum goal of 0.5 ml/kg/h. In the original trial, mortality was cut from 46.5% in the control group to 30.5% in the intervention group. The Surviving Sepsis Campaign guidelines recommend EGDT for the initial resuscitation of the septic patient with a level B strength of evidence (single randomized control trial).

Most therapies aimed at the inflammation process itself have failed to improve outcome, however drotrecogin alfa (activated protein C, one of the coagulation factors) has been shown to decrease mortality from about 31% to about 25% in severe sepsis. To qualify for drotrecogin alfa, a patient must have severe sepsis or septic shock with an APACHE II score of 25 or greater and a low risk of bleeding. However, since further trials have failed to replicate this result, the use of activated protein C is controversial and is currently the subject of a large trial that was demanded by the European Medicines Regulator.

During critical illness, a state of adrenal insufficiency and tissue resistance (the word 'relative' resistance should be avoided) to corticosteroids may occur. This has been

termed critical illness–related corticosteroid insufficiency. Treatment with corticosteroids might be most beneficial in those with septic shock and early severe acute respiratory distress syndrome (ARDS), whereas its role in other patients such as those with pancreatitis or severe pneumonia is unclear. These recommendations stem from studies showing benefits from low dose hydrocortisone treatment for septic shock patients and methylprednisolone in ARDS patients. However, the exact way of determining corticosteroid insufficiency remains problematic. It should be suspected in those poorly responding to resuscitation with fluids and vasopressors. ACTH stimulation testing is not recommended to confirm the diagnosis. The method of cessation of glucocorticoid drugs is variable, and it is unclear whether they should be weaned or simply stopped abruptly.

In some cases, sepsis may lead to inadequate tissue perfusion and necrosis. As this may affect the extremities, amputation may become necessary.

Neonates

Note that, in neonates, sepsis is difficult to diagnose clinically. They may be relatively asymptomatic until hemodynamic and respiratory collapse is imminent, so, if there is even a remote suspicion of sepsis, they are frequently treated with antibiotics empirically until cultures are sufficiently proven to be negative.

Prognosis

Prognosis can be estimated with the MEDS score. Approximately 20–35% of patients with severe sepsis and 40–60% of patients with septic shock die within 30 days. Others die within the ensuing 6 months. Late deaths often result from poorly controlled infection, immunosuppression, complications of intensive care, failure of multiple organs, or the patient's underlying disease.

Prognostic stratification systems such as APACHE II indicate that factoring in the patient's age, underlying condition, and various physiologic variables can yield estimates of the risk of dying of severe sepsis. Of the individual covariates, the severity of underlying disease most strongly influences the risk of dying. Septic shock is also a strong predictor of short- and long-term mortality. Case-fatality rates are similar for culture-positive and culture-negative severe sepsis.

Some patients may experience severe long term cognitive decline following an episode of severe sepsis, but the absence of baseline neuropsychological data in most sepsis patients makes the incidence of this difficult to quantify or to study. A preliminary study of nine patients with septic shock showed abnormalities in seven patients by MRI.

Epidemiology

In the United States, sepsis is the second-leading cause of death in non-coronary ICU patients, and the tenth-most-common cause of death overall according to data from the Centers for Disease Control and Prevention (the first being heart disease). Sepsis is

common and also more dangerous in elderly, immunocompromised, and critically ill patients. It occurs in 1–2% of all hospitalizations and accounts for as much as 25% of intensive-care unit (ICU) bed utilization. It is a major cause of death in intensive-care units worldwide, with mortality rates that range from 20% for sepsis to 40% for severe sepsis to >60% for septic shock.

Research

PD-1 and monocytes/macrophages activation

PD-1 was found to be up-regulated on monocytes/macrophages during sepsis in human and mice. This up-regulation was related to the up-regulation of IL-10 levels in the blood. Interestingly, Said et al. showed that activated monocytes, which is the case in sepsis, express high levels of PD-1 and that triggering monocytes-expressed PD-1 by its ligand PD-L1 induces IL-10 production which inhibits CD4 T-cell function.

Inflammatory signal blocker

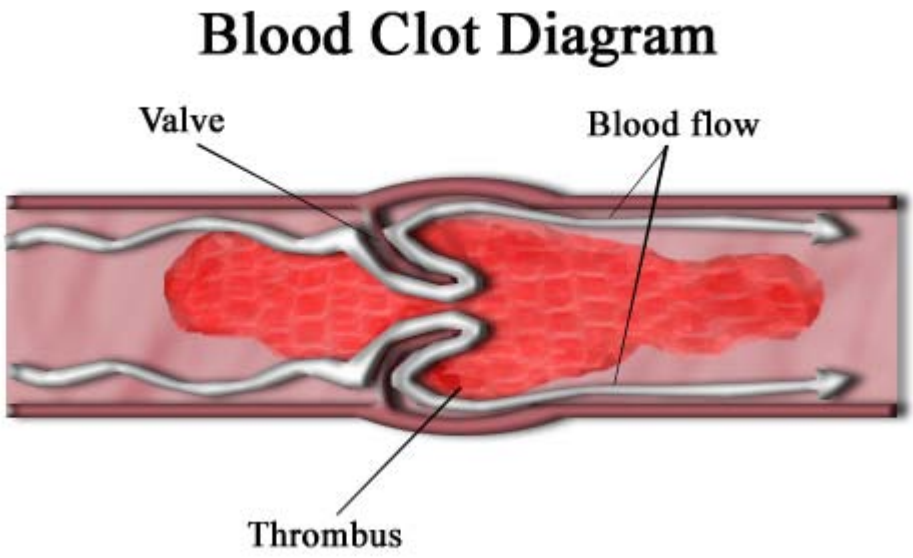
A study reported in Science (journal) showed that SphK1 is highly elevated in inflammatory cells from patients with sepsis and inhibition of the molecular pathway reduced the proinflammatory response triggered by bacterial products in the human cells. Moreover, the study also showed the mortality rate of mice with experimental sepsis was reduced when treated with a SphK1 blocker.

Nitric oxide

Medical research is focused on combating nitric oxide. Attempts to inhibit its production paradoxically led to a worsening of the organ damage and in an increased lethality, both in animal models and in a clinical trial in sepsis patients. In a study published in the Journal of Experimental Medicine, nitrite treatment, in sharp contrast with the worsening effect of inhibiting NO-synthesis, significantly attenuates hypothermia, mitochondrial damage, oxidative stress and dysfunction, tissue infarction, and mortality in mice

Chapter 16

Thrombus (Liver Transplantation Complication)



Blood clot diagram

A **thrombus** (Greek θρόμβος), or **blood clot**, is the final product of the blood coagulation step in hemostasis. It is achieved via the aggregation of platelets that form a platelet plug, and the activation of the humoral coagulation system (i.e. clotting factors). A thrombus is normal in cases of injury, but pathologic in instances of thrombosis.

Pathophysiology

Specifically, a thrombus is the inappropriate activation of the hemostatic process in an uninjured or slightly injured vessel. A thrombus in a large blood vessel will decrease blood flow through that vessel (termed a mural thrombus). In a small blood vessel, blood flow may be completely cut-off (termed an occlusive thrombus) resulting in death of tissue supplied by that vessel. If a thrombus dislodges and becomes free-floating, it is termed as an embolus.

Some of the conditions which elevate risk of blood clots developing include atrial fibrillation (a form of cardiac arrhythmia), heart valve replacement, a recent heart attack (also known as a myocardial infarction), extended periods of inactivity, and genetic or disease-related deficiencies in the blood's clotting abilities.

Formation

Platelet activation can occur through different mechanisms such as a vessel wall breach that exposes collagen, or tissue factor encryption. The platelet activation causes a cascade of further platelet activation eventually causing the formation of the thrombus.

Treatment

Blood clot prevention and treatment reduces the risk of stroke, heart attack and pulmonary embolism. Heparin and warfarin are often used to inhibit the formation and growth of existing thrombi; the former binds to and activates the enzyme inhibitor antithrombin III, while the latter inhibits vitamin K epoxide reductase, an enzyme needed to synthesize mature clotting factors.

Presentation

Virchow's triad describes the pathogenesis of thrombus formation:

1. Endothelial injury (injury to the endothelial cells that line enclosed spaces of the body, such as the inside of blood vessels) (e.g. trauma, atheroma)
2. Abnormal blood flow (loss of laminar flow resulting from stasis in veins or turbulence in arteries) (e.g. valvulitis, aneurysm)
3. Hypercoagulability (e.g. leukaemia, Factor V mutation (Leiden))

Disseminated intravascular coagulation (DIC) involves widespread microthrombi formation throughout the majority of the blood vessels. This is due to excessive consumption of coagulation factors and subsequent activation of fibrinolysis using all of the body's available platelets and clotting factors. The end result is hemorrhaging and ischaemic necrosis of tissue/organs. Causes are septicaemia, acute leukaemia, shock, snake bites, fat emboli from broken bones, or other severe traumas. DIC may also be seen in pregnant females. Treatment involves the use of fresh frozen plasma to restore the level of clotting factors in the blood, platelets and heparin to prevent further thrombi formation.

Prognosis

Thrombus formation can have one of five outcomes: propagation, embolization, dissolution, organization and organization with recanalization.

1. Propagation of a thrombus occurs towards the direction of the heart. This means that it is anterograde in veins or retrograde in arteries.

2. Embolization occurs when the thrombus breaks free from the vascular wall and becomes mobile. A venous emboli (most likely from deep venous thrombosis in the lower extremities) will travel through the systemic circulation, reach the right side of the heart, and travel through the pulmonary artery resulting in a pulmonary embolism. On the other hand, arterial thrombosis resulting from hypertension or atherosclerosis can become mobile and the resulting emboli can occlude any artery or arteriole downstream of the thrombus formation. This means that cerebral stroke, myocardial infarction, or any other organ can be affected.
3. Dissolution occurs when fibrinolytic mechanisms break up the thrombus and blood flow is restored to the vessel. This may be aided by drugs (for example after occlusion of a coronary artery). The best response to fibrinolytic drugs is within a couple of hours, before the fibrin meshwork of the thrombus has been fully developed.
4. Organization and recanalization involves the ingrowth of smooth muscle cells, fibroblasts and endothelium into the fibrin-rich thrombus. If recanalization proceeds it provides capillary-sized channels through the thrombus for continuity of blood flow through the entire thrombus but may not restore sufficient blood flow for the metabolic needs of the downstream tissue.