A Brief History of Transfusion Safety
With an even briefer look into the near future

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Objectives

By the end of this presentation the attendee should be able to:

1. Be familiar with important historical progresses in transfusion safety

2. Be familiar with signs and symptoms of an acute transfusion reaction

3. Understand that despite how much we know, there is still much to learn about blood transfusions
Blood in History

China, 1000 BC
The soul was contained in the blood.

Egyptians bathed in blood for their health.

Leviticus 17:11
“…the life of the flesh is in the blood…”

Pliny and Celsus describe Romans drinking the blood of fallen gladiators to gain strength and vitality and to cure epilepsy.

Taurobolium, the practice of bathing in blood as it cascaded from a sacrificial bull, was practiced by the Romans.
“First Transfusion” Myth

• In 1492, Pope Innocent VIII is said to have received, at the behest of a Jewish physician, a transfusion of the blood of three ten-year-old boys.

• Probably the blood was drawn, intended to be taken orally.

• There is no reliable evidence that the sickly pope accepted the blood.

• This story is most likely apocryphal and has the flavor of an early urban legend in its details and its anti-Semitic and anti-Catholic overtones.
Andreas Libavius, 1615

He was the first person to advocate transfusion, though he is not known to have actually attempted to perform a transfusion.

“Let there be a young man, robust, full of spirituous blood, and also an old man, thin, emaciated, his strength exhausted, hardly able to retain his soul. Let the performer of the operation have two silver tubes fitting into each other. Let him open the artery of the young man, and put it into one of the tubes, fastening it in. Let him immediately after open the artery of the old man, and put the female tube into it, and then the two tubes being joined together, the hot and spirituous blood of the young man will pour into the old one as it were from a fountain of life, and all of his weakness will be dispelled.”
Understanding the concept of circulation was critical to developing the reality of blood transfusion.

Ancient Greeks believed that blood was formed in the heart, then consumed as it flowed out to the body in veins, while air was passed from the lungs to the body in arteries.

Erasistratos (~270 BC) envisioned the heart as a pump.

Galen (131-201 AD) proved that arteries contain blood, but thought that blood was formed in the liver, not suspecting that arteries and veins are attached.
Circulation

Andrea Cesalpino (1519-1603) used the term ‘circulation’ and believed that the veins and arteries were connected by a fine vascular network.

William Harvey is generally credited with the discovery in 1616 (published in 1628) of the circulation of blood as we know it today.
In 1658, Christopher Wren and William Boyle performed a series of experiments injecting various medicaments into the veins of dogs utilizing a bladder with an attached quill and then observing the effects.

Infusion solutions included wine, beer, opium, emetics, water, nitric acid, and sulfuric acid.

Willis injected dyes into the blood vessels supplying the brain in order to trace its vasculature (thus the Circle of Willis).
Richard Lower (1631-1691)

Richard Lower is credited with performing, in 1665, the first authentic blood transfusion (animal to animal).

He kept exsanguinated dogs alive by connecting the carotid artery of the donor dog to the jugular vein of the recipient dog with a quill.
Jean Baptiste Denys (1643 – 3Oct 1704)

• Jean-Baptiste Denys was a frenchman and personal physician for Louis XIV

• notable for performing the first fully documented human blood transfusion, a xenotransfusion.
  – He performed transfusion of lamb blood into the carotid artery of a young woman in 1667.

• Our story is not of this young woman, but of the reportedly 4th patient to receive a transfusion under Dr. Denis’ care…
It was a dark and stormy night...

- Winter 1667, near Paris…
  - lived a madman named Antoine Mauroy who suffered “phrensies” during which he would batter his wife, strip off his clothes, and run naked through the streets, setting houses on fire.
  - He was brought to Jean-Baptiste Denys, who gave him a cupful of calf’s blood, in hope that “by its mildness and freshness might possibly allay the heat and ebullition of [the patient’s] blood.”
Seventeenth Century Medicine

• Scientists since Galen believed – disease arose from an imbalance of invisible fluids or vapors in the body, called “humors”.

• “The vital spirits are made in the heart of the natural, which by the arteries are transported to all the other parts”
Our story resumes…

- They watched for signs that the transfusion had taken effect.
- Mauroy complained of a great heat moving up his wrist.
- Two hours later, the patient, upon waking up from a nap, “ate a hearty supper and amused himself in whistling and in song.”...His pain was gone…
Two days later, …

• An even larger dose of blood was given.
  – As soon as the blood entered the veins, Mauroy complained of the same heat traveling up his arm.
  – His pulse raced, then slowed, then raced again.
  – “We observed a plentiful sweat all over his face”.
  – “He complained of great pains in his Kidneys [and] stomach, and that he was ready to [die].”
  – He urinated goblets of fluid as black “as if it had been mixed with the soot of Chimneys.”
The next morning…

• “he shewed surprising calmness, and a great presence of mind…” to the amazement of everyone, including his wife, Perrine.

• Mauroy was later discharged with advice to conduct himself “modestly.”

The experiment was a resounding success!
About six months later…

• A knock at the door revealed Antoine Mauroy and his wife, both looking tired and ragged, Perrine with several bruises.
• Antoine was having “the frenzies”, again.
• Perrine begged for another procedure, but Denis doubted that Antoine was strong enough to endure it.
• Denis ultimately agreed because of Perrine’s persistence.
No good deed goes unpunished

• Antoine was seized by such a violent fit, that the cannula fell out of his arm before a drop of blood was transfused.

• The next night, Antoine died.

• Denis was labeled a murderer and a fool and was soon after sued by Perrine at the encouragement of Denys’ enemies.
Final Ruling, April 17, 1668

- Denys was absolved of malpractice.
- Perrine was found to have been putting “certain powders” [arsenic] in Antoine’s soup.
- The court ruled that any physician wishing to perform a transfusion, must first seek permission from the Faculty of Medicine in Paris.
- The practice of transfusion faded away for one and a half centuries…
“Concerning the Origin and Decline of Blood Transfusion”

- A 1679 treatise banned blood transfusions. The author maintained that…
  - Animal-to-man had been “shown to be wrong”.
  - Man-to-man should be “left to the test of experience”.

- The British Royal Society (1668) and the Vatican (1669) had also laid prohibitions against blood transfusions.
  - The procedure didn’t gain popularity again until Karl Landsteiner discovered the four human blood groups in 1902.
The rest of the story...

- An Englishman, Samual Pepys, who had observed the experiments noted that Mauroy’s madness was “Original of … Love.”
- Prior to antibiotics in the early 20th century, heat and fever were commonly used to treat Treponema Pallidum.
The Eighteenth Century

- Transfusions were done only sporadically, and were generally animal to human.

- Transfusion was generally thought of as a cure for mental aberration or as a youth potion for the aged, rather than as a treatment for blood loss.

- Reciprocal transfusions were suggested as a cure for marital discord.
James Blundell (Jan 1791 – Jan 1878)

- By 1829, James Blundell, an English Obstetrician, successfully performed the first documented human (husband) to human (wife) transfusion.
James Blundell – inventor of several blood collection and transfusion apparatus

- Blundell’s transfusion devices included the impellor, which consisted of a cup, tube, and syringe; and the gravitator, consisting of a receptacle held high above the patient with an attached tube through which the blood was injected into the patient.

Article on transfusions by Dr. Blundell in The Lancet, 1829.
State of the Art - 19th Century Medicine

- In the 1830’s a doctor in Paris named Pierre-Charles-Alexander Louis began gathering patient information.

- He began asking strange questions like…
  - When did the disease begin?
  - What were the symptoms?

The beginning of epidemiology.
The Nineteenth Century

- Transfusions in the 1800s were plagued by the complications of transfusion reactions.

- Panum and Landois showed that same species transfusions were more efficacious than interspecies transfusions.

- Landois noted that in interspecies transfusion red blood cells were hemolyzed and white blood cells would cease their amoeboid motion and die.

- However, animal to human transfusions were performed as late as 1890.
The Nineteenth Century

- Saline infusion was observed to be safer than, and frequently as effective as, blood transfusion.
- Milk was advocated as a potentially effective infusion, because it was thought that the “white corpuscles of milk were capable of being transformed into red blood corpuscles.”
- Two instances of successful transfusion, both administered during leg amputation, are documented from the Civil War.
Karl Landsteiner (Jun 1868 – Jun 1943)
1930 Nobel Prize Laureate

• In 1900, Landsteiner showed that serum from some individuals could agglutinate or hemolyze the red blood cells of certain, but not all, other individuals. The serum of the latter would likewise agglutinate the red blood cells of the former. Still other individuals’ red cells were unaffected by the serum from either of these.

• He named these three different types A, B, and O, since the third one looked “other than” A&B. He found AB shortly thereafter
Blood Typing

- Sturli and DeCastello described the fourth blood group, AB, in 1902.

- Levine and Stetson, in 1939, describe a severe reaction in a Type O woman given a transfusion of her husband’s Type O blood following a stillbirth. Her serum agglutinated 80% of Type O blood.

- Landsteiner and Wiener, in 1940, describe Rh typing. This leads to a dramatic decrease in the incidence of hemolytic disease of the newborn.

- Over 250 different antigens categorized into 23 major discrete systems are now known.
Major Innovations in the 20th Century

- Compatibility testing
- Anticoagulant solutions
- Preservative solutions
- Refrigeration
- Blood Banks
- Venous access
- Plastic blood bags
- Component administration
- Infectious disease testing
- High-risk donor screening
Compatibility testing

- Landsteiner pointed out the importance of his findings in his original paper. (1900)

- Ottenberg and Schultz were the first to apply this information in an actual transfusion. (1907)

- In 1911, Hektoen suggested that blood groups be made the basis for selection of donors for blood transfusion.

- World War I experiences led to the universal adoption of blood typing to select blood donors.

- Coombs described antiglobulin testing in 1945.
Anti-coagulation

Blundell had observed the need for rapid transfusion in order to prevent coagulation.

Direct transfusion (artery to vein for speed) was advocated.
Anti-coagulation

• In 1835, Bischoff proposed defibrination. Brown-Sequard also experimented with defibrination in the 1850s. It was generally accomplished by whipping or twirling the blood, then removing the clot and transfusing the remaining fluid.

• Neudorfer, in 1860, recommended sodium bicarbonate.

• Braxton Hicks unsuccessfully used sodium phosphate.

• Lewisohn (1914) used citrate. Weil noted that citrated blood could be stored in the refrigerator for several days.
Lewisohn’s Method of Transfusion

Blood is collected in a citrated flask.........and immediately transfused.
The Kimpton-Brown transfusion apparatus was commonly used before citration. It consisted of a paraffin-coated gradient glass cylinder with a horizontal side tube for suction. It was in use until approximately 1918.
Preservation

- Furthering the work of Lewisohn and Weil, Rous and Turner developed a solution of salt, isocitrate and dextrose in order to both anticoagulate and preserve blood.

- This mixture made the blood extremely dilute, so it had to be removed prior to transfusion. (1:1 solution:blood ratio)

- This method, with minor variations, was used through most of World War II.

- Loutit and Mollison introduced ACD (acid-citrate-dextrose) as a preservative in 1943. It was adopted by the Army in 1945.
  - (1:4 solution:blood ratio)
Preservation

- ACD preservative was supplanted by citrate-phosphate-dextrose (CPD) in 1957, CPD with adenine in 1965, and CPD-A1 in the 1980s.

- Effective preservation and refrigeration lead to the ability to bank blood.

- Cryoprotective agents, such as glycerol, gain use in the 1960s, enabling freezing of blood for long-term storage.
Plastic Blood Bags

• Blood was collected into reusable glass bottles in the first half of the twentieth century. Whole blood was transfused.

• Pyrogenic reactions from contamination due to incomplete cleaning were frequent. Air embolism was a common complication due to the vacuum systems used on glass bottles.

• In 1949, trials of plastic bags eventually led to their widespread use.

• Plastic bags were disposable and, because of their flexibility, facilitated the separation of blood components and the advent of component therapy.

• At least 17 different components are available through a blood bank.
Plastic Blood Bags and Component Separation
Blood Banks

- During the Spanish Civil War, the Republican Army banked 9000 liters of blood later administered at casualty stations and base hospitals.

- Bernard Fantus, at Chicago’s Cook County Hospital, established the first blood bank in the United States in 1937.

- Blood banks now standard in communities and hospitals, with regional blood centers collecting approximately 75% of the blood supply for the United States.

- Over 30 million components are transfused each year in the US
Changes over Time

• In 1943, Beeson described posttransfusion hepatitis.

• The donor pool has changed from a frequently paid group to an mandated voluntary donation system.

• The worldwide pandemic of Human Immunodeficiency Virus.

• Transition from Blood Banking to Transfusion Medicine.
We have made real improvements to some areas of patient risk

From Blood Unit Safety to Transfusion (Outcome) Safety

Shifting the focus to the entire Vein-to-Vein Transfusion Safety Chain

“Unsafe at Any Speed: Dangerous Focal Points in the Transfusion Process”¹

Safe transfusion therapy depends upon an interconnected series of processes that begin with the donor and ends with the patient.¹

¹ Dzik, Transfusion 2003;43
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>400 BC</td>
<td>Democritus proposes everything composed of minute particles</td>
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<tr>
<td>~350 BC</td>
<td>Hippocrates &amp; Aristotle formulates causal theory</td>
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<tr>
<td>1658</td>
<td>Swammerdam describes RBCs</td>
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<tr>
<td>1667</td>
<td>Denis performs 1st transfusion, describes 1st reaction</td>
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<tr>
<td>1683</td>
<td>van Leeuwenhoek discovers bacteria</td>
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<tr>
<td>1771</td>
<td>Hewson describes clotting factors</td>
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<tr>
<td>1818</td>
<td>Blundell performs 1st published human to human Transfusion</td>
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<tr>
<td>1835</td>
<td>Louise proves bloodletting is an ineffective treatment</td>
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<td>1843</td>
<td>Holmes advocates hand washing (Semmelweis)</td>
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<tr>
<td>1874</td>
<td>Osler discovers platelets</td>
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<tr>
<td>1876</td>
<td>Koch demonstrates microbes (bacteria) cause contagious illnesses</td>
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<tr>
<td>1901</td>
<td>Landsteiner describes ABO</td>
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<td>1912</td>
<td>Chromosomes are bearers of heredity (1866 Mendel)</td>
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<tr>
<td>1932</td>
<td>Oliver operates donor “services” out of London home</td>
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<tr>
<td>1937</td>
<td>Fantus coins term “blood bank”</td>
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<td>1940(a)</td>
<td>Landsteiner et al describe Rh group, Cohn develops fractionation process</td>
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<tr>
<td>1940(b)</td>
<td>Drew develops sterile plasma process for war (Britain)</td>
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<tr>
<td>1943</td>
<td>Beeson publishes 7 cases of Transfusion-Transmitted Hepatitis</td>
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<tr>
<td>1947</td>
<td>AABB formed following Texas City explosion</td>
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<tr>
<td>1950</td>
<td>Healthcare uses computers for the first time</td>
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<tr>
<td>1962</td>
<td>Evidence-based relationship between platelet count &amp; bleeding est</td>
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<tr>
<td>1965</td>
<td>Pool describes factor cryoprecipitate</td>
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<tr>
<td>1971</td>
<td>Blumberg’s discovery leads to mandated anti-HBc test</td>
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<tr>
<td>1982</td>
<td>Evatt suspects GRID infections in hemophiliacs are TTD</td>
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<tr>
<td>1988+</td>
<td>RBC Optimal Transfusion Triggers/Dosages begin to be explored</td>
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System reengineering requires common grounds?
The Rights of Transfusion
a layered, rational framework for a systematic approach to PBM

Patient Blood Management Goals\(^1\) (adapted)

A. Promote better patient outcomes
   • Reduce complications and infection rates
   • Shorten length of stay

B. Optimize blood usage (by reason and dose)
   • Peri-operative blood
   • Blood product utilization
RBC Storage Lesion

- Membrane changes
  - Phospholipid loss
  - Phospholipid re-distribution: ↑ PS
  - Lipid peroxidation
  - Protein oxidation
- Plasma changes
  - ↑ Pro-inflammatory Lipids
  - Release of intracellular proteins

- Biochemical Changes
  - ↓ 2,3 DPG
  - ↓ ATP
  - ↓ Ca2+
  - ↓ NO
  - ↓ pH

- Consequences: RBC
  - Deformability
  - ↑ NO scavenging
  - Release of vesicles
  - ↑ Aggregation/adherence
Potential AE associated with storage lesions of PRBCs

• Postoperative bacterial infection
  – Pneumonia
  – Nosocomial infections
  – Bacteremia

• Increased ICU/Hospital Stay to Mortality
  – Immunomodulation

• Post-Injury Multiple Organ Failure

• Acute Lung Injury
  – Acute respiratory distress syndrome
  – Transfusion-related acute lung injury
• Add < 5 slides on proteomics and filter studies
<table>
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<tr>
<th><strong>Transfusion Service Operations</strong></th>
<th><strong>Laboratory Efficiency and Compliance</strong></th>
<th><strong>Special Patient Support</strong></th>
<th><strong>Patient Care and Safety</strong></th>
<th><strong>Transfusion Analytics and Education</strong></th>
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<td><strong>Transfusion Service Diagnostic</strong></td>
<td><strong>Automatic Case Consultation</strong></td>
<td><strong>National Patient Antibody Registry (NPAR™) Subscription</strong></td>
<td><strong>TSO Training Program</strong></td>
<td><strong>BloodStat® Multidimensional Analytics</strong></td>
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<td>Two-day onsite assessment of transfusion service operational Workflows</td>
<td>Blood Products CPT Coding &amp; Reimbursement</td>
<td>Online, national database of searchable patient antibody histories</td>
<td><strong>TSO Recruitment</strong> Assistance with job description, organizational reporting structure, job/salary leveling and candidate selection</td>
<td>National blood usage benchmark data, by facility, service line or physician</td>
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<td><strong>Transfusion Practice Analysis</strong></td>
<td>Lean Performance Improvement</td>
<td>Reference Laboratory Network</td>
<td><strong>Interim TSO Support</strong> Short-term or extended TSO staffing</td>
<td><strong>PBM Modules</strong> Series of easy-to-read documents summarizing best practices in project management, professional skill development and transfusion practices</td>
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<td>Three-day, onsite assessment of physician blood ordering and utilization practices</td>
<td>Metrics and Dashboard Support</td>
<td>Antigen Negative RBCs Screened units, prepositioned based on local need</td>
<td><strong>TSO Onsite Training</strong> Hands-on guidance to close skill gaps and to refine TSO processes and tools</td>
<td><strong>Blood Management Exchange®</strong> Online resource library for transforming transfusion practices</td>
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<td><strong>Policy in Practice</strong></td>
<td>Targeted Chart Review</td>
<td>Platelet Support • HLA and platelet antibody screen and identification</td>
<td><strong>Adjunct TSO Support</strong> Adjunct TSO staffing for short-term, individual or group projects</td>
<td><strong>Blood Management University®</strong> CME /CEU webinars and clinical educational programs</td>
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<td>Physician-led review of hospital leadership, governance, culture, ordering practices and policies for blood transfusions</td>
<td>Blood Inventory Management Process Redesign</td>
<td>• Donor HLA/PLT antigen screening</td>
<td>Blood &amp; Tissue Committee Effectiveness</td>
<td>Grand Rounds, Custom Presentations and PACE Self-study</td>
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<td>Accreditation/Standard Implementation</td>
<td><strong>Cellular Therapy</strong> • Bone marrow transplant support</td>
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<td>Regulatory GAP Assessments</td>
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<td>Regulatory &amp; Crisis Management</td>
<td>• Novel cell-based therapeutics</td>
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“Passionate about patients and those who care for them”