



Worldwide Heparin Shortage

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Background

Heparin is a hundred-plus-year-old anticoagulant still used in therapy. It is an effective and relatively safe drug. Despite the development of several other anticoagulants in recent years, heparin has held its place in hospitals and pharmacies. In recent years, disturbing news has emerged about a global heparin shortage due to African Swine Fever, which has caused physicians and pharmacists to be naturally scared.

In this presentation, the authors researched the various aspects of the global heparin shortage. Each involved party, such as the FDA, manufacturers, physicians, and pharmacists, must play a synergistic role in preventing and combating this global shortage of a life-saving anticoagulant.

What is Heparin?

Heparin is an injectable anticoagulant (Figure 1)

- Chemical Formula: $C_{12}H_{19}NO_{20}S_3$
- A heterogeneous mixture of sulfonated polysaccharides, consisting of 15-100 repeating units of monosaccharides: D-glucosamine, D-glucuronic acid, and L-iduronic acid.
- Prevents blood clots
- Unfractionated heparin is an anticoagulant indicated for both the prevention and treatment of thrombotic events such as deep vein thrombosis (DVT), pulmonary embolism (PE), and atrial fibrillation (AF).

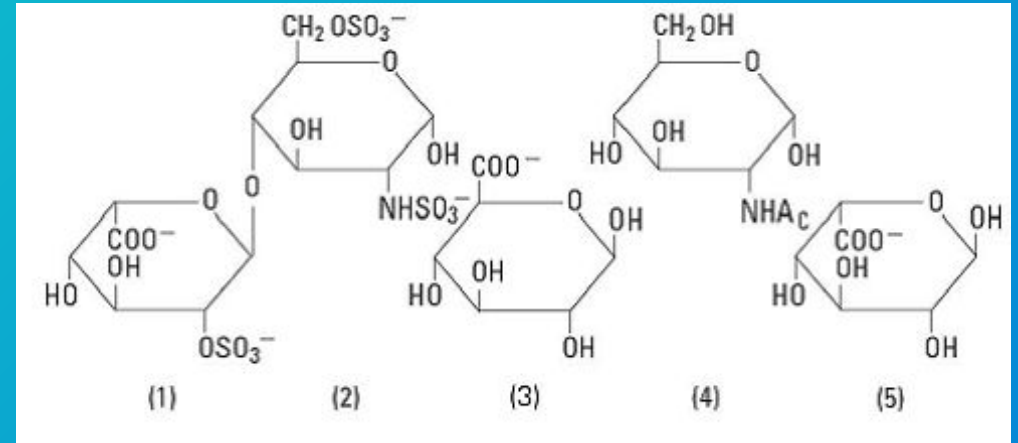


Figure 1: Chemical Structure of Heparin

What is the structure?

- Commercial heparin contains compounds with varying chain lengths and molecular masses between 5,000 and 30,000 daltons.
- Monosaccharides are modified by N-acetyl, N-sulfate, or O-sulfate groups.
- These units are linked by glycosidic bonds, forming polymers of different chain lengths.

What is the Source of Heparin?

- Porcine Intestinal Mucosa
- Chinese Pharmaceutical Companies



China is the world's largest pork producer, accounting for more than half of the current production of 113 million tons per year, worth nearly US\$128 billion. Although China can produce more than 30 trillion Heparin International Units (IUs) annually, the Chinese heparin industry relies on supplying vast amounts of local animal material (pig intestine) to sustain production under economically viable conditions.

How does heparin work?

- An effective anticoagulant by catalyzing the anticoagulation pathway (Figure 2)

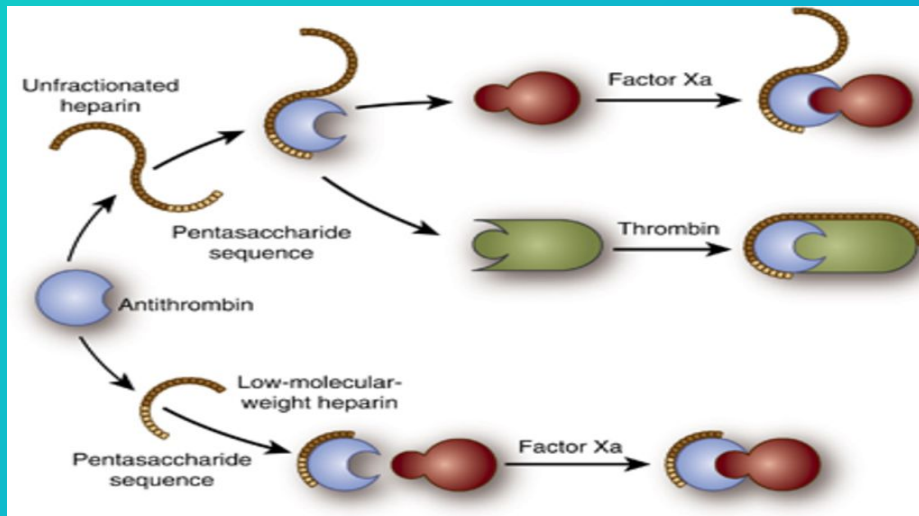


Figure 2: Mechanism of Action of Heparin

- It binds to Antithrombin III, which causes a conformational change, allowing it to bind to thrombin and factor Xa more easily and quickly.
- The inhibition of thrombin results in a lack of fibrin formation, which is needed to make a fibrin clot.
- LMWH (Low molecular weight heparin) or pentasaccharide heparin can inhibit factor Xa

The Uses and Adverse Effects

The Uses of Heparin

- The most widely used parenteral anticoagulant is considered to be integral in cardiac surgeries.
- Used to prevent/treat blood vessel, lung, and heart conditions and to prevent clotting during open-heart surgery.
- Used to diagnose and treat disseminated intravascular coagulation.

The Adverse Effects of Heparin

- Bruises easily, and it takes the body longer to stop bleeding.
- Bleeding
- Long-term treatment may cause low platelet levels (heparin-induced thrombocytopenia or HIT).

History of Heparin Shortage

African Swine Fever

2018



Late 2019

Outbreaks of African Swine Fever (ASF), a highly contagious and fatal disease of pigs, have been reported in seven Chinese provinces since August 3rd, 2018. Besides the high virulence, the arrival of ASF is very worrisome because there are no vaccines to immunize or medicines to treat the animals. China has a population of more than 430 million pigs; most of them are raised in small farmyards with minimal biosecurity standards, which makes the containment of an untreatable disease with the potential to be highly infectious, such as ASF, a difficult task, often accomplished by decimating entire pig populations from the affected areas. The asfivirus (Family Asfviridae) causing ASF does not harm humans but spreads quickly among pigs by direct contact, exposure to contaminated surfaces, or ticks. The main symptoms are high fever, internal bleeding, and, often, the death of the animals.

Rumors of a heparin shortage after the manufacturers developed significant deficits of heparin, as reported by Cian P. McCarthy, MD, a cardiology fellow at the Massachusetts General Hospital (MGH). The shortage was attributed to manufacturing disruptions, and an outbreak of African swine fever in China in August 2018 exacerbated the issue.

History of Heparin Shortage

Porcine Reproductive and Respiratory Syndrome

The worst crisis in the worldwide supply of heparin so far has been linked to a sudden shortage of porcine raw material caused by a viral disease. In 2007, a highly infectious virus provoked massive porcine reproductive and respiratory syndrome (PRRS) outbreaks in China, drastically decreasing availability and inflating pork product prices.

Information about our Situation

- By 2000, some 12 million patients in the U.S. were receiving heparin products.
- Sourced from cattle, sheep, and turkeys.
- After an outbreak of bovine disease in the 90s, the U.S. shifted to pig-derived heparin.
- China is the world's largest swine producer, making 80% of the world's heparin.
- African swine fever killed over one-third of the country's pigs, threatening the more than 30 trillion international units of heparin produced annually in China.

Heparin exists in two forms:

- Unfractionated Heparin (UFH)
- Low-Molecular Weight Heparins (LMWHs).
 - LMWH stocks are currently preserved, but this could easily change as we deplete UFH stocks and the use of LMWH increases.
- Alternatives for UFH do exist in some clinical scenarios.
- Other alternatives (bivalirudin and argatroban) are costly.

Information about our Situation

- 2007: Asia: An outbreak of blue ear pig disease, a respiratory disease, resulted in considerable shortages of heparin worldwide.
- One year later, a significant scandal emerged: heparin products from China were contaminated with oversulfated chondroitin sulfate.
- Several hundred people were injured, and 81 died in the U.S. from anaphylaxis-like reactions to the tainted heparin.
- About 30-40% of pigs in China died from African swine fever, with no evidence that viral transmission of the disease has curtailed.
- In October 2019, the FDA reported that the outbreak of swine fever in China had not affected the manufacturing or distribution of heparin in the U.S. Still, several institutions have begun preparing for the possibility of a shortage.
- The global presence of COVID-19 has decreased foreign interaction and trade between countries, particularly China.
- The current pandemic will undoubtedly exacerbate the Global Heparin shortage as countries refuse to trade with China, where the Coronavirus originated.

Implications of Worldwide Heparin Shortage

A worldwide heparin shortage, particularly of porcine-sourced heparin, could significantly impact healthcare globally. It would jeopardize surgeries requiring extracorporeal circulation, dialysis, and treatment of thromboembolic diseases. This shortage is exacerbated by the reliance on China for a large portion of the global heparin supply, and recent outbreaks of African swine fever in China have further strained the supply chain.

Preventing Heparin Shortages-3 Key Strategies

1. Improve disease surveillance

- Proactively monitor livestock health to catch outbreaks early.

2. Incentivize domestic production

- Reduce dependence on foreign suppliers, especially China.

3. Accelerate regulatory response

- Approve new manufacturing sites faster during crises.

Strategy I : Disease Surveillance Success (Brazil)

- **Brazil + Embrapa: Used geotracking and outbreak modeling in pigs.**
 - Brazil partnered with Embrapa, its national agricultural research agency, to implement real-time livestock monitoring using satellite data and AI-based disease forecasting models.
- **Detected ASF risk zones before outbreaks spread.**
 - The system flagged high-risk areas for African Swine Fever (ASF) before outbreaks spread, allowing targeted interventions like quarantines and testing.
- **Brazil preserved pig populations → no major heparin shortage.**
 - By stopping ASF early, Brazil maintained a stable pig supply—avoiding the major shortages seen in China and continuing domestic heparin production.
- **Proactive disease monitoring protects both animals and drug supply chains.**
 - Early disease surveillance isn't just good for agriculture—it's a critical safeguard for the pharmaceutical supply chain, especially for biologic drugs like heparin.

Strategy 2 : Boosting Domestic Production

- **Pfizer & Amphastar lobbied for support** → **received permits & limited funding.**
 - These U.S. pharmaceutical companies pushed for government assistance, including fast-tracked permits and limited funding, to expand domestic heparin production capacity.
- **Built U.S. purification facilities** → **reached 10% production by 2021.**
 - With this support, both companies constructed and upgraded heparin purification plants, allowing for domestic processing of raw pig mucosa.
 - Although still modest, this milestone marked a significant step toward reducing total dependence on Chinese imports.
- **Still small, but reduces dependency and adds resilience during global disruption.**
 - Having U.S.-based facilities acts as a regional buffer during global disruptions like disease outbreaks or international trade issues.

Strategy 3 : Faster Regulatory Response

- **Brazil's ANVISA: Emergency license in 60 days for new plant.**
 - In response to ASF-related supply threats, Brazil's regulatory agency ANVISA fast-tracked approval for a new heparin manufacturing facility—ensuring continued local supply during a high-risk period.
- **U.S. FDA: Normal process takes 6+ months, often too slow in crisis.**
 - In contrast, the FDA's standard approval timeline for new drug manufacturing facilities often exceeds 6 to 12 months, delaying the ability to respond to urgent shortages.
 - In crisis situations, delays in regulatory action can exacerbate shortages, especially for essential drugs like heparin.
- **Need for emergency fast-track pathways in the U.S. and globally.**
 - Countries need flexible, rapid-approval systems for essential medications to respond effectively during public health emergencies.

The Root Cause

Overdependence

- China dominates global crude heparin production.
 - China processes the majority of the world's heparin due to its large pig population and manufacturing infrastructure. This creates a single point of failure in the supply chain.
 - Just 10 firms \approx 100% of global exports (PMC, 2020)
 - According to a 2020 PMC report, only about 10 Chinese companies control nearly all crude heparin exports. A shutdown at even one could disrupt global supply.

Fragile Supply

No U.S reserve (GAO 2019) → no backup if supply fails

- The U.S. lacks a backup stockpile of heparin. If imports stop, hospitals face immediate shortages with no cushion to fall back on.
- Global ASF outbreak (2018) wasn't reported in time, delaying hospital responses.
 - African Swine Fever devastated Chinese pig farms, but poor international communication delayed awareness. By the time hospitals reacted, shortages had already begun.
- This supply chain is vulnerable to disease, politics, and disruption.
 - The supply chain depends on a single animal source in one region. Disease outbreaks, trade tensions, or factory issues can quickly trigger global crises.

Public & Institutional Actions

- **PAF + Change.org petitions → NIH increased funding for synthetic alternatives.**
 - The Patient Advocate Foundation (PAF) and grassroots campaigns on Change.org successfully lobbied for increased NIH funding to support research into synthetic, non-animal-based heparin alternatives.
- **Argentina: Color-coded caps + shared inventory reduced med errors by 40%.**
 - Public hospitals in Argentina introduced color-coded medication caps and a centralized inventory system, which led to a 40% reduction in medication errors and allowed hospitals to share supplies more efficiently during shortages.
- **Hospitals adopted AI dosing tools and daily pharmacy audits.**
 - Leading institutions in the U.S. and abroad began using AI-based dosing tools and conducting daily pharmacy audits to reduce waste and personalize heparin usage—especially important during tight supply periods.

Alternative Therapies in Use

- **Post-2008 Shift to Alternative Anticoagulants**

- Following a major contamination event in China's heparin supply chain in 2008, many U.S. hospitals began adopting alternative anticoagulants to reduce reliance on pig-derived heparin.

- LMWH usage ↑ 50% & Fondaparinux usage ↑ 30%

- These drugs became trusted substitutes in clinical settings, especially for lower-risk patients and short-term treatment plans.

- These alternatives provide safe, short-term substitutes during shortages.

- When heparin supply is unstable, LMWH and fondaparinux serve as effective and scalable substitutes, giving hospitals more options and time to adapt.

- **Cleveland Clinic Strategy Reduced Heparin Use Without Risk**

- Cleveland Clinic (2020): Used enoxaparin in low-risk patients → 20% reduction in heparin use.
- During a heparin shortage, the Cleveland Clinic replaced heparin with enoxaparin (a type of low molecular weight heparin) in low-risk patients. This strategy led to a 20% reduction in overall heparin use—without compromising patient safety.

Future Solutions – Synthetic & Biosynthetic Heparin

- **Breakthroughs in Synthetic and Biosynthetic Production**

- Rensselaer Polytechnic Institute (RPI) developed a synthetic heparin process
- RPI researchers replicated the active pentasaccharide unit of heparin using a 12-step chemoenzymatic process. They combined E. coli fermentation with chemical modifications to create a lab-made version of heparin that avoids the use of animal tissue.
- MIT engineered CHO cells to biosynthesize glycosaminoglycans
At MIT, scientists inserted sulfotransferase genes into Chinese Hamster Ovary (CHO) cells, allowing them to biosynthesize heparin-like glycosaminoglycans. This method enables scalable, controlled production of synthetic anticoagulants with consistent properties.

- **Advantages of these innovations**

- Eliminate risk of contamination from animal-derived products
- Reduce dependency on pig mucosa
- Enable precise dosing and greater batch-to-batch consistency
- Improve resilience of the global heparin supply chain

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