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# Sepsis

The Past, The Present, and The Future



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## Overview

# Learning Objectives

- ✓ Describe the global and U.S. epidemiology of sepsis, including incidence and mortality rates.
- ✓ Explain the pathophysiology of sepsis, focusing on immune response and organ dysfunction.
- ✓ Review historical and current approaches to treating sepsis.
- ✓ Summarize the latest 2026 Surviving Sepsis Guidelines.
- ✓ Explore emerging trends and innovations shaping the future of sepsis care, including AI and personalized medicine.

## Epidemiology

# Global Sepsis Burden

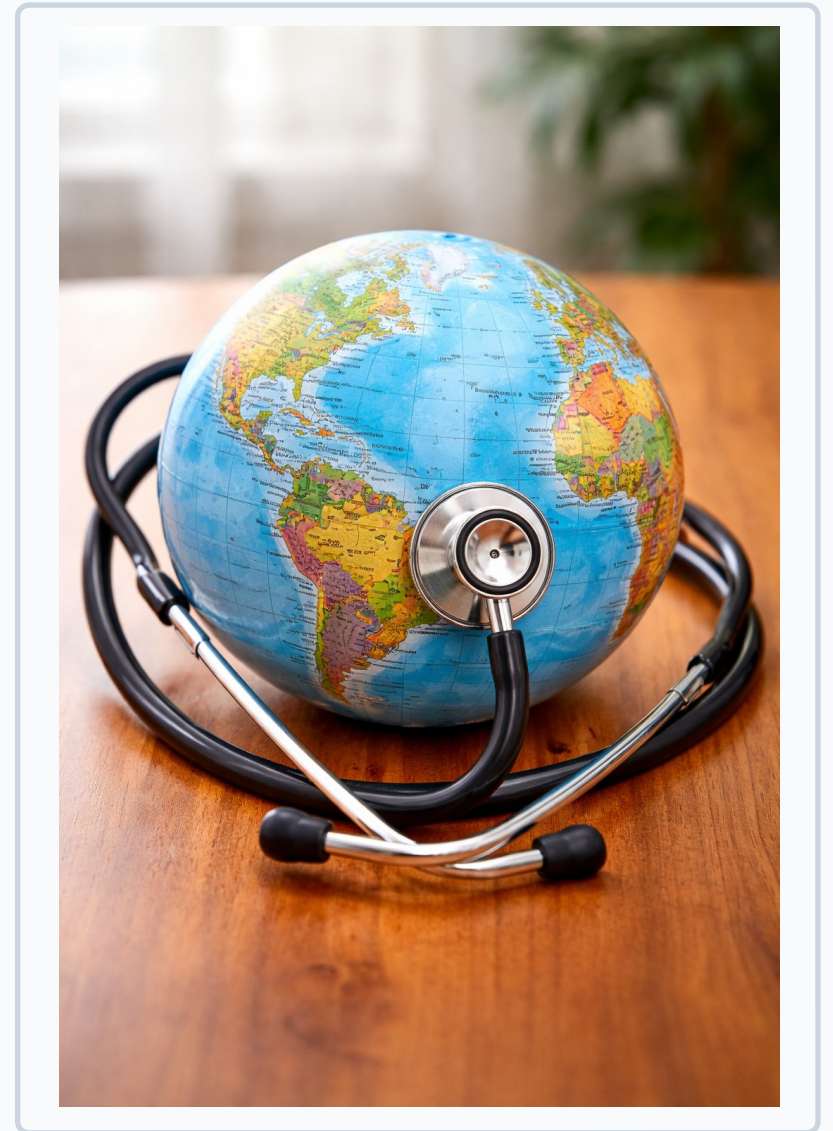
 **49M**  
Cases worldwide yearly

 **11M**  
Deaths annually

 **20%**  
Of global deaths

 **LMIC**  
Highest burden regions

- ✓ **~49 million** sepsis cases occur worldwide yearly, affecting nearly 1% of the global population
- ✓ **~11 million deaths** annually, representing 1 in 5 deaths globally
- ✓ Higher mortality in regions with **limited healthcare access**
- ✓ **Neonates and elderly** face greater sepsis risk



## Overview

# U.S. Epidemiology

- 👤 Approximately **1.7 million** sepsis cases occur annually in the United States.
- ☠️ Sepsis causes about **265,000 deaths** each year, making it a leading cause of in-hospital mortality.
- 🏥 It is the **primary reason for ICU admissions** across hospitals nationwide.
- 🔄 The readmission rate for sepsis survivors is approximately **16%**, indicating ongoing health risks.
- 🕒 Average hospital length of stay ranges from **10 to 14 days**, placing substantial strain on healthcare systems.



## Analysis

# Mortality Rises Sharply With Severity



### Sepsis: 5–10% Mortality

Early-stage sepsis carries a 5–10% mortality risk. Prompt identification and treatment can significantly improve outcomes at this stage.

**5-10%**



### Severe Sepsis: 15–20% Mortality

Mortality rises to 15–20% in severe sepsis with organ dysfunction. Delays in antibiotics and source control increase risk.

**15-20%**



### Septic Shock: 30–40%+ Mortality

Septic shock results in the highest mortality, exceeding 30–40%. Mortality worsens with progressive organ failure and treatment delays.

**30-40%+**

Overview

# Post-Sepsis Sequelae

## 01 Long-Term Mortality

Up to **50% of sepsis survivors** die within 2 years post-discharge, often due to persistent organ dysfunction and secondary infections.

 50% mortality within 2 years

## 02 Physical & Cognitive Effects

Many survivors experience **ICU-acquired weakness**, ongoing organ dysfunction, memory loss, and difficulties with executive functions.

 Cognitive & physical impairment

## 03 Psychological Impact

**Depression, anxiety, and PTSD** are common, affecting quality of life and complicating recovery for sepsis survivors.

 Mental health complications



 Post-sepsis syndrome affects up to 50% of survivors, requiring long-term monitoring and care.

## Concepts

# Definitions



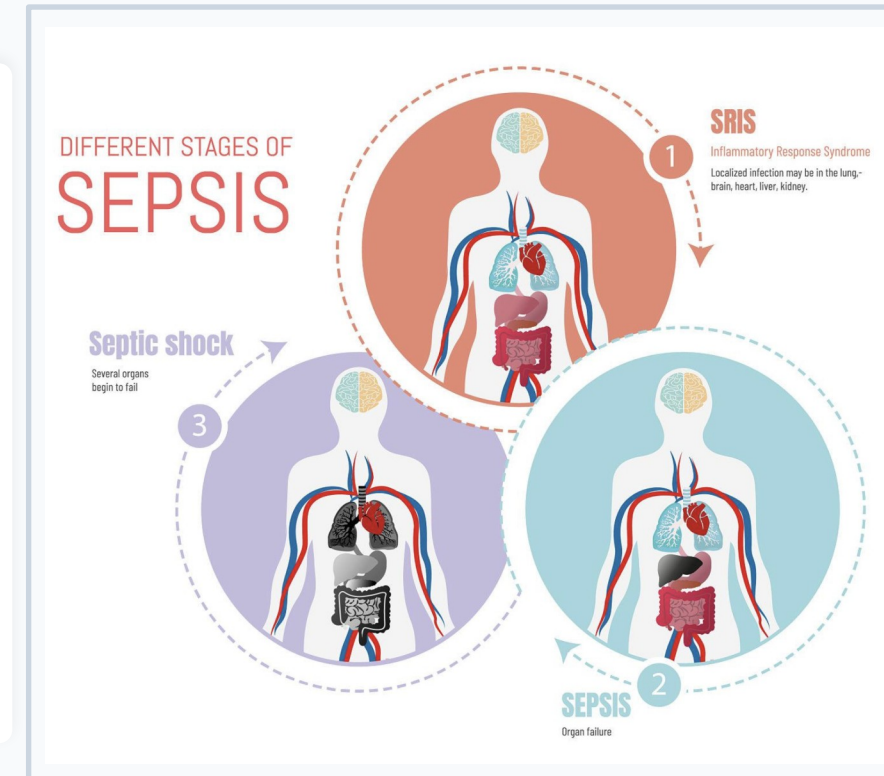
## Sepsis Progression & Modern Definitions

- **SIRS:** Systemic Inflammatory Response Syndrome, initial broad inflammatory state.
- **Sepsis:** Confirmed or suspected infection plus new organ dysfunction.
- **Septic Shock:** Sepsis with persistent hypotension requiring vasopressors and/or lactate  $\geq 4$  mmol/L.
- Modern definition focuses on **organ dysfunction** rather than just inflammation.



## Key Shift in Diagnostic Criteria

- Decreased emphasis on **SIRS criteria** due to poor specificity.
- Greater focus on **clinical signs of organ dysfunction** (e.g., altered mental status, hypotension).
- Use of **SOFA score** or quick SOFA for bedside assessment.
- Sepsis diagnosis prioritizes identifying **life-threatening organ failure**.



## Overview

# Pathophysiology Overview

## 01 Triggers



Pathogen-associated molecular patterns (PAMPs) from microbes and damage-associated molecular patterns (DAMPs) from injured cells activate the innate immune system to initiate the sepsis response.

## 02 Cascade

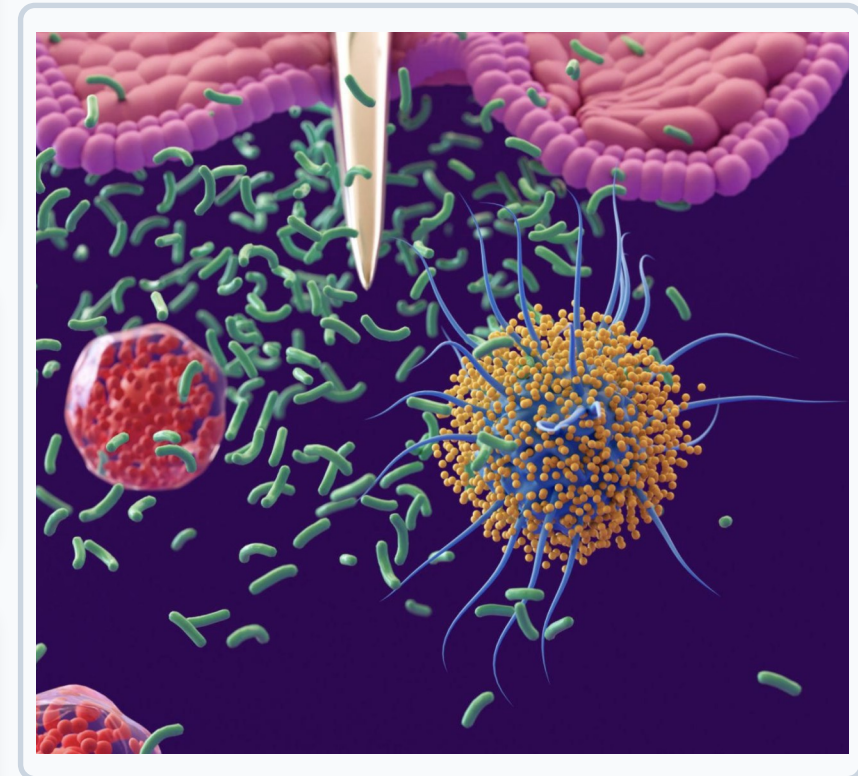


Excessive release of cytokines such as TNF, IL-1, and IL-6 leads to endothelial injury, capillary leak, and a dysregulated immune response worsening inflammation and tissue damage.

## 03 Result



The ongoing inflammatory cascade causes progressive organ dysfunction, including cardiovascular collapse, respiratory failure, renal impairment, and multi-organ failure.

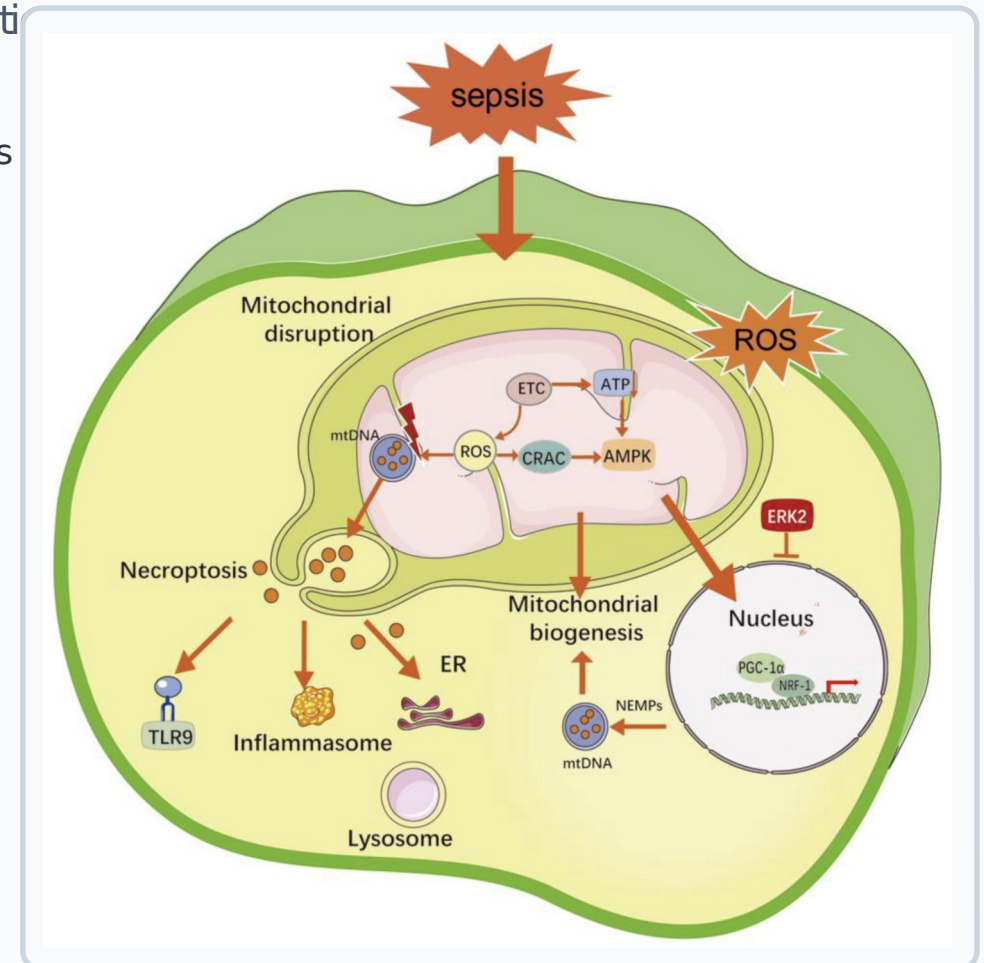


Overview

# Cellular-Level Organ Failure

Organ failure begins at the cellular level due to complex biochemical disruptions

- 📌 **Increased membrane permeability** causes edema and fluid shift into tissues
- ⚡ **Mitochondrial dysfunction** lowers ATP production and cellular energy
- 🔥 **Cellular hypoxia** occurs despite normal oxygen delivery
- 🧬 **Apoptosis and necrosis** drive progressive organ damage
- ⚠️ These cellular changes lead to **multi-organ failure** if not addressed



Overview

# Microvascular Progression

01

## Capillary Leak



Inflammatory mediators increase endothelial permeability, allowing plasma and fluid to escape from capillaries into the interstitial space, causing tissue edema and impaired oxygen diffusion.

02

## Flow Disruption



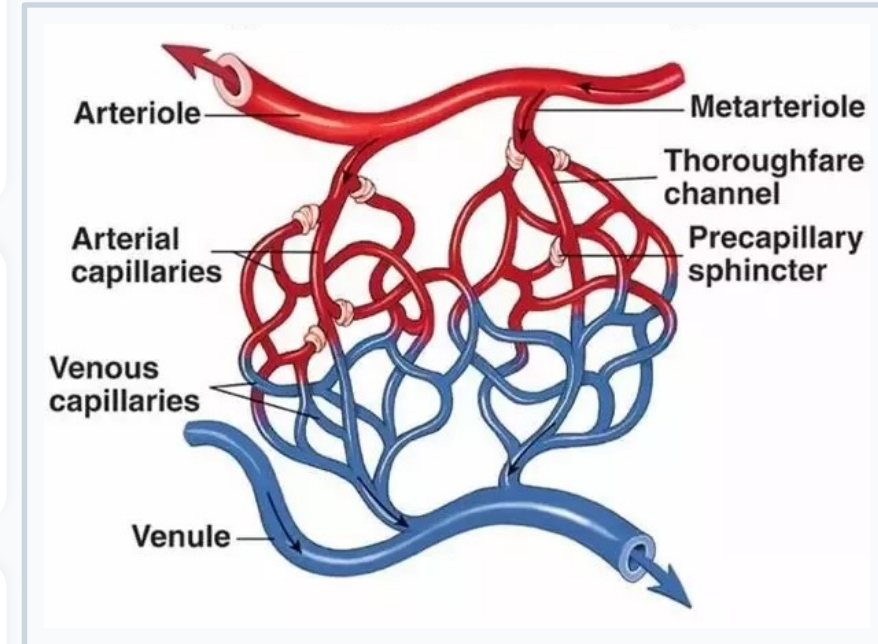
Formation of microthrombi within the microvasculature obstructs blood flow, further impairing tissue perfusion and exacerbating ischemia despite normal or elevated systemic blood pressure.

03

## Perfusion Failure



Oxygen delivery to tissues becomes inadequate, resulting in cellular hypoxia, rising serum lactate levels, and progressive organ dysfunction despite maintained systemic hemodynamics.



## Overview

# Systemic & Organ-Level Effects



## Cardiovascular Effects

Sepsis causes vasodilation and a significant drop in systemic vascular resistance (SVR), leading to hypotension and impaired tissue perfusion that often requires vasopressor support.



## Respiratory Dysfunction

Acute Respiratory Distress Syndrome (ARDS) develops due to increased vascular permeability and inflammation, causing hypoxia and increased work of breathing in septic patients.



## Renal Impairment

Acute kidney injury (AKI) results from hypoperfusion and microvascular thrombosis, leading to reduced urine output and electrolyte imbalances requiring close monitoring.



## GI & Liver Impact

Sepsis disrupts the GI barrier causing bacterial translocation and systemic inflammation; liver dysfunction manifests as cholestasis and impaired metabolism.

Mechanism

# Cytokine-Driven Vasodilation

## Core Points

**Vasodilation caused by cytokine-induced nitric oxide release** leads to refractory hypotension, requiring vasopressor support to maintain adequate perfusion pressure.

✓ Refractory hypotension

✓ Vasopressor support needed

✓ MAP  $\geq$ 65 mmHg target

## Key Mechanism and Treatment Target

Sepsis triggers an overwhelming immune response where cytokines induce the release of **nitric oxide**, a potent vasodilator. This results in **vasoplegia**, leading to a significant decrease in systemic vascular resistance (SVR) and refractory hypotension. Maintaining a mean arterial pressure (MAP) of **65 mmHg or higher** is critical to ensure organ perfusion and prevent end-organ damage.

## Overview

# Cardiac & Pulmonary Dysfunction



## Septic Cardiomyopathy

- Marked by **decreased ejection fraction**, often reversible with treatment.
- Leads to **reduced cardiac output** and compromised tissue perfusion.
- Requires **careful balance of fluid resuscitation** to avoid overload.
- Vasopressors used judiciously to support blood pressure and cardiac function.



## Pulmonary Dysfunction and ARDS

- **Increased vascular permeability** causes pulmonary edema and fluid leakage.
- **Impaired gas exchange** results in hypoxia and increased work of breathing.
- ARDS characterized by **diffuse alveolar damage** and refractory hypoxemia.
- Management includes **lung-protective ventilation** and supportive care.

# Sepsis Induced Myocardial Dysfunction

## ✓ Normal Cardiac Function

Normal EF, vigorous wall motion

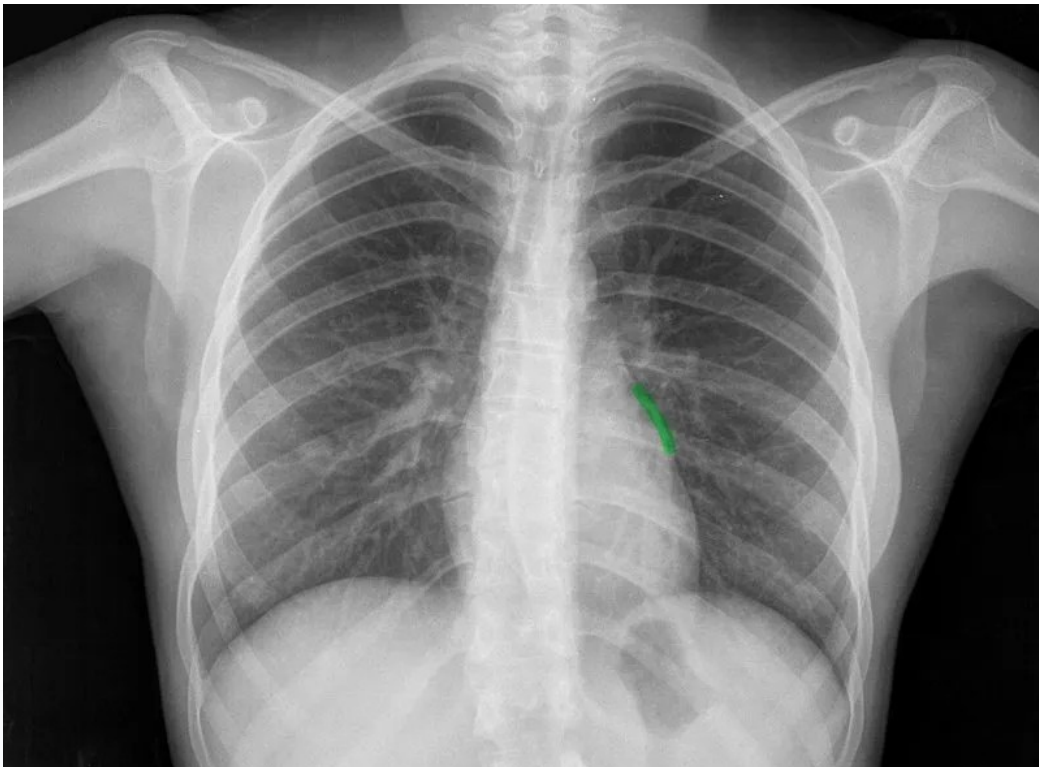
## ⚠ Septic Cardiomyopathy

Severely reduced EF, dilated LV, poor contractility

# Non-Cardiogenic Pulmonary Edema

## ✔ Normal Chest X-Ray

Clear lung fields, normal cardiac silhouette



## ⚠ Non-Cardiogenic Pulmonary Edema

Bilateral infiltrates, normal heart size



## Treatment

# Lung-Protective Ventilation

- ✓ **Use low tidal volumes** of 4–6 mL/kg of ideal body weight to avoid overdistension of alveoli.
- ✓ **Maintain plateau pressures below 30 cmH<sub>2</sub>O** to reduce barotrauma risk.
- ✓ **Accept permissive hypoxemia** with target PaO<sub>2</sub> between 55–80 mmHg to limit oxygen toxicity.
- ✓ **Employ prone positioning** to enhance oxygenation by improving ventilation-perfusion matching.
- ✓ **Focus on strategies** that reduce ventilator-induced lung injury and support lung recovery in ARDS.



## Overview

# Renal Pathophysiology & Support

## Renal Injury in Sepsis

- **Hypoperfusion** reduces renal blood flow, causing ischemic injury to kidney tissue.
- **Microthrombi formation** obstructs renal microcirculation, worsening kidney damage.
- **Acute kidney injury (AKI)** manifests as decreased glomerular filtration rate and oliguria.
- **Electrolyte imbalances** such as hyperkalemia and acidosis frequently accompany AKI.
- Renal dysfunction contributes significantly to sepsis morbidity and mortality.

## Indications for CRRT

- **Refractory metabolic acidosis** unresponsive to medical management.
- **Volume overload** not relieved by diuretics, risking pulmonary edema.
- **Severe hyperkalemia** posing life-threatening cardiac risks.
- **CRRT supports** gradual fluid and solute removal, stabilizing critical patients.
- Early CRRT initiation can improve outcomes in septic patients with renal failure.



Overview

# Liver, GI Dysfunction & Kupffer Cells

## 01 Liver Dysfunction

Sepsis causes **cholestasis** and impaired drug metabolism due to hepatic inflammation. Rising bilirubin levels signal liver injury and contribute to systemic toxin accumulation.

 Hepatic inflammation & cholestasis

## 02 GI Barrier Failure

Disruption of the **intestinal mucosal barrier** leads to bacterial translocation into the bloodstream, exacerbating systemic inflammation.

 Bacterial translocation risk

## 03 Kupffer Cell Dysfunction

**Kupffer cells** normally clear bacteria from portal circulation, but in sepsis, their overactivation triggers excessive cytokine release.

 Excessive cytokine release

## Overview

# Treatment: The Core Pillars



## IV Fluids

Initiate rapid crystalloid fluid resuscitation, typically about 30 mL/kg, to restore circulating volume and improve organ perfusion. Use balanced fluids preferentially.



## Blood Cultures

Obtain blood cultures before starting antibiotics whenever possible to identify the causative pathogen and tailor therapy. Avoid delays in antibiotic initiation.



## Vasopressors

Start norepinephrine promptly for patients with persistent hypotension despite adequate fluid resuscitation to maintain organ perfusion.



## Early Antibiotics

Administer broad-spectrum antibiotics within the first hour for patients with septic shock. Early antimicrobial therapy significantly reduces mortality.



## Coordinated Care

Implement a time-sensitive, multidisciplinary approach involving nursing, physicians, pharmacy, and support staff for rapid recognition and treatment.



## Lactate Measurement

Measure serum lactate promptly to assess tissue perfusion and guide resuscitation efforts. Elevated lactate signals hypoperfusion and higher mortality risk.

## Compliance

# SEP-1 Bundle Compliance



## 3-Hour Bundle

Critical

- ✓ **Measure serum lactate** to assess tissue perfusion status.
- ✓ **Obtain blood cultures** prior to antibiotic administration if possible.
- ✓ **Administer broad-spectrum antibiotics** promptly to cover likely pathogens.
- ✓ **Give 30 mL/kg** of isotonic IV crystalloid fluid for hypotension or lactate  $\geq 4$  mmol/L.



## 6-Hour Bundle

Follow-up


- ✓ **Reassess volume status** and tissue perfusion after initial resuscitation.
- ✓ **Apply vasopressors** if MAP remains below 65 mmHg despite fluid resuscitation.
- ✓ **Repeat lactate measurement** if initial was elevated to guide ongoing resuscitation.
- ✓ **Ensure timely documentation** and adherence to SEP-1 bundle protocols.


## Detection

# Nurses: First Line of Detection


**"Using EHR-based early warning alerts, nurses execute screening protocols, lead sepsis huddles for rapid care escalation, and activate rapid response teams to improve patient outcomes."**

Nurses are the **critical first line** in identifying sepsis early and initiating timely interventions. Their clinical judgment and vigilance are essential for early detection and rapid response.

 Early screening

 Alert activation

 Team coordination

 Patient monitoring

## Treatment

# Blood Cultures and Antibiotic Timing



## Blood Cultures

- ✓ **Obtain blood cultures before starting antibiotics** whenever possible to identify the causative pathogen.
- ✓ **Do NOT delay antibiotic administration** in cases of septic shock, even if cultures are pending.
- ✓ **Accurate pathogen identification** allows for targeted antibiotic therapy and safer de-escalation.
- ✓ **Timely cultures support antimicrobial stewardship** and reduce broad-spectrum antibiotic overuse.



## Antibiotic Strategy

- ✓ **In septic shock, administer broad-spectrum antibiotics within 1 hour** of recognition for best outcomes.
- ✓ **Narrow antibiotic spectrum at 48–72 hours** guided by culture results and clinical response to minimize toxicity.
- ✓ **Delays in antibiotic initiation correlate with increased mortality**; early treatment is critical.



## Perfusion

# Lactate: A Marker of Perfusion



## Key Points on Lactate

- ✓ **Trends in lactate levels are more informative** than single readings alone.
- ✓ **Initial lactate measurement should be done within 3 hours** of patient arrival.
- ✓ **Repeat lactate testing is recommended** if levels exceed 2 mmol/L.
- ✓ **Rising lactate suggests worsening tissue hypoxia** and perfusion deficits.



## Lactate Monitoring Essentials

- ✓ **Monitoring lactate trends provides critical insights** into patient perfusion and guides effective resuscitation strategies in sepsis care.
- ✓ **Initial measurement should occur within 3 hours** of presentation. Repeat measurements are crucial if lactate is above 2 mmol/L to assess worsening or improving perfusion.
- ✓ **Falling lactate indicates effective resuscitation** and improved cellular oxygen delivery.

## Overview

# Fluid Resuscitation



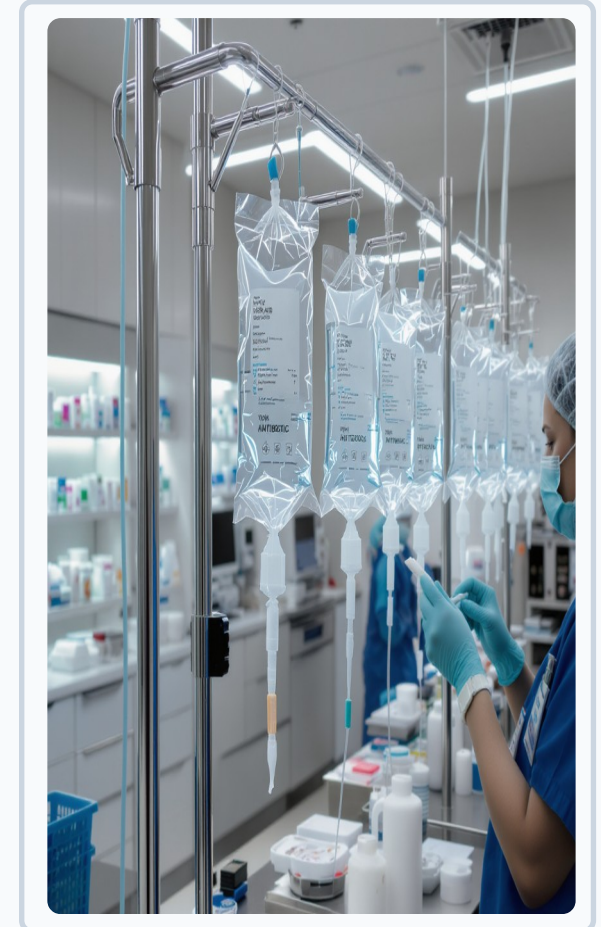
## Initial Strategy for Fluid Resuscitation

- Administer approximately **30 mL/kg of isotonic crystalloid fluids** to restore circulating volume.
- Prefer **balanced crystalloids** such as Lactated Ringer's or Plasma-Lyte over normal saline.
- Begin fluid resuscitation **promptly within the first 3 hours** of sepsis recognition.
- Early fluid administration aims to **restore circulating volume** and improve tissue perfusion.
- Avoid delay to reduce risk of worsening organ dysfunction.



## Reassessment and Monitoring

- Perform **frequent clinical reassessment** after each fluid bolus to evaluate response.
- Monitor for signs of **fluid overload**: peripheral edema, pulmonary crackles, rising JVP.
- Use **dynamic measures of fluid responsiveness** when possible to guide resuscitation.
- Avoid excessive fluid administration to prevent complications like pulmonary edema.



# Assessing Fluid Responsiveness



## Preferred Dynamic Tools

- ✓ **Passive leg raise (PLR)** is highly accurate and reversible, simulating a fluid challenge without volume administration.
- ✓ **Stroke volume variation (SVV)** effectively predicts fluid responsiveness in mechanically ventilated patients.
- ✓ **Point-of-care ultrasound (POCUS)** allows real-time assessment of cardiac function and volume status at bedside.
- ✓ **Dynamic measurements** respond to changes in preload and provide actionable data to guide fluid therapy.



## Avoid Static Measures

- ✗ **Central venous pressure (CVP)** is unreliable due to variability and poor correlation with fluid responsiveness.
- ✗ **Static blood pressure measurements** do not reflect dynamic changes in volume status.
- ✗ **Relying solely on static measures** can lead to inappropriate fluid administration, risking overload or under-resuscitation.
- ✗ **Dynamic assessment tools** are the current standard of care recommended by sepsis guidelines.

## Treatment

# Vasopressors: Norepinephrine First


**Norepinephrine is the first-line vasopressor for septic shock. Start early if MAP <65 mmHg despite fluids. Peripheral use is safe temporarily; central line should be placed as soon as possible.**

Norepinephrine provides reliable vasoconstriction with minimal arrhythmogenic effects compared to other vasopressors.

 MAP >65 mmHg

 First-line agent

 Start early

 Safe peripherally



### **Do NOT delay vasopressors waiting for central line access**

Start norepinephrine via peripheral IV if needed. Central line placement should not delay vasopressor initiation in septic shock.

## Treatment

# Perfusion Targets



**MAP (Mean Arterial Pressure)**

**$\geq 65$  mmHg**

Maintain MAP above 65 mmHg to ensure adequate organ perfusion and prevent tissue hypoxia.



**Capillary Refill Time**

**$< 3$  seconds**

Capillary refill should be less than 3 seconds to indicate adequate peripheral perfusion.



**Urine Output**

**$\geq 0.5$  mL/kg/hr**

Monitor urine output to assess renal perfusion and fluid status.



**Lactate Trend**

**Decreasing**

Falling lactate levels indicate effective resuscitation and improved tissue oxygenation.

## Overview

# Advanced Management & Organ Support



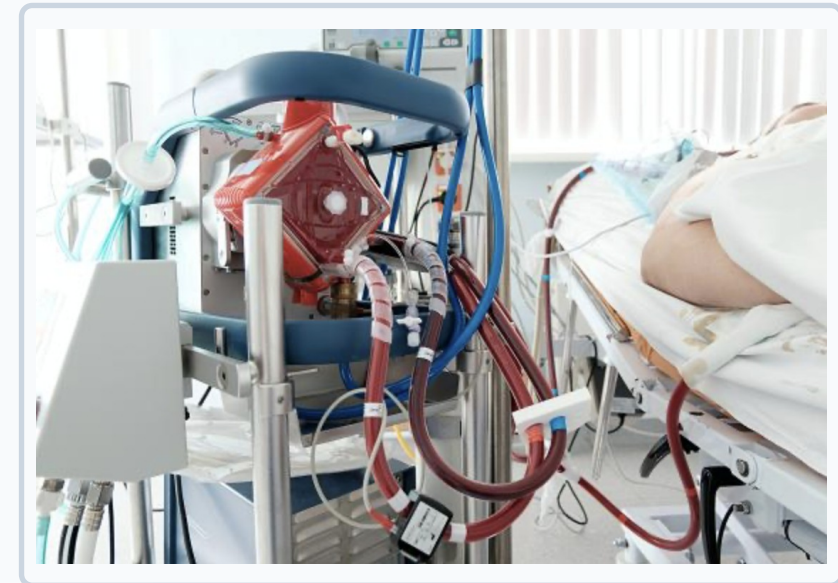
## Organ Support Strategies

- **Avoid over-resuscitation** to prevent fluid overload and edema.
- **Implement lung-protective ventilation** with low tidal volumes and controlled pressures.
- **Utilize CRRT** for acute kidney injury requiring renal support.
- **Consider ECMO** in refractory respiratory or cardiac failure cases.



## Source Control

- **Promptly drain abscesses** to reduce infectious burden.
- **Remove infected devices** to eliminate infection source.
- **Debride necrotic tissue** to prevent ongoing inflammation.
- **Engage early surgical consultation** for complex infections.



## History

# History Overview



## Evolution of Sepsis Care

Sepsis treatment evolved from medieval humoral theories and spiritual practices to antiseptic techniques introduced by Lister, followed by the antibiotic revolution, culminating in sophisticated ICU management strategies.



## Key Lesson Learned

Progress against sepsis has been driven by deepening understanding of infection mechanisms and the crucial importance of early and appropriate intervention to reduce mortality.



## Foundation for Modern Care

This historical journey set the stage for today's evidence-based protocols, integrating prevention, early detection, and individualized treatment to improve patient outcomes worldwide.

## History

# How Were Infections Treated in the Middle Ages?

**? No germ theory or understanding of pathogens** — disease causes were unknown.  
No knowledge of bacteria or viruses — infection etiology was mysterious and unexplained.

**📖 Treatments based on tradition, religion, and ancient theories** — emphasizing spiritual and philosophical approaches rather than scientific methods.

Medical interventions were largely empirical and varied widely based on local customs and beliefs.

**✝ Religion and spiritual healing** — Disease was interpreted as a punishment from God.  
People sought healing through prayer, confession, pilgrimages, and protective charms.

**🌿 Herbal & natural remedies** — Medieval medicine commonly used garlic, onion, and honey.  
Herbal poultices were applied to wounds, and willow bark was used for pain and fever relief.



## History

# Humoral Theory (The Core Framework)



### Balance of Four Humors

Health was believed to depend on the equilibrium of four humors: **Blood**, **Phlegm**, **Black bile**, and **Yellow bile**. Each humor was associated with specific qualities and bodily functions, and maintaining their balance was considered essential for health.



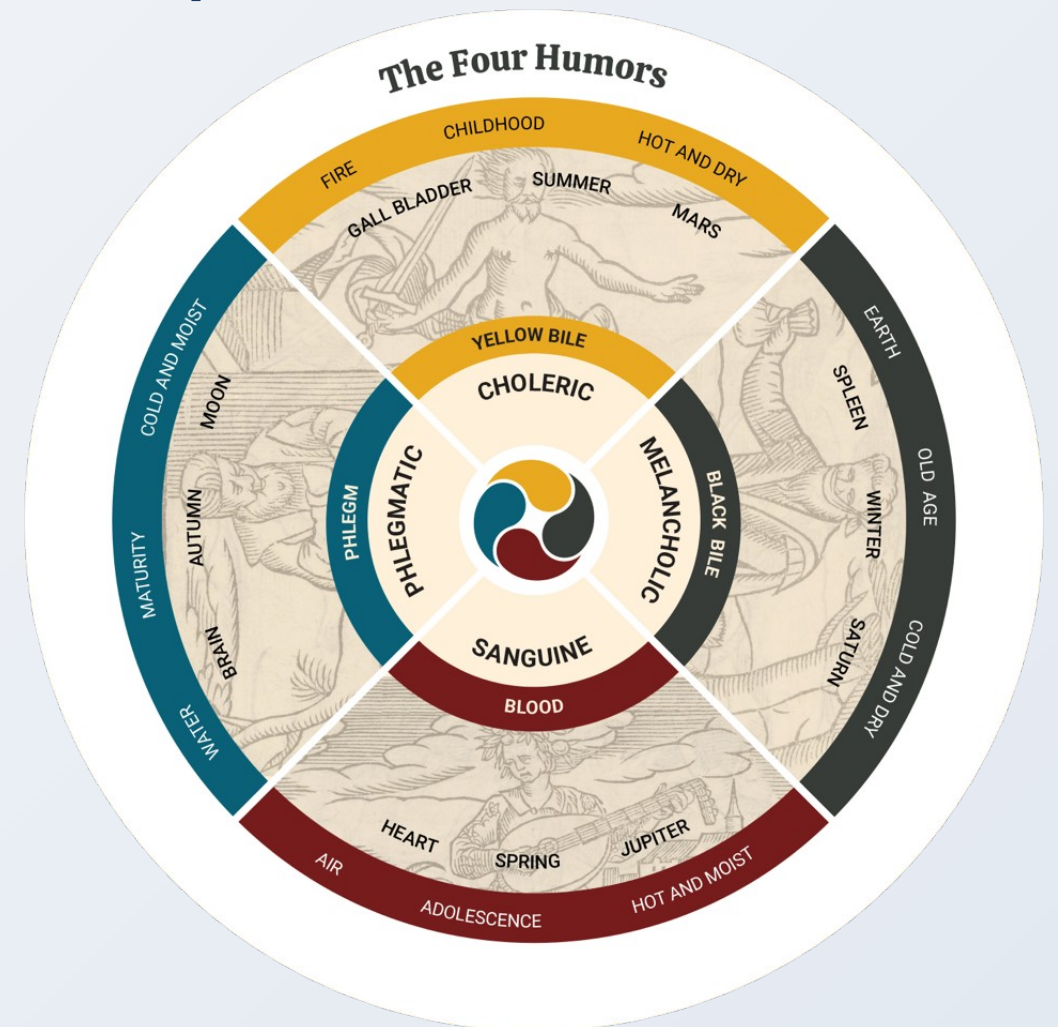
### Infection as Imbalance

Disease and infection were thought to arise from an **imbalance or excess** of one or more humors, disrupting the body's harmony and causing symptoms. This imbalance was believed to be the root cause of all illness.



### Treatment Focused on Balance

Therapies aimed to **restore humor balance** through methods such as bloodletting, purging, and diet changes, targeting the perceived imbalance rather than any microbial cause.





## History

# Bloodletting & 'Balancing the Body'

 **Bloodletting involved cutting veins or applying leeches** to remove supposed excess blood humor.

This practice was based on the belief that removing blood would restore balance to the four humors.

 **Induced vomiting or diarrhea** were used to purge bile humors believed to cause illness. The goal was to remove 'excess' humor and restore the body's physiologic equilibrium.

 **The goal was to remove 'excess' humor** and restore the body's physiologic equilibrium according to humoral theory. These practices often worsened illness by depleting blood volume and weakening patients.

 **Compounding infection risks** — Bloodletting often worsened illness by depleting blood volume. These practices frequently caused physical harm and delayed effective treatment.



## History

# Herbal & Natural Remedies



## Common Treatments

Medieval medicine commonly used garlic, onion, and honey, now known to have antibacterial properties. Herbal poultices were applied to wounds, and willow bark was used for pain and fever relief, acting as a precursor to aspirin.



## Monastic Preservation

Monasteries were centers of botanical knowledge where monks acted as primary healthcare providers. They preserved herbal traditions and applied these natural remedies systematically in care.



## Real Benefits

Some herbal treatments had genuine mild antimicrobial or anti-inflammatory effects, providing limited but meaningful therapeutic benefits despite the era's overall lack of germ theory.



## History

# Religion & Spiritual Healing



### Divine Punishment Concept

Disease was interpreted as a punishment from God, reflecting moral failings or sin. Illness required spiritual remedies to restore divine favor and health.



### Common Spiritual Responses

People sought healing through prayer, confession, pilgrimages to holy sites, and wearing protective charms or amulets believed to ward off evil influences.



### No Biological Impact

Despite widespread use, these spiritual practices had no physiological effect on infections or sepsis, as the true microbial causes were unknown.



## History

# Superstition & Extreme Practices

**⚡ Fear-driven practices during outbreaks** led to desperate and often harmful behaviors driven by panic and lack of medical knowledge. People reacted to disease with extreme measures rather than understanding the true causes of infection.

**✝ Flagellation**, or self-punishment by whipping, was performed to seek divine forgiveness during plague epidemics. This reflected the belief that disease was a punishment for sin, causing physical harm without medical benefit.

**🕊 Spiritual cleansing rituals** aimed to expel evil spirits or divine wrath were common. These included prayers, amulets, and symbolic acts with no biological effect on infection.

**⚠ Harmful effects** — These practices reinforced cultural and religious beliefs rather than providing medical benefit.



## History

# Miasma Theory ('Bad Air')



## Disease Spread by Foul Air

Medieval belief held that diseases were caused by miasma — harmful vapors from decaying organic matter, swamps, and filth. This 'bad air' was thought to be the primary source of contagion and illness.



## Prevention Strategies

People burned herbs and incense to purify the air, carried aromatic flowers or spices, and wore plague doctor masks filled with herbs to filter out the miasma, hoping to avoid infection.



## Lack of True Infection Control

Despite widespread adoption of miasma-based practices, these methods had no biological effect on pathogens, resulting in ineffective disease prevention and continued epidemics.



## History

# Surgery Without Sterility



### No Germ Awareness

Surgeons had no knowledge of germs or cleanliness. They performed operations using bare, unwashed hands and reused unsterilized instruments, unknowingly spreading infections.



### Common Surgical Interventions

Typical procedures included amputation of infected limbs and cauterization—burning tissue to close wounds and try to stop infection spread—often causing severe pain and tissue damage.



### High Infection and Mortality

Due to unsterile conditions, surgical patients frequently developed systemic infections, leading to very high mortality rates following procedures.



## History

# The Black Death Experience



## Black Death Pandemic

**1347-1351:** The Black Death killed an estimated 30-60% of infected individuals across Europe, making it one of the deadliest pandemics in human history.

The plague swept through Europe in just 4 years, decimating entire communities and causing massive social and economic disruption.



## Treatments Attempted

### Common interventions included:

Lancing of buboes to drain swollen lymph nodes

Use of herbal mixtures and poultices

Bloodletting to "balance humors"

Prayer and religious rituals



## High Mortality Rates

**30-60% mortality** despite numerous treatment attempts, underscoring the failure of medieval medicine to control systemic infectious diseases. The high death rate was due to lack of understanding of the true cause - *Yersinia pestis* bacterium.



## History

# What Actually Helped (By Accident)



**Isolation of sick individuals** through early quarantine measures inadvertently reduced transmission of contagious diseases. Basic isolation practices helped contain infections even without understanding of germ theory.



**Basic wound care** such as cleaning and dressing wounds provided some protection against infection. Even without knowledge of microbes, proper wound care reduced infection risk.



**Certain herbs like garlic, honey, and willow bark** contained antimicrobial or anti-inflammatory properties. These natural remedies helped limit infection and reduce symptoms.



**Monastic hygiene practices** maintained cleaner environments, reducing infection spread. Religious communities preserved health through better sanitation.



## History

# The Birth of Antisepsis: Joseph Lister



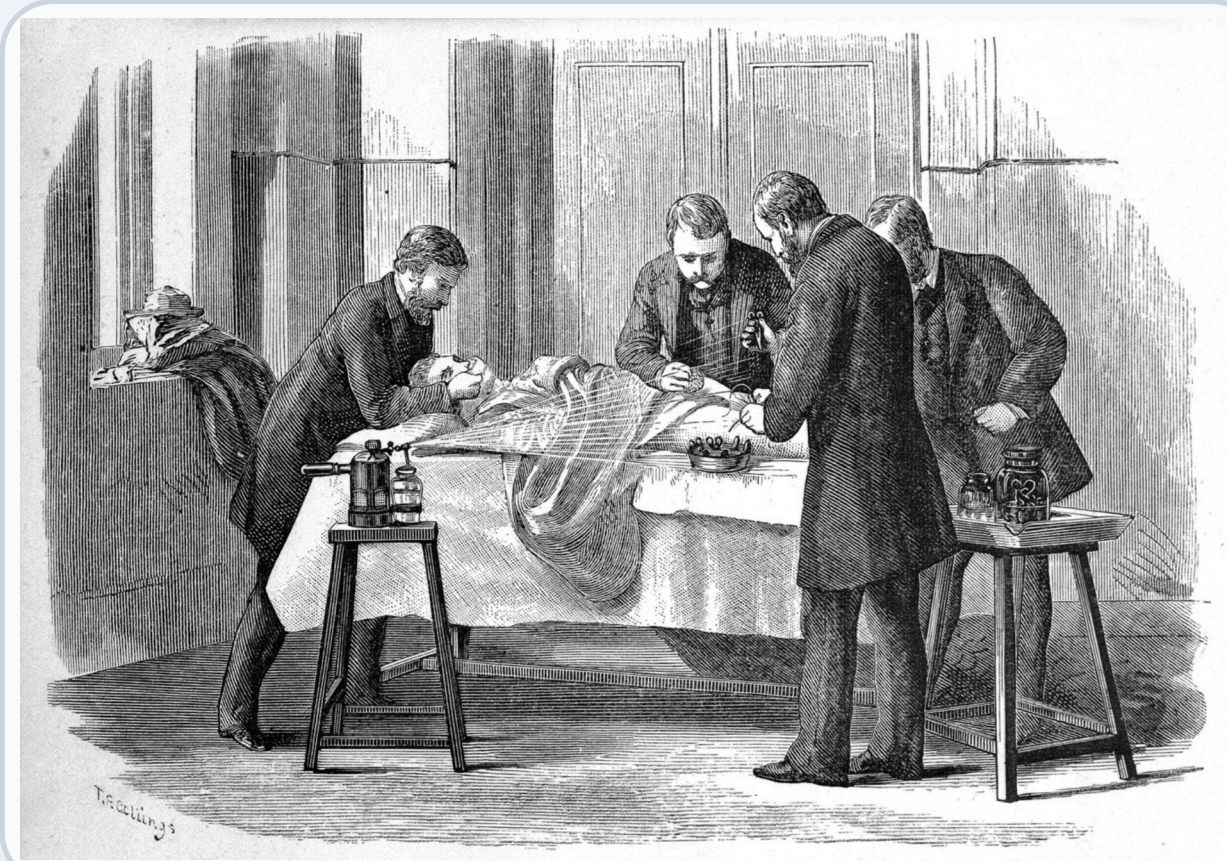
### Key Facts on Antiseptic Surgery

- ✓ Introduced antiseptic techniques in the 1860s
- ✓ Used carbolic acid (phenol), called 'Lister's solution'
- ✓ Applied antiseptic to wounds, instruments, and surgical areas
- ✓ Dramatically lowered rates of surgical infections
- ✓ Marked shift from theoretical to practical infection control



### Teaching Point: Infection Prevention Milestone

- ✓ First time medicine actively prevented infection, reducing sepsis
- ✓ Built on Pasteur's germ theory and Semmelweis's hand hygiene findings
- ✓ Transformed surgical safety and patient outcomes
- ✓ Laid foundation for modern sterile surgical practices



## Overview

# Antisepsis → Asepsis



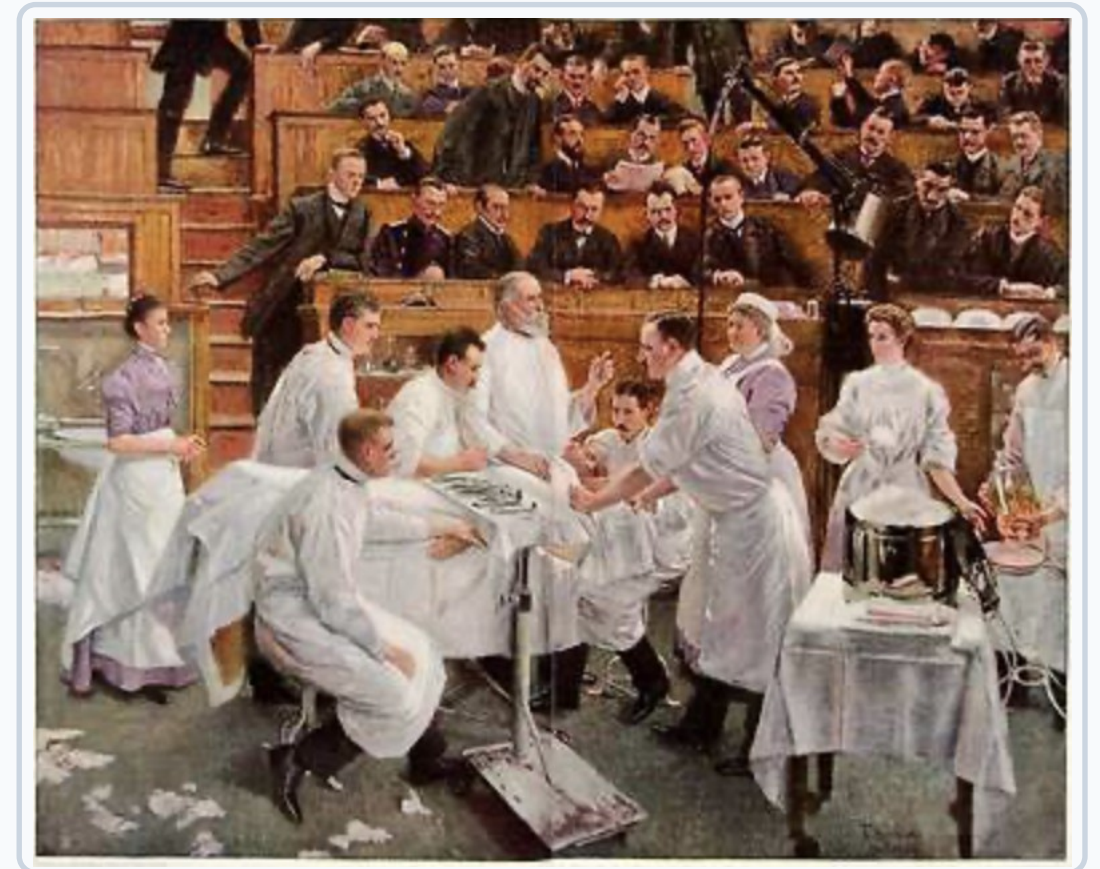
## Evolution of Sterile Technique

- **Shifted focus** from killing germs after contamination to preventing exposure.
- **Development of sterile** surgical instruments and sterilization methods.
- **Introduction of surgical gloves** to protect patients and staff.
- **Establishment of hand hygiene** as a fundamental practice.
- **Significant reduction** in hospital-acquired infections.



## Nursing Impact

- **Hand hygiene** became one of the most powerful medical interventions.
- **Nurses lead enforcement** of aseptic protocols in clinical settings.
- **Nursing vigilance** ensures adherence to sterile technique.
- **Nurses bridge** germ theory and everyday clinical practice.
- **Ongoing nursing education** sustains high asepsis standards.



## History

# Germ Theory Changes Everything



### Louis Pasteur's Breakthrough

Demonstrated that microorganisms cause disease, overturning prevailing miasma and humoral theories and establishing germ theory as the foundation of infectious disease science.



### Shift to Evidence-Based Medicine

Understanding pathogens enabled targeted treatments, shifting medicine from empirical approaches to evidence-based interventions.



### Robert Koch's Contributions

Linked specific bacteria to specific diseases through Koch's Postulates, establishing a scientific framework for identifying causative pathogens.



## History

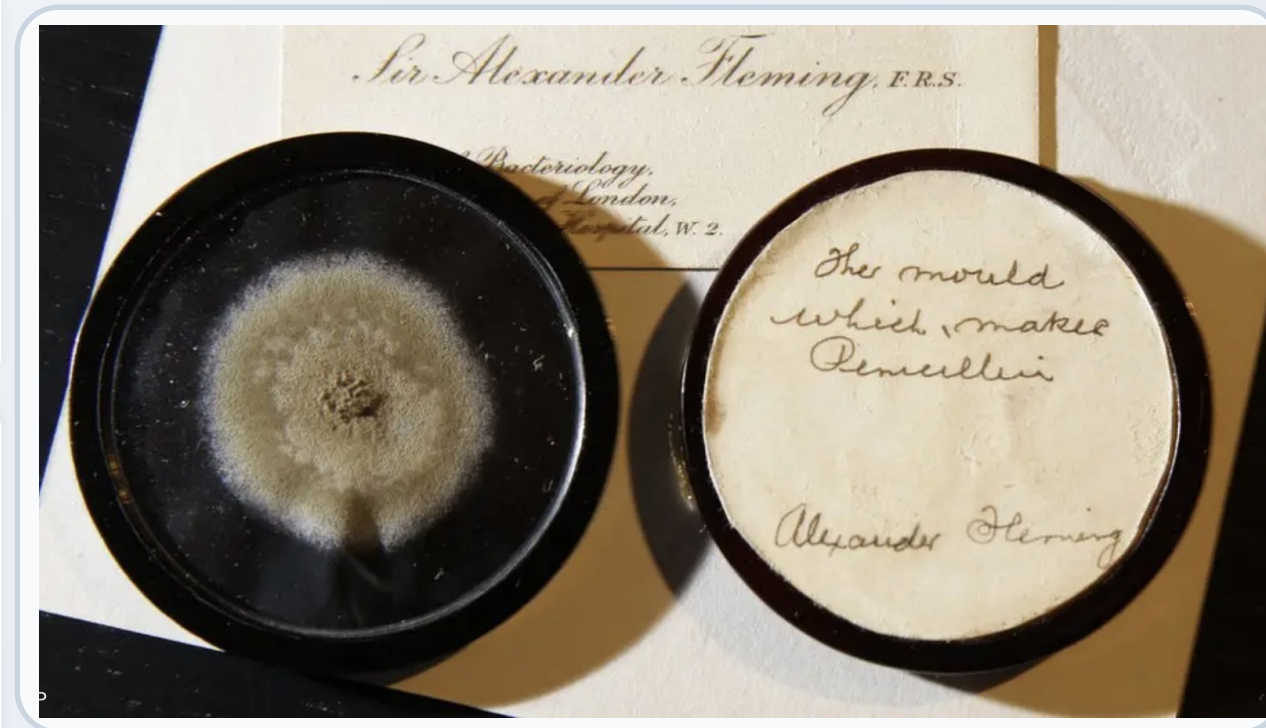
# Antibiotic Revolution Begins: Alexander Fleming

### Key Facts

- ✓ Discovered penicillin in 1928 by accidental mold contamination of bacterial cultures
- ✓ Mass production achieved during World War II to meet wartime medical needs
- ✓ First effective systemic antibiotic treatment for bacterial infections
- ✓ Significant mortality reduction from pneumonia, wound infections, and sepsis

### Historical Impact

- “ “For the first time, clinicians could treat the cause, not just the symptoms.”
- i Pre-antibiotic mortality for *Staphylococcus aureus* septicemia reached up to 82%
- i Penicillin shifted medicine from symptomatic care to targeted infection control
- i This breakthrough laid the foundation for modern antimicrobial therapy



## History

# Expansion of Antibiotics (1940s-1960s)



### Rapid Antibiotic Development

Multiple new antibiotic classes emerged quickly during this period, including **streptomycin, tetracyclines, and cephalosporins**, greatly expanding treatment options for bacterial infections.

The introduction of **broad-spectrum antibiotics** allowed clinicians to empirically treat infections without knowing the exact pathogen, improving early intervention.



### Early & Empiric Treatment

Medical practice shifted toward administering antibiotics **as early as possible** and using broad coverage strategies—embodied in the "hit early, hit broadly" philosophy.

**Sepsis mortality significantly reduced** during this era as early and broad antibiotic use became standard care, transforming sepsis outcomes worldwide.



## History

# Pre-ICU Era (1960s-1970s): 'Support What You Can'



**Limited Monitoring:** Patients lacked continuous hemodynamic monitoring; vital signs were checked intermittently, preventing real-time assessment of cardiovascular status.



**Unstandardized Fluid Use:** Intravenous fluids were administered, but no standardized resuscitation protocols existed, leading to inconsistent volume management.



**Inconsistent Vasopressor Use:** Vasopressors were available but applied inconsistently without clear blood pressure targets or guidelines, limiting effectiveness.



**Delayed Antibiotic Therapy:** Antibiotics became more common but were often initiated late or targeted poorly due to limited diagnostic capabilities.



**Basic Oxygen Support:** Oxygen therapy was used, but mechanical ventilation and advanced respiratory support were rare and rudimentary.



**Minimal Organ Support:** There was no systematic approach to managing multi-organ failure; treatments focused on isolated symptoms rather than comprehensive support.



## History

# ICU Birth-1990s



## Focus on Macro-Hemodynamics

Sepsis resuscitation targeted blood pressure, cardiac output, and oxygen delivery to vital organs as primary goals. Stabilizing these parameters aimed to prevent organ failure and improve survival in critically ill patients.

**i** Goal: Prevent organ failure through hemodynamic stabilization



## Anti-Inflammatory Medication Trials

High-dose corticosteroids, anti-TNF agents, and anti-endotoxin therapies were extensively studied to reduce sepsis inflammation. Despite initial hope, these treatments largely failed to improve mortality.

**⚠** Key finding: Anti-inflammatory therapies showed limited benefit



## 'Supranormal' Oxygen Delivery Strategies

Trials tested pushing cardiac output and oxygen delivery above normal physiological levels to enhance tissue oxygenation. These aggressive approaches did not consistently improve outcomes.

**📉** Result: No survival benefit from supranormal targets

## History

# The Game Changer: Early Goal-Directed Therapy (2001)



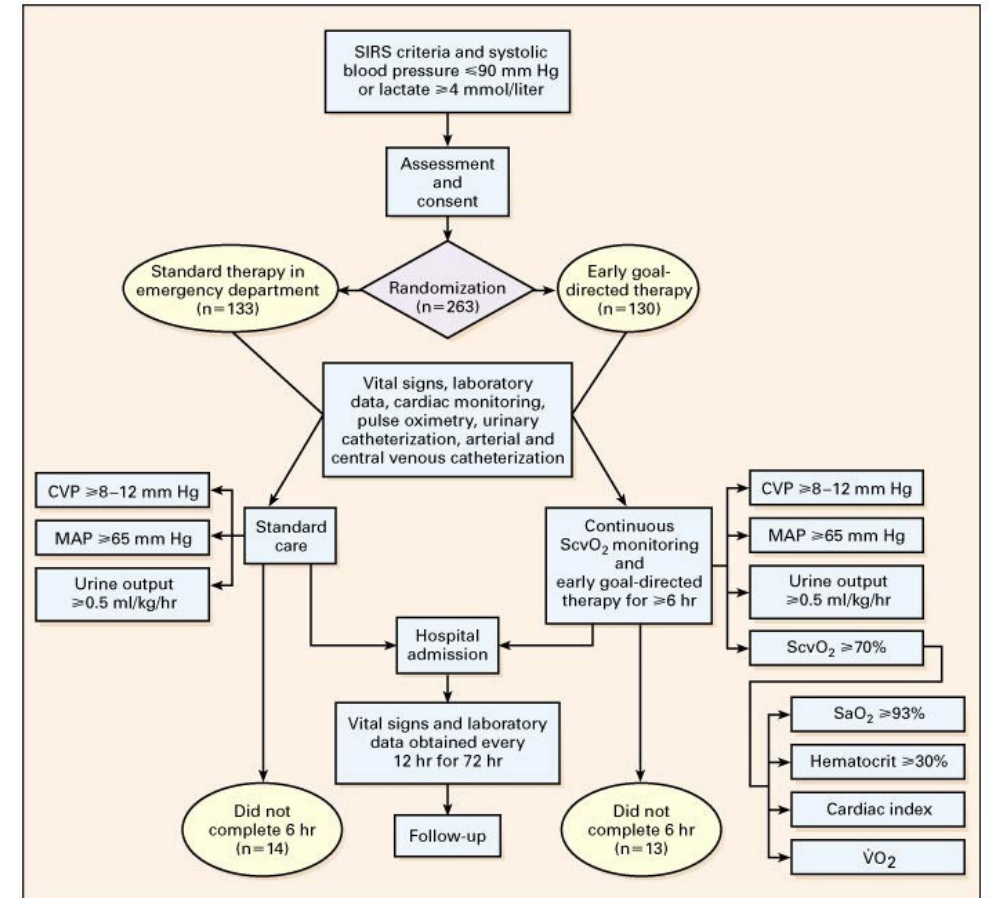
### Key Facts of EGDT Trial

- ✓ **Landmark trial** by Emanuel Rivers in 2001 revolutionized sepsis treatment
- 🕒 **First 6 hours** of resuscitation post-diagnosis - critical time window
- ✓ **Protocolized care** monitoring CVP, MAP, and ScvO<sub>2</sub> levels
- 💧 **Interventions:** aggressive fluid resuscitation, vasopressors, blood transfusions, inotropes
- ✂️ **Mortality reduction: 33% vs 49%** 28-day mortality compared to usual care



### Teaching Point: Sepsis as a Time-Sensitive Emergency

- ✓ Sepsis recognized as urgent like **acute myocardial infarction, stroke, and trauma**
- ✓ **Early intervention** within the first 6 hours is critical for survival
- ✓ Prior to EGDT, severe sepsis and septic shock mortality ranged between **40-50%**
- ✓ EGDT established the foundation for **rapid, protocol-driven sepsis management**
- ✓ Shifted clinical focus to **early goal-directed resuscitation** to improve outcomes



## History

# Surviving Sepsis Campaign (SSC) Begins



### Global Collaboration Launch

Initiated in the early 2000s, the SSC was co-founded by SCCM and ESICM with involvement from 11 international societies to unify efforts against sepsis.



### First Guidelines Published

Around 2004, SSC released the first comprehensive international guidelines offering consensus recommendations for managing severe sepsis and septic shock.



### Standardizing Care Worldwide

The campaign's goal was to reduce treatment variability and mortality by promoting consistent, evidence-based sepsis management practices globally.



### Turning Evidence Into Practice

SSC operationalized research findings into practical protocols, empowering frontline clinicians to apply best practices at the bedside effectively.

## Overview

# The Era of Sepsis Bundles



### Core Bundle Components Introduced

- **Lactate measurement** to assess tissue hypoxia and guide resuscitation.
- **Blood cultures** obtained before antibiotics to identify pathogens.
- **Early administration** of broad-spectrum antibiotics to combat infection quickly.
- **IV fluids** given promptly to treat hypoperfusion and support circulation.
- Bundles evolved from 3-hour to 6-hour, culminating in the **Hour-1 bundle**.



### Key Paradigm Shifts and Nursing Impact

- Shift from **individual clinical decisions** to standardized, protocolized team care.
- **Nurses as central figures** in early detection and rapid execution of sepsis bundles.
- Protocol-driven approach improved **consistency and timeliness** of interventions.
- Empowered nursing roles enhanced **interdisciplinary communication** and patient outcomes.



## History

# The 'Deconstruction' of EGDT (2014-2015 Trials)



### Major Trials

ProCESS (US, 2014), ARISE (Australia/New Zealand, 2014), and ProMISe (UK, 2015) trials each compared strict Early Goal-Directed Therapy (EGDT) protocols to contemporary usual care in severe sepsis and septic shock.



### Trial Outcomes

All three trials showed no significant difference in 90-day all-cause mortality between strict EGDT and usual care, challenging the added benefit of rigid protocolized management.



### Changes in Practice

Following these results, routine use of central venous pressure (CVP) targets and mandatory central venous oxygen saturation (ScvO2) monitoring decreased, and transfusion triggers became less aggressive.



### Key Insight

Usual care had already incorporated EGDT principles such as early antibiotics and fluid resuscitation, so standard practice evolved to align with the protocol, reducing the need for strict protocol enforcement.

## History

# Fail Paradigm: Anti-Inflammation Gone Too Far



## High-Dose Steroids (1970s-80s)

● Failed

Use of high-dose steroids aimed to reduce inflammation but led to increased mortality and infection rates; currently replaced by low-dose hydrocortisone reserved for refractory septic shock cases only.



## Anti-Cytokine Therapies (1990s)

● Failed

Extensive trials of anti-TNF agents and IL-1 blockers sought to curb excessive inflammation, but multiple randomized controlled trials failed to show survival benefits.



## Key Takeaway

Sepsis is characterized by immune dysregulation, not just excessive inflammation. Over-suppressing the immune system can be as dangerous as failing to control infection.



## History

# Failed Paradigm: Normalizing Numbers ≠ Saving Lives

## 01 Tight Glycemic Control

The NICE-SUGAR Trial revealed increased mortality due to hypoglycemia when aggressively targeting normoglycemia in sepsis patients

Current guidelines recommend a safer glucose range of 140-180 mg/dL to avoid harm

Over-aggressive glucose control can be as dangerous as hyperglycemia

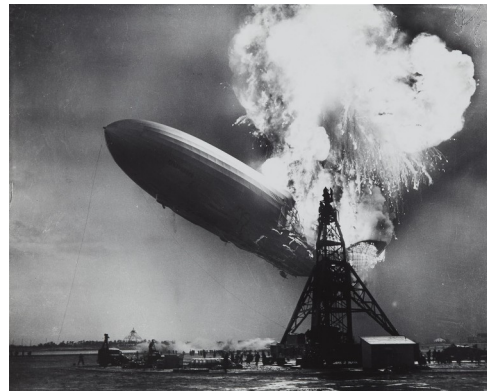


## 02 Supranormal Oxygen Delivery

Strategies aimed at pushing cardiac output and oxygen delivery above normal thresholds showed no survival benefit

May have caused additional harm from hyperoxia and increased cardiac workload

Supranormal targets did not improve tissue oxygenation in septic patients



## 03 Routine Bicarbonate for Acidosis

Use of bicarbonate to correct lactic acidosis did not improve patient outcomes

Risked physiological complications from pH overcorrection

Normalizing lab values alone is insufficient for sepsis management



## History

# Failed Paradigms: Resuscitation Missteps

### **Hydroxyethyl Starch (HES)**

The CHEST Trial revealed that HES increased acute kidney injury and the need for dialysis in septic patients, leading to its near-complete abandonment in sepsis fluid resuscitation protocols. This highlighted the importance of careful fluid selection.

### **Dopamine as First-Line Vasopressor**

Dopamine use was linked to higher rates of arrhythmias without renal protection benefits, prompting a shift to norepinephrine as the preferred first-line vasopressor in septic shock. This change improved patient safety and outcomes.

### **Liberal, Unstructured Fluid Use**

Excessive fluid administration often caused fluid overload and worsened outcomes. Current practice emphasizes careful reassessment and early initiation of vasopressors to avoid harm from over-resuscitation.

### **Activated Protein C / Xigris**

**Initially approved** based on promising early trial results for severe sepsis **APPROVED**  
**PROWESS-SHOCK Trial** showed no mortality benefit and increased bleeding risks **FAILED**  
Drug was **withdrawn from the market** due to safety concerns and lack of efficacy

## Guidelines

# 2026 Surviving Sepsis Guidelines: Key Updates

01



## Resuscitation Targets

- ✓ Refined goals for MAP  $\geq$ 65 mmHg
- ✓ Dynamic lactate clearance targets
- ✓ Optimize perfusion while avoiding over-resuscitation

02



## Antibiotic Stewardship

- ✓ Rapid antibiotic de-escalation at 48-72 hours
- ✓ Based on clinical response and culture data
- ✓ Reduce resistance and adverse effects

03



## Biomarker Guidance

- ✓ Procalcitonin for antibiotic guidance
- ✓ Emerging biomarkers for precise management
- ✓ Guide initiation, duration, cessation of therapy

04



## Individualized Care





- ✓ Risk stratification tools for phenotyping
- ✓ Personalized resuscitation strategies
- ✓ Tailored to patient-specific factors

Guidelines Update




# Antibiotics Still Matter Most

 Delay in antibiotics remains strongly linked to increased mortality

## Timing Guidance

-  **Septic shock:** Antibiotics ASAP — goal  $\leq 1$  hour
-  **Sepsis without shock:** More flexibility ( $\leq$  ~3 hours if evaluation ongoing)
-  **Avoid unnecessary antibiotics** if infection suspicion is low
-  **De-escalate early** when culture data becomes available

## Nursing Impact

-  **Reduce delays:** prioritize IV access, blood cultures, and antibiotic administration
-  **Prompt reassessment** when culture results return
-  **Advocate for de-escalation** when appropriate

Treatment Protocol

# Fluids Are Still First — But Not Unlimited

## Initial Approach

- ~30 mL/kg **crystalloid** remains the common starting point, but frequent reassessment is now required.
- **Balanced crystalloids** are preferred over normal saline due to better acid-base balance.
- **Stop fluids** if pulmonary edema develops or perfusion does not improve.
- **Early fluid administration** aims to restore circulating volume and improve tissue perfusion.

## Nursing Monitoring

- Monitor **lung exam, urine output, and mental status** continuously.
- **Speak up** when the patient appears fluid overloaded — clinical judgment at the bedside is critical.
- Watch for signs of **fluid overload**: peripheral edema, pulmonary crackles, rising JVP.



## Key Takeaway

'One-size-fits-all fluids' is being abandoned. The shift is toward individualized, reassessment-driven fluid management that balances resuscitation with the risks of fluid overload.

## SSC 2026 Update

# Therapies That Are No Longer Recommended



## Therapies That Are No Longer Recommended

- ✘ **Routine vitamin C, thiamine, and metabolic "cocktails"** — No evidence of mortality benefit
- ✘ **Routine bicarbonate for lactic acidosis** — Does not improve outcomes
- ✘ **Overuse of fluids after initial resuscitation phase** — Risk of fluid overload
- ✘ **Routine aggressive glucose control** — Risk of hypoglycemia



## New Emphasis

- ✓ Avoid low-value or potentially harmful interventions
- ✓ Focus clinical effort and resources on early, high-impact care
- ✓ Prioritize proven mortality-reducing interventions



## Future

# The Future of Sepsis Care



### AI & Predictive Analytics

- ✓ EHR-integrated AI models analyze real-time patient data
- ✓ Predict sepsis onset hours before clinical signs
- ✓ Enable earlier intervention and improved survival



### Immunotherapy

- ✓ Precision biologics modulate immune response
- ✓ Target hyperinflammation & immune suppression
- ✓ Reduce organ damage and mortality



### Microbiome Research

- ✓ Modulate gut microbiome with probiotics
- ✓ Restore intestinal barrier function
- ✓ Reduce bacterial translocation



### Point-of-Care Diagnostics

- ✓ Rapid bedside pathogen identification
- ✓ Real-time antimicrobial susceptibility
- ✓ Faster targeted antibiotic therapy



### Personalized Medicine

- ✓ Phenotyping based on genetic profiles
- ✓ Individualized treatment plans
- ✓ Tailored to specific sepsis subtypes

# Thank You

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## Sepsis

The Past, The Present, and The Future



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