Sepsis and Septic Shock

Sepsis and Septic Shock Definitions

- **Sepsis**
- **Septicemia**
- **SIRS**
- **Severe Sepsis**
- **Septic Shock**
- **MODS**
- **ARDS**
- **CARS**

Shock

Most common cause of death

- **Human SMICU**
- **Large animal NICU**

Fatality rate

- **Human medicine 20-80%**
- **NBC NICU - 137 cases**
  - **Sepsis without shock - 17%**
  - **Septic Shock - 90%**

Fatalities

- **Refractory hypotension**
- **ARDS**
- **MODS**

Sepsis and Septic Shock Etiology

Infectious causes

- **Bacterial infections**
  - **Gram negative pathogens – 60%**
  - **Gram positive pathogens – 40%**
- **Viral pathogens**
- **Fungal pathogens**

Bacteremia detected in neonate

- **Sepsis < 30%**
- **Septic Shock > 70%**

Localized infections

May never isolate causative agent

Noninfectious causes

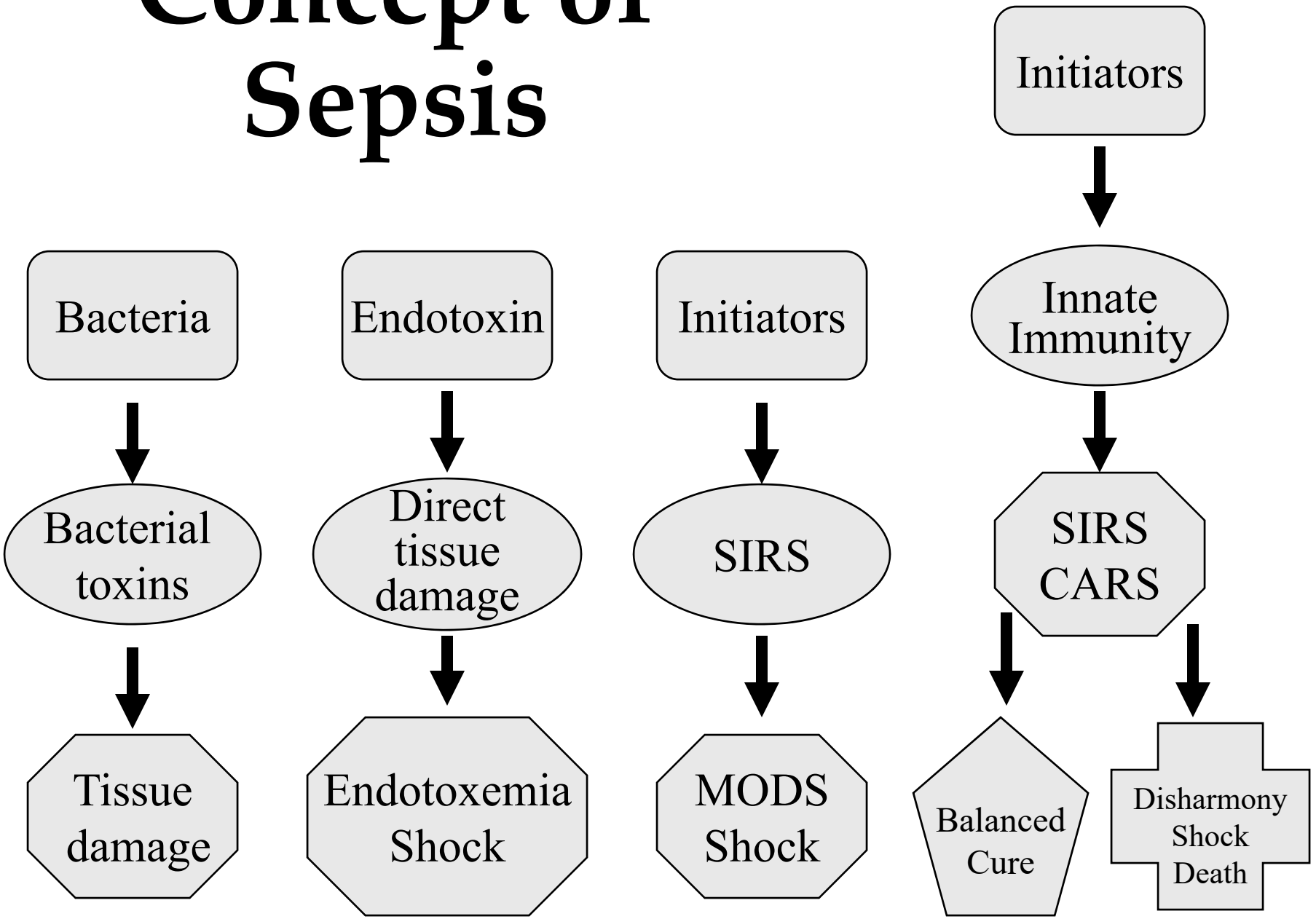
Septic Shock Pathogenesis

Septic shock

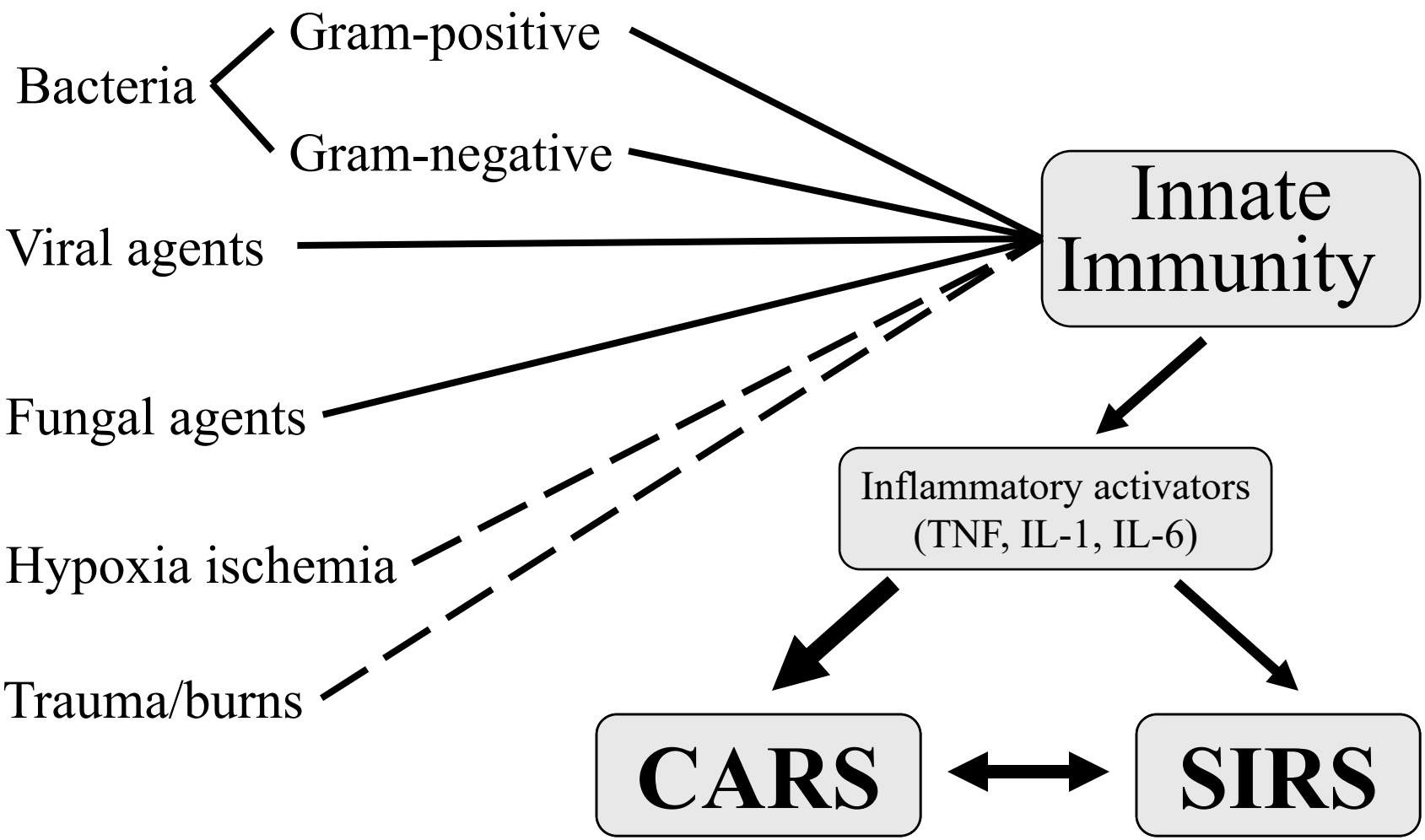
Inflammatory response (SIRS)

Immunosuppression (CARS)

Concept of Sepsis



Initiation of Inflammatory Reactions



Initiators of mediator response

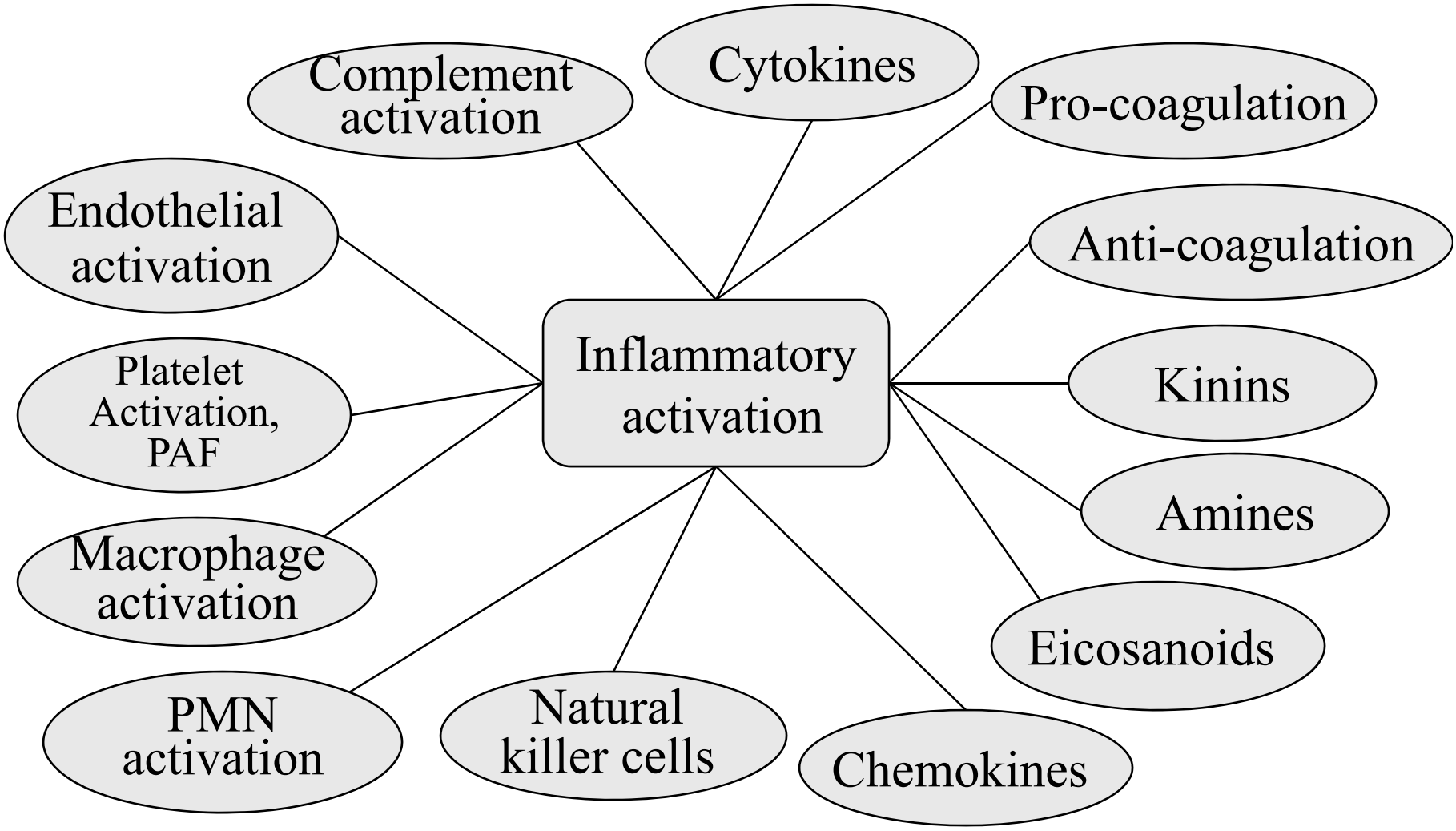
Gram negative pathogens

- **Endotoxin**
- **Formyl peptides**
- **Exotoxins**
- **Proteases**

Gram positive pathogens

- **Exotoxins**
- **Enterotoxins**
- **Hemolysins**
- **Peptidoglycans**
- **Lipoteichoic acid**

Inflammatory Cascade



Septic Shock

Pathogenesis - Cardiovascular Effects

- **Heart rate increases**
- **Cardiac output increases**
- **Systemic vascular resistance low**
  - **Arteriolar tone is decreases - hypotension**
  - **Venus tone decreased - venous pooling**
- **Pulmonary vascular resistance is high**
  - **Right-to-left shunt**
- **Despite increase cardiac output**
  - **Tissue hypoperfusion - malperfusion**
  - **Increased lactate**
  - **Decreased oxygen utilization**

Septic Shock

Pathogenesis - Cardiovascular Effects

- **Decreased sensitivity to catecholamines**
  - **Circulating vasodilator substances**
  - **Adrenergic receptor down-regulation**
- **Loss of microvascular autoregulatory mechanisms**
  - **Microvascular damage**
- **Distributive shock**
  - **Maldistribution of blood flow**
  - **Dilation of most vascular beds**
  - **Constriction of some**

Sepsis and Septic Shock Portals of Entry

- **GIt - Translocation**
- **Respiratory tract - Aspiration**
- **Placenta - *in utero***
- **Umbilicus**

Sepsis and Septic Shock Predisposing factors

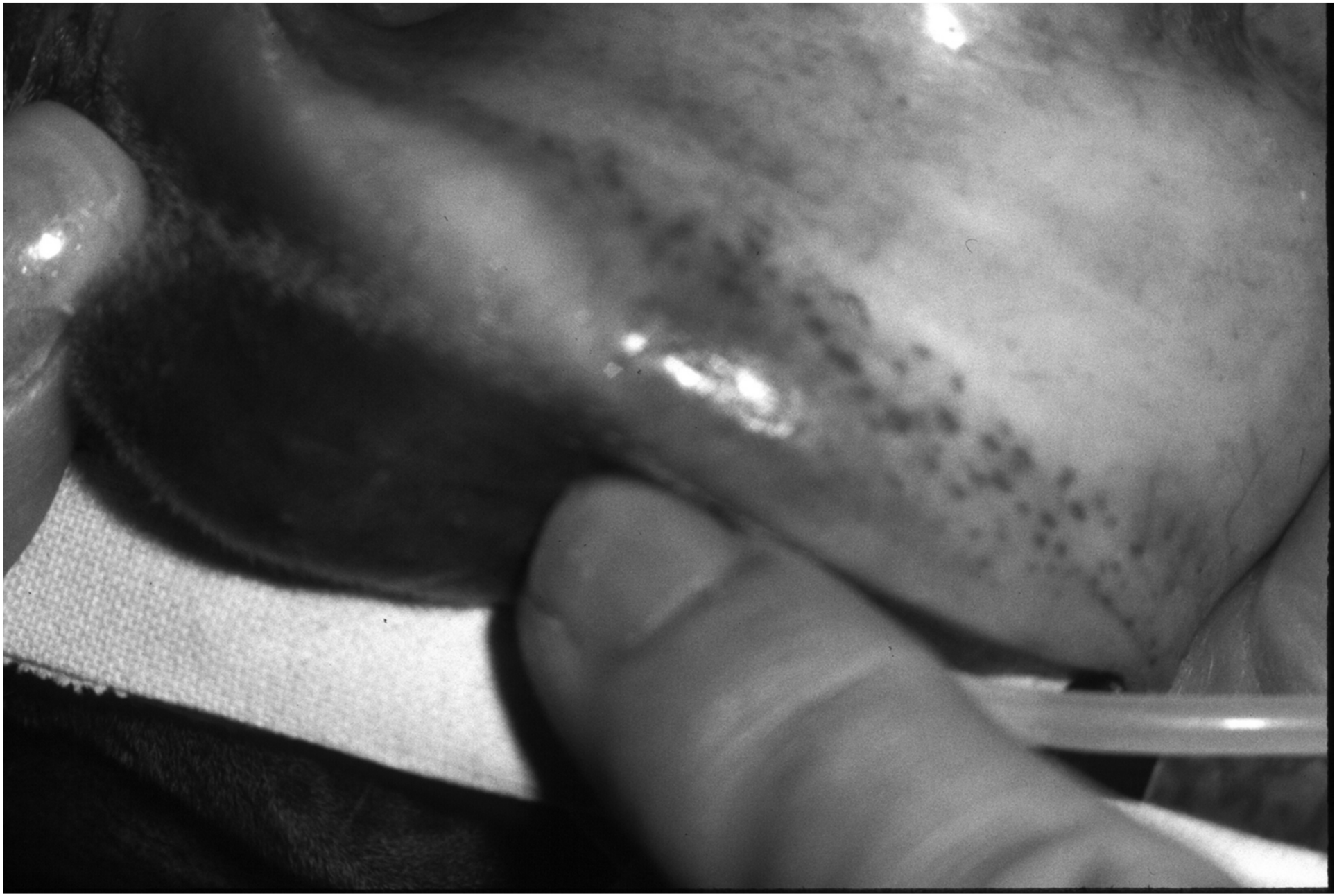
- **Placentitis – may be protective**
- **Prematurity**
- **Hypoxic-Ischemic disease**
- **Hypothermia**
- **Failure of Passive Transfer**
- **Stress**
- **Poor nutrition**
- **Poor husbandry**

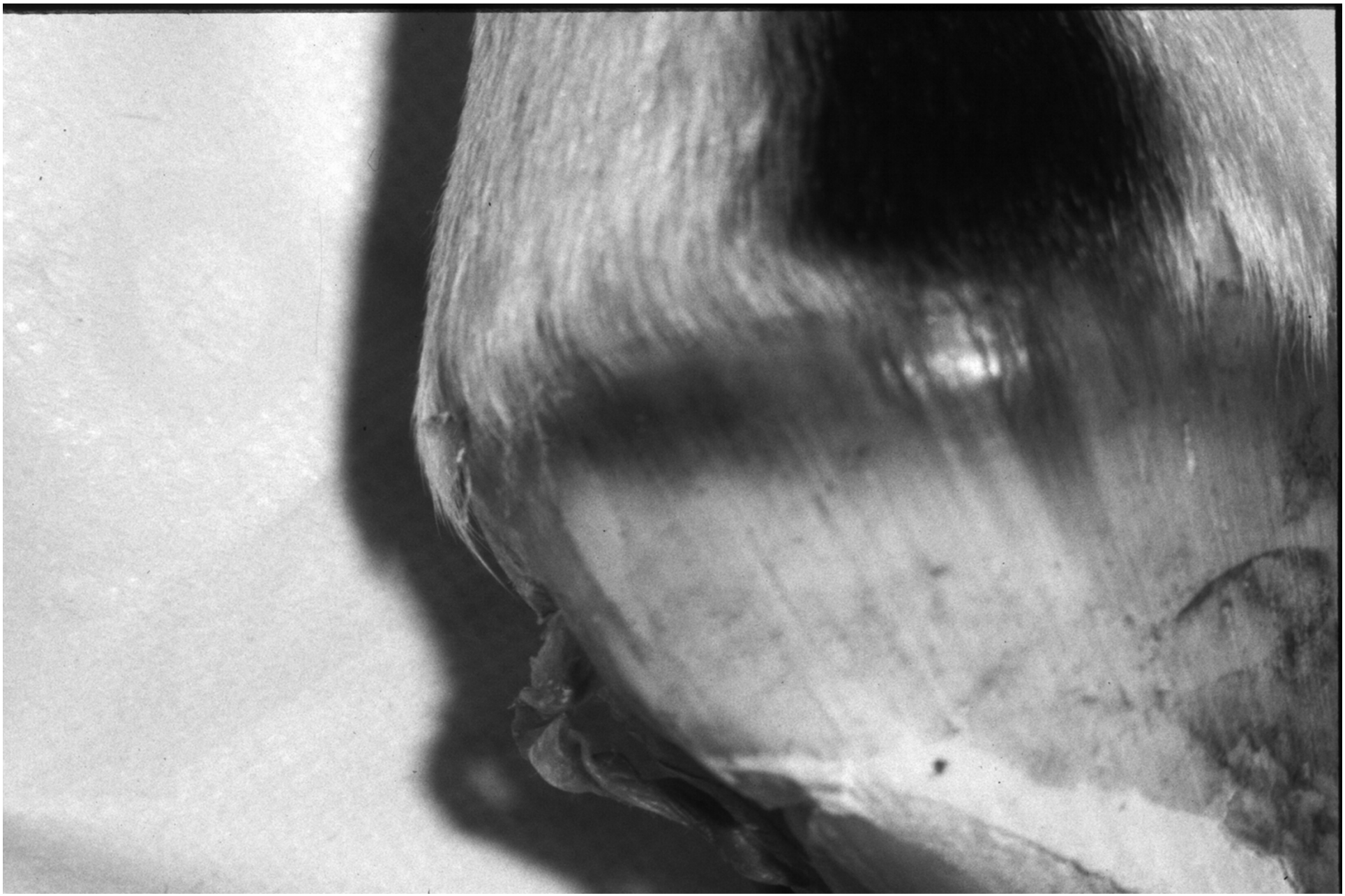
Sepsis and Septic Shock Localized Infections

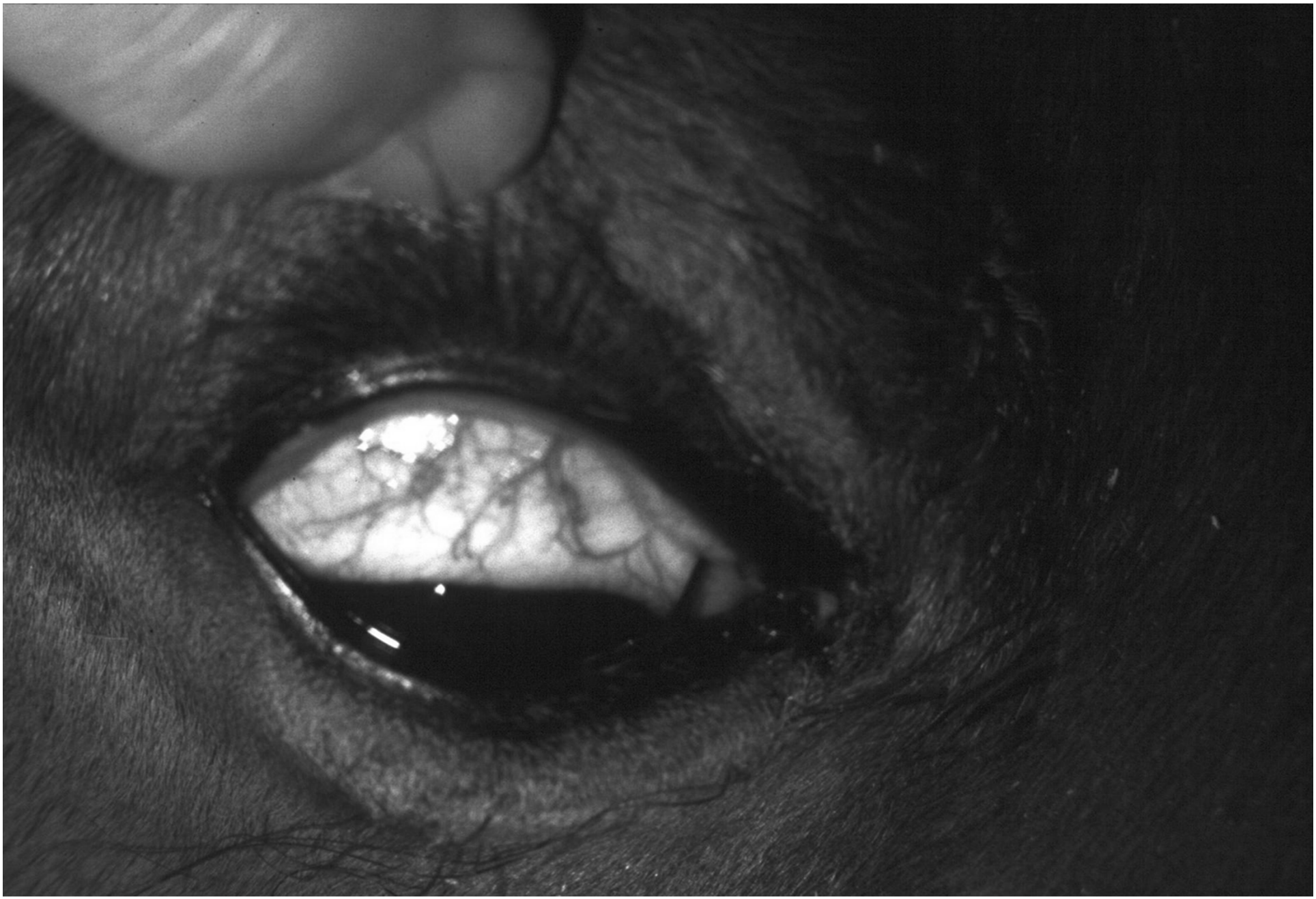
- **Pneumonia**
- **Enteritis**
- **Arthritis**
- **Osteomyelitis**
- **Meningitis**
- **Omphalitis**
- **Uveitis**

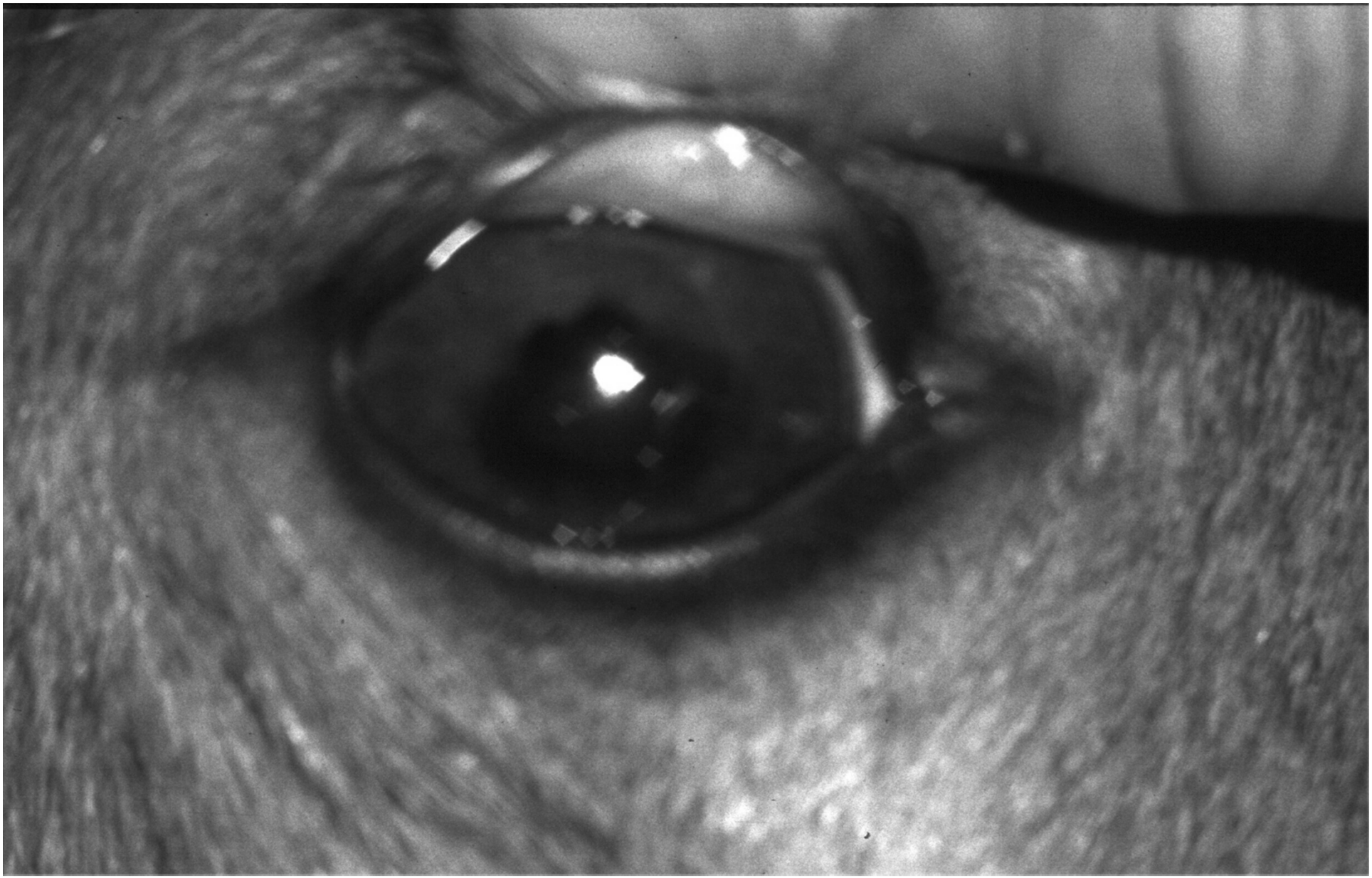
Sepsis and Septic Shock
Signs of Sepsis

- **Fever/hypothermia**
- **Loss of suckle, lethargy, weakness**
- **Tachycardia, tachypnea**
- **Injection, Icterus – oral, scleral**
- **Petechia - oral, scleral, aural**
- **Hyperemic coronary bands**
- **Linear dermal necrosis**
- **Increased/decreased CRT**
- **Shock**









Systemic Inflammatory Response Syndrome

SIRS

- **Over activation of the inflammatory response**
- **Constellation of signs**

  Fever or hypothermia

  Leukopnea

  Tachycardia, Tachypnea
- **Septic Shock**

SIRS Damage
MODS

GI tract

- **Breach of the intestinal barrier**
- **Translocation of bacteria**

Lungs

- **Acute Respiratory Distress Syndrome (ARDS)**

CNS

- **Breakdown blood brain barrier**
- **Inflammatory mediators**
- **Neurosteroid balance**

Renal failure

- **Decreased renal blood flow – vascular damage**
- **Acute tubular necrosis**

Recognition of SIRS

Release of inflammatory mediators

- **Fever**
- **Tachycardia**
- **Tachypnea**
- **Vasodilatation (warm skin)**
- **Mild controlled infection or systemic responses**

Recognition of SIRS/Septic Shock

Bounding pulses

- **Widen pulse pressure**
- **Increased cardiac output**
- **Increased systemic vascular resistance**

Hypoperfusion

- **Somnolence**
- **Fall asleep on feet**
- **Decreased urine output**

Before endothelial damage/dysfunction

- **Intervention is most dramatic**

Recognition of SIRS/Septic Shock

Shock progresses

Other signs of decreased perfusion

- **Cool extremities**

  Secondary to increase vasomotor tone

  Normal or high BP

  Cold progressing to ice cold legs

Recognition of SIRS/Septic Shock

- **Homeostatic mechanisms fail**
  - **Hypotension occurs**
  - **Pulse pressure narrows**
- **Legs cold**
- **Tachycardia**
- **Tachypnea**
- **Recumbent and nonresponsive**
- **Decreased cardiac output**
- **Hypoxia and metabolic acidosis**

Sepsis and Septic Shock Therapeutic interventions

Key interventions

- **Treat underlying infection**
- **Provide hemodynamic support**
- **Support during MODS and metabolic crisis**
- **Block proinflammatory mediators**

Sepsis and Septic Shock Therapeutic interventions

- **Treat underlying infection**
- **Anticipate bacteria infection**

  Antimicrobial therapy
- **Viral infections**

  Acyclovir
- **Hyperimmune plasma transfusion**

Sepsis and Septic Shock Antimicrobials

- **Penicillin**
- **Amikacin**
- **Cephalosporins**
- **Potentiated Penicillin**

  Beta-Lactamase Inhibitor
- **Imipenim**

Septic Shock
Hemodynamic support

Goals

- **Decrease blood lactate**
- **Correct perfusion**
- **Optimize cardiac output**
- **Increase systemic oxygen delivery**

Septic Shock

Hemodynamic support - Fluid Therapy

Crystalloids or colloids?

Crystalloid push

- **Bolus 10-20 ml/kg over 10-20 minutes**
  - **Mini-bolus therapy?**
- **Reassess patient after every push??**
  - **Blood pressure**
  - **Leg temperature**
  - **Peripheral pulse - arterial fill**
  - **Urine production**
  - **Mental status**

Transfusions

- **Plasma**
- **Whole blood**

Don't fluid overload

Septic Shock

Pressors/Inotropes

- **Therapeutic goal**
  - **Increase perfusion**
  - **Not “get good BP numbers”**
- **Inotropic effect most important**
  - **Increase cardiac output**
- **Pressor effect**
  - **Can negate inotropic effect**
  - **Hopefully will correct malperfusion**
- **Use a mix of inotropes and pressors**
- **Each patient - pharmacokinetic experiment**
- **Arrhythmias - tachycardia**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73
PULSE
97
DIASTOLIC
35
AUTO MANUAL
START
CUFF
POWER
OFF
ON

Septic Shock

Pressors/Inotropes

- **Dopamine**
- **Dobutamine**
- **Norepinephrine**
- **Epinephrine**
- **Vasopressin**

Septic Shock
Oxygen therapy

- **Optimize O2 availability**
- **Internasal O2 as soon as shock recognized**
  - **High flows 8-10 lpm**
  - **Utilize even if Pao2 appears adequate?**
- **Ventilate early**
  - **Decrease work of breathing**
    - **25% of O2 consumption to support respiration**
  - **Cardiovascular function improves**
  - **Make respiratory failure easier to manage**
  - **Modest PEEP**
    - **Decrease work of breathing, pulmonary resistance**
    - **Decrease hypoxia, need for high FIO2**
- **Improve gas exchange with inhaled NO**


VITALMIX
CLINIC

Sepsis and Septic Shock Nutritional Support

Sepsis is associated with

- **Hypermetabolism**
- **Catabolism**

Hyperglycemia

- **Catecholamine stimulated glycolysis**
- **Catecholamine mediated insulin resistance**
- **Insulin therapy**
  - **Strict glucose control**

Hypoglycemia

- **Often profound, refractory hypoglycemia**
- **Monitor blood glucose levels frequently**
- **IV glucose therapy**

Sepsis and Septic Shock Inhibiting Toxic Mediators

Antitoxins - Antiendotoxin

Anti-interleukin-1 receptor

Antibradykinin, AntiPAF

AntiTNF, TNF antagonists, NSAIDs

Steroids, Interleukin-1 antagonists

Bradykinin antagonists, Modulate NO

Antiadhesion factors

Large clinical trials in man

- **Not show improvement of survival**
- **Activated protein C (Xigris)**

SIRS/Septic Shock Inhibiting toxic mediators

Why the failures?

Interactions are very complex

Compensatory anti-inflammatory response syndrome (CARS)

Genetic variations in mediators

Timing – interactions

SIRS/Septic Shock
SIRS – CARS Balance

Effective therapy for septic shock await

- **Understanding the interactions and balance**
- **Understanding the timing**

FEAST Study

- **Fluid Expansion As Supportive Therapy**
- **Septic African Children**
- **3,000+ children**
- **Saline/albumin bolus vs. maintenance fluids**
- **Fluid bolus increased mortality by 50%**

FEAST Study

- **Do fluid boluses help in septic shock?**
  - **Observe hypotension**
  - **Assume poor perfusion is bad**
  - **Assume reversing with fluids good**
- **Questions**
  - **Do boluses actually increase organ perfusion?**
  - **How long? Does it last?**
  - **What cost?**
    - **Organ edema, gas exchange, acid base chages**

FEAST Study

- **Acidosis may be protective**

  Permissive/ therapeutic hypercapnia

- **Permissive/Theraputic hypoxemia**

- **Questions?**

  Is hypotension protective?

  Prevent increased exposure of organs to

  - **Inflammatory mediators**
  - **Other circulating toxins**

FEAST Study

- **Logical/pathophysiological fallacy**

  If patients with good perfusion live, transforming a patient with poor perfusion with fluids will make him live

  Analogy: Repainting the façade of a crumbling building will not prevent its collapse

- **If something appears obvious, not mean it's true**
- **It's not embracing new ideas that slows advances in medicine but letting go of ideas so entrenched that they have become axiomatic**

Treatment of Septic Shock

- **Early recognition**
- **Early administration of antibiotics**
- **Early reversal of the shock state**

  Aggressive fluid resuscitation

  Vasoactive medications

Recent evidence

- **Early recognition**
- **Early administration of antibiotics**

  Too early – distribution and connects not ideal

  Second dose effective – really “delayed” Rx
- **Early reversal of the shock state**

  Fluid overload = poor outcome

  FEAST Study – aggressive fluids = poor outcome

Recent evidence

- **Septic Shock – response to aggressive fluid therapy**

  Die in first hours

  Dramatic rapid reversal

    - **Drives the desire to repeat the same on the next case**

  Not die but also perfusion remains marginal

    - **Should these patients continue to receive aggressive fluid therapy?**
    - **Inevitable fluid overload = negative outcomes**

New Concepts

- **Allostatic (over)Load**

  Cells primitive response to prolonged hypoperfusion

  - **Protective response – "hibernation"**

    Downregulate metabolic demands

    Turn off normal cell functions until support returned

    Basis for multiorgan dysfunction syndrome

    New idea – cells are waiting to return to normal

  - **Trying to return perfusion – unsuccessful**

    Sending "all clear" signal to cells

    May result in more severe insult

    Better to wait until sepsis controlled

    - **Before returning perfusion to normal**