Foal Sepsis and Prematurity

Jon Palmer, VMD

Septic Shock

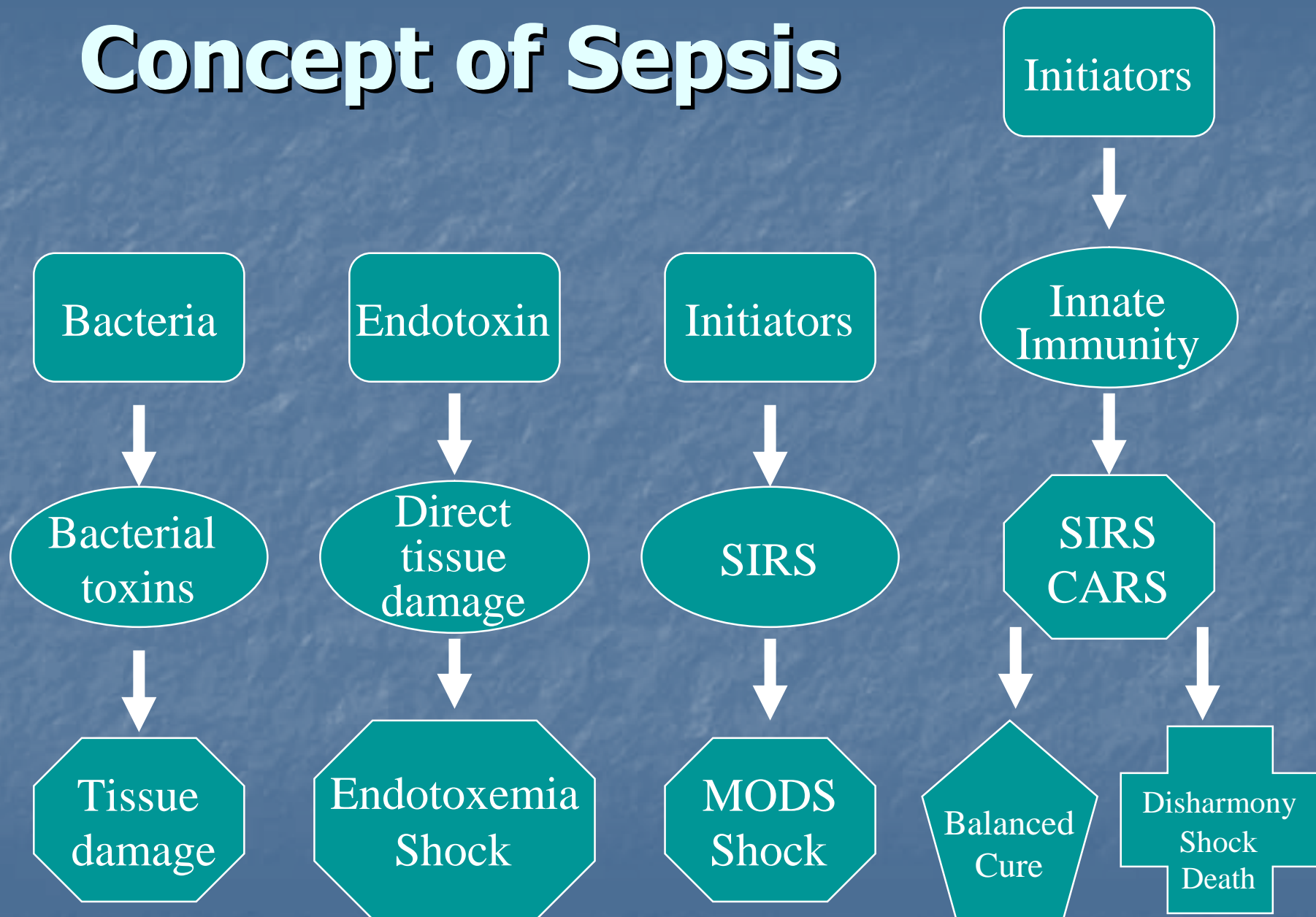## Most common cause of death
- Human SMICU
- Large animal NICU

Fatality rate
- Human medicine 20-80%
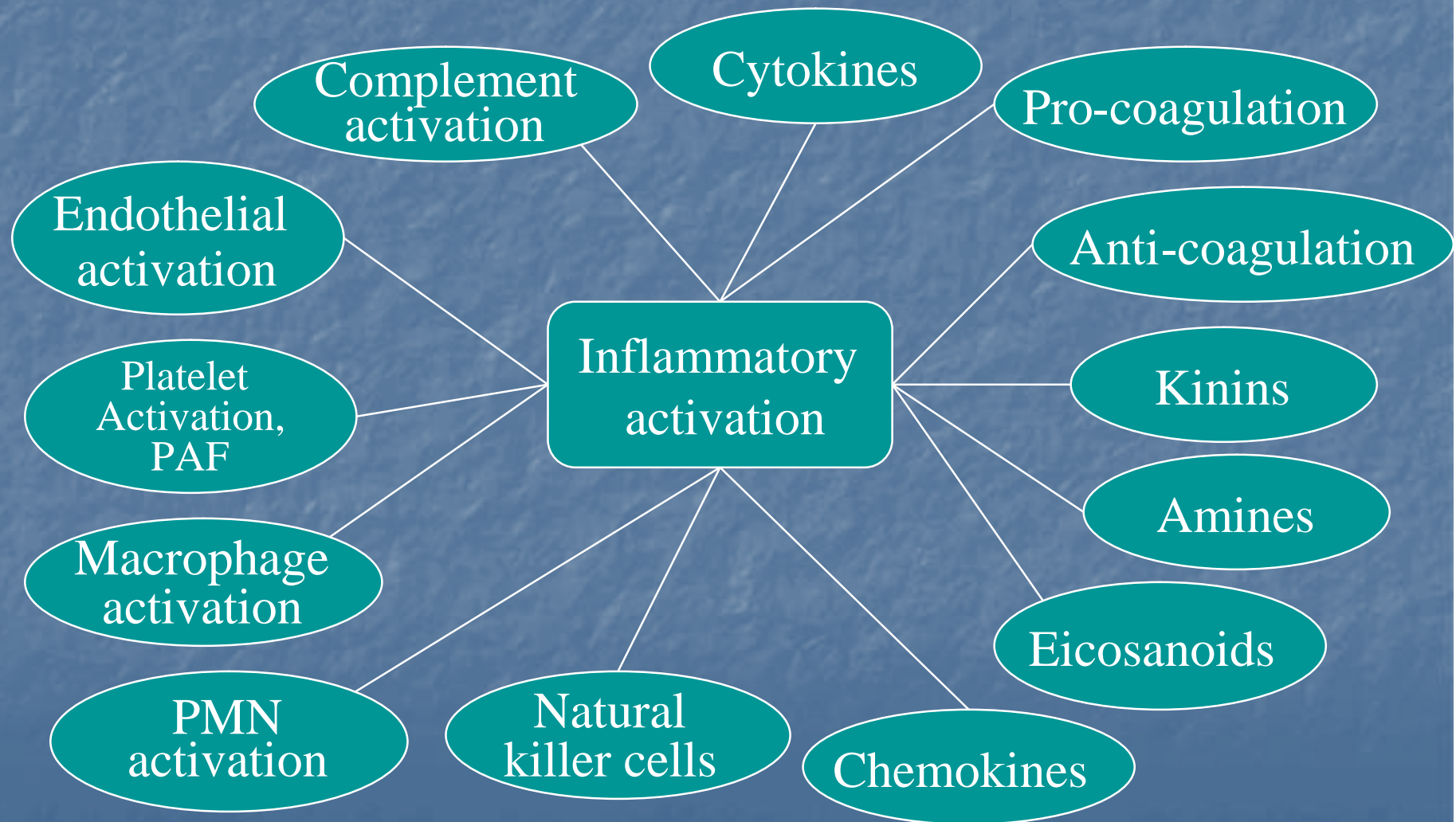- NBC NICU
  Sepsis without shock - 17%
  Septic shock - 70%

Fatalities
- Refractory hypotension
- ARDS
- MODS

Concept of Sepsis

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Bacteria              Endotoxin            Initiators                         Initiators
   │                      │                    │                                 │
   ▼                      ▼                    ▼                                 ▼
Bacterial            Direct                 SIRS                             Innate
 toxins              tissue                                                 Immunity
                     damage                                                    │
   │                    │                     │                                ▼
   ▼                    ▼                     ▼                               SIRS
 Tissue            Endotoxemia             MODS                              CARS
 damage              Shock                 Shock                           │       │
                                                                           ▼       ▼
                                                                      Balanced   Disharmony
                                                                        Cure       Shock
                                                                                   Death
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Inflammatory Cascade

Inflammatory Cascade

- Sepsis

- Severe Sepsis

- Septic Shock

Sepsis and Septic Shock
Portals of Entry

- GIt - Translocation

- Respiratory tract - Aspiration

- Placenta - *in utero*

- Umbilicus

Sepsis and Septic Shock
Localized Infections

- Pneumonia
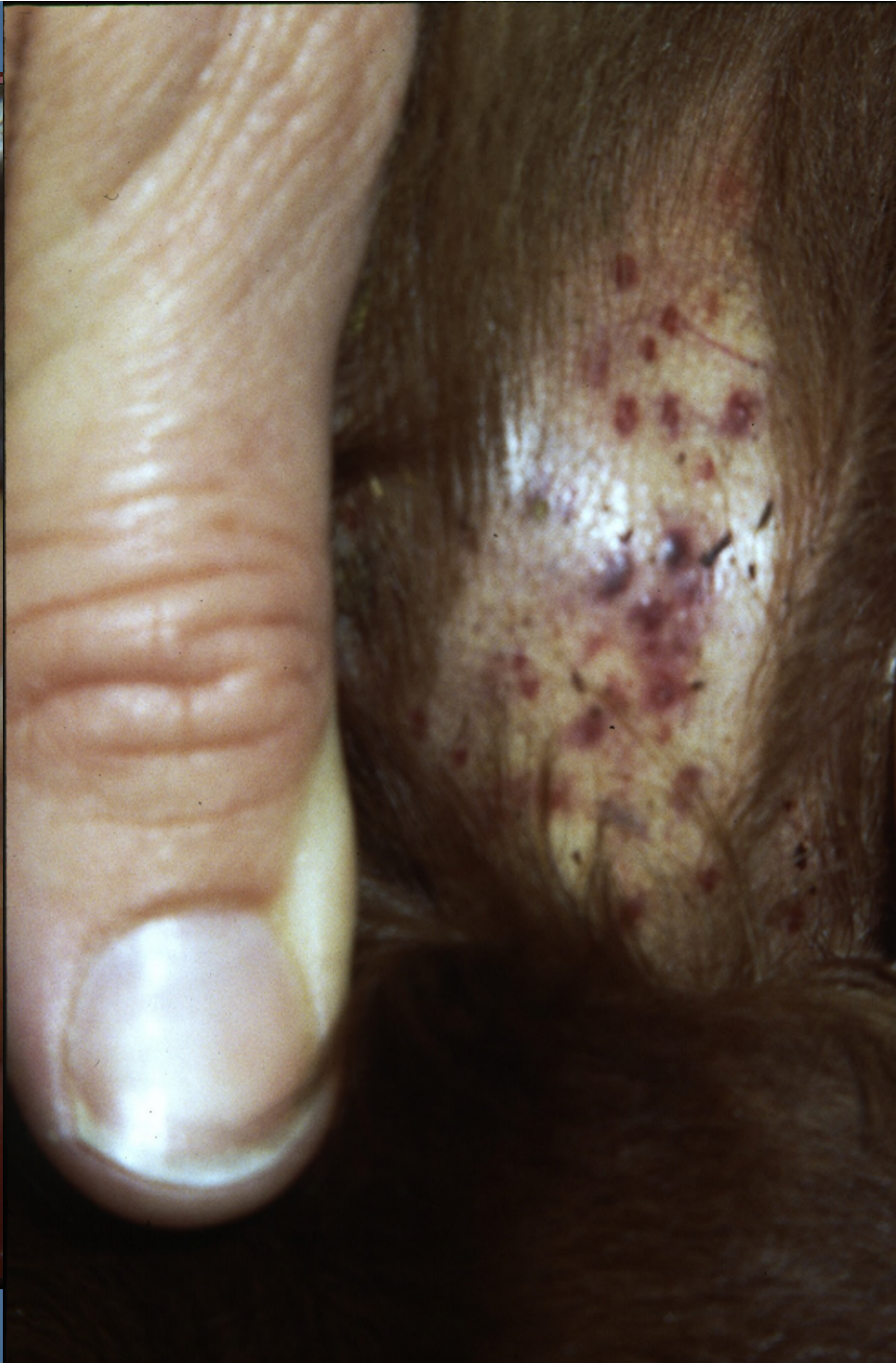
- Enteritis

- Osteomyelitis

- Meningitis
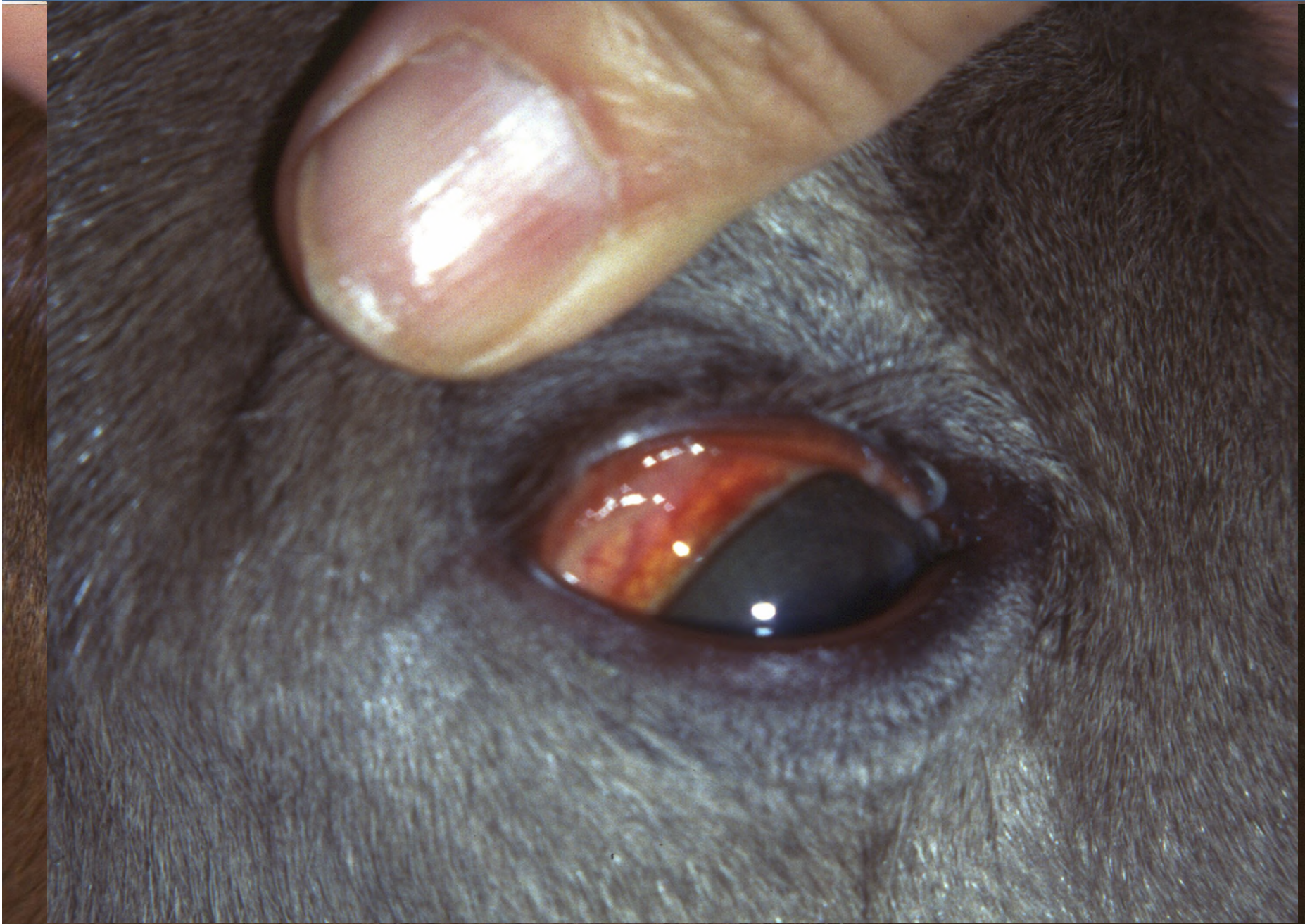
- Omphalitis

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
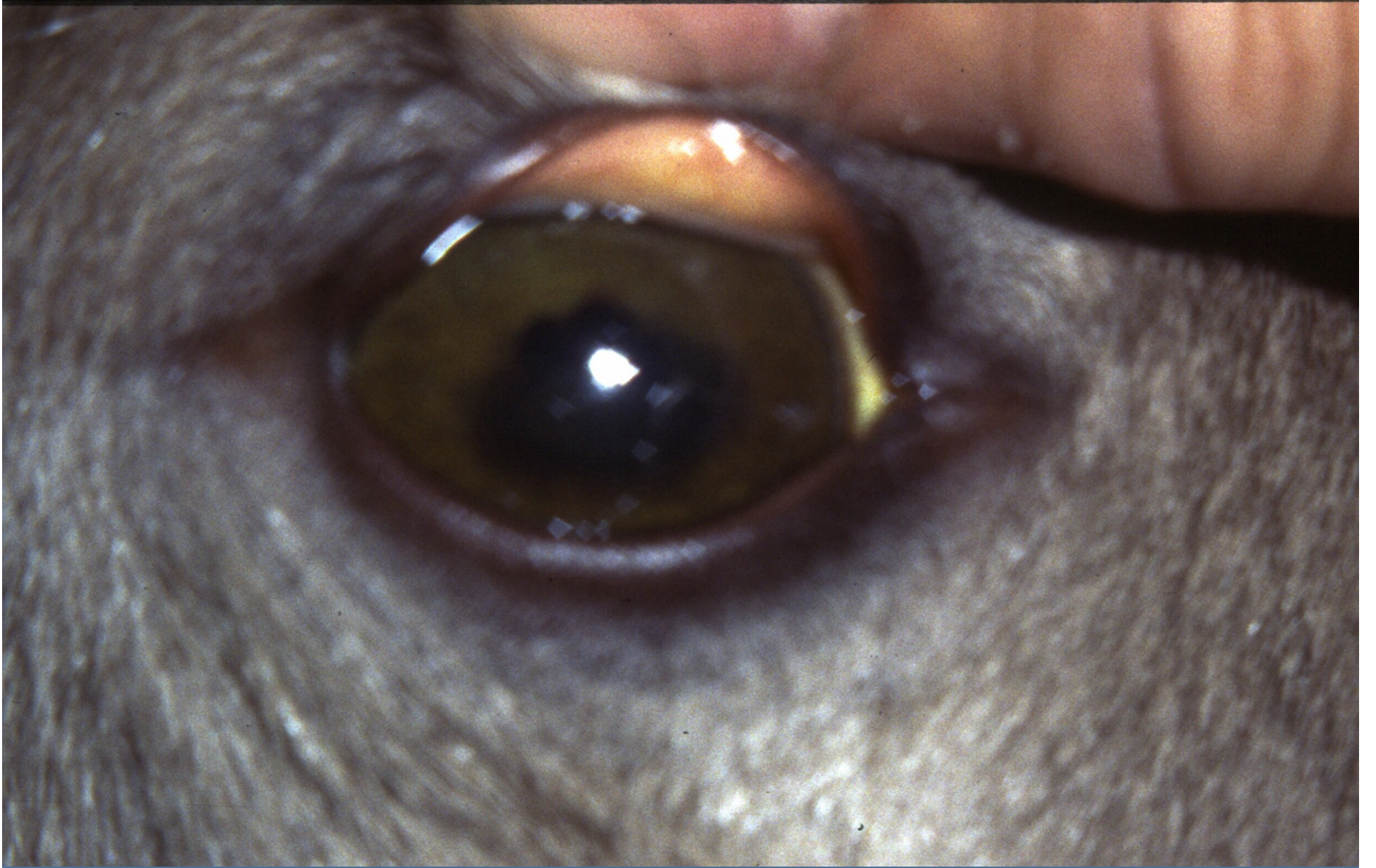- Linear dermal necrosis
- Increased/decreased CRT
- Shock

SIRS damage
MODS

GI tract
- Breach of the intestinal barrier
- Translocation of bacteria

Lungs
- Acute Respiratory Distress Syndrome (ARDS)

CNS
- Breakdown blood brain barrier
- Neonatal Encephalopathy

Renal failure
- Decreased renal blood flow – vascular damage
- Acute tubular necrosis

Sepsis and Septic Shock Therapeutic Interventions

Key interventions

- Sepsis vs Severe Sepsis vs Septic Shock

  - Treat underlying infection

  - Provide hemodynamic support

  - Support during MODS and metabolic crisis

  - Block proinflammatory mediators

Treat Infection

- Plasma transfusion therapy

- Antimicrobial

  - Based on likely sensitivity

  - Community isolates vs. nosocomial isolates

  - Avoid

    - Commonly used antimicrobials
    - Toxic effects

Community Acquired Isolates

- 22% *E coli*
- 19% *Enterococcus*
- 19% *Pantoea agglomerans*
- 5% *Klebsiella*
- 5% *Streptococcus*
- Others
  - *Acinetobacter* , *Aeromonas,* Alpha *Strep*
  - *Burkholderia, Listeria, Mannheimia*
  - *Comamonas, Salmonella, Staphylococcus*
- 60% Gram-negative and 40% Gram-positive

Nosocomial Bacterial Isolates

- 23% *Enterococcus*
- 18% *E coli*
- 11% *Enterobacter cloacae*
- 9% *Acinetobacter baumannii*
- 7% *Pantoea agglomerans, Pseudomonas*
- 5% Coag neg *Staphylococcus*
- 4% *Klebsiella pneumonia, Streptococcus*
- Others
- 68% Gram-negative and 32% Gram-positive

Antimicrobial Choices

- Community acquired infection
  - Ambulatory patient, controlled sepsis
    - Cefuroxime
    - TMS - IV
  - Critically ill neonate, uncontrolled sepsis
    - Ceftiofur Na - IV
      - 10 mg/kg IV QID
      - Continuous rate infusion (CRI)
- Nosocomial infection
  - Penicillin and amikacin – IV
  - Ticarcillin with clavulancic acid - IV
- Last line
  - Imipenem
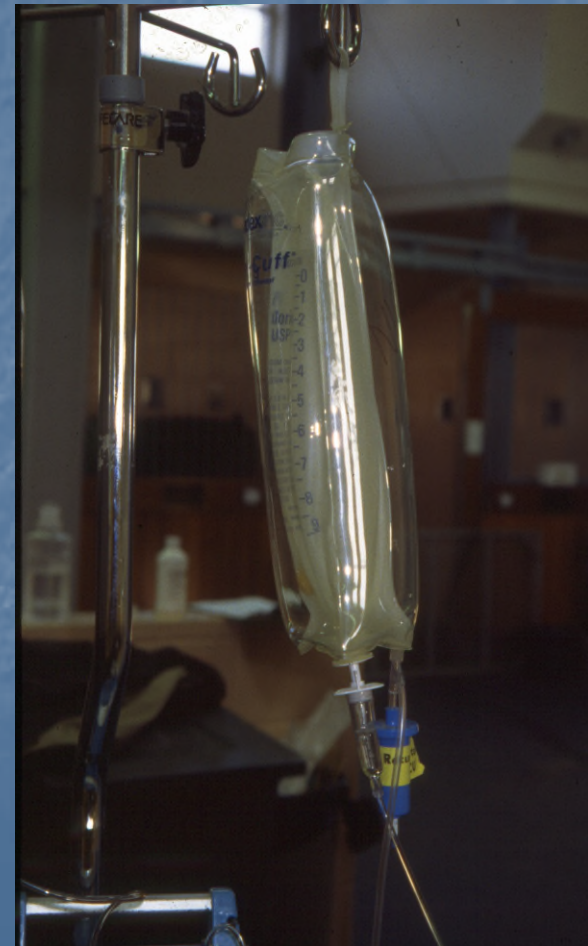
Septic Shock
Hemodynamic support

Goals

- Normalize perfusion

- Optimize cardiac output

- Increase systemic oxygen delivery

Septic Shock
Hemodynamic Support
Fluid Therapy

- Crystalloids or colloids?
- Crystalloid push
  - Bolus 20 ml/kg over 10-20 minutes
  - Reassess patient after every push
    - Blood pressure
    - Leg temperature
    - Peripheral pulse - arterial fill
    - Urine production
    - Mental status
- Transfusions
  - Plasma
  - Whole blood
- **Don't overhydrate**

Septic Shock
Pressors/Inotropes

Septic Shock
Oxygen therapy

Optimize O_2 delivery

Intranasal O_2
- High flows 8-10 lpm
- Utilize even if Pao_2 normal

Ventilate early
- Decrease work of breathing
  25% of O_2 consumption
  - Support respiration

Central venous O_2 Saturation
- $ScvO_2 > 70\%$
- EGDT

Sepsis and Septic Shock Nutritional Support

Sepsis is associated with
- Hypermetabolism
- Catabolism

Hyperglycemia
- Catecholamine stimulated glycolysis
- Cortisol hyperglycemia
- Catecholamine mediated insulin resistance
- Insulin therapy

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)

- Inhibitors of hosts inflammatory response
  Block pathogenic effects of SIRS
- Inhibiting mediators prevents effective CARS
- Undermine the protective mechanisms

Colostrum
Mother Nature's Wonder Elixir

Colostrum

- Passive transfer of colostral goodness
  - Traditional view
    - Primary role transfer IgG
  - New view
    - Primary function establishment of a healthy immune barrier
      - GI mucosa
   - Between luminal bacteria and foal

Colostrum

- Source of IgG
- Other biologically active substances
  - Other proteins
  - Immune modulators
  - Pro and anti-inflammatory substances
  - Inflammatory cells – neutrophils, plasma cells
  - Trophic substances
- Role
  - Targeting potential pathogens
    - Before invasion
  - Insuring GIt development
    - Not disrupted by inflammatory damage

Colostral Transfer
of Protective Factors
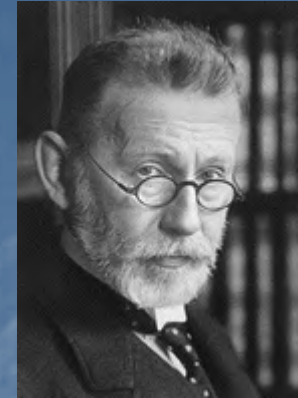
- Paul Ehrlich in 1891

- Colostrum is tailored for the neonate

  - Incomplete compliment of immune functions

  - Initiate or augment immune functions

    - Maturation of equine neutrophils

  - Immune functions absent - replaced

Colostral Protective Factors Tailored for the Neonate

- Defense agents in colostrum
  - Enhanced survival in the gastrointestinal tract
  - Protect without provoking inflammation
  - Inhibit inflammation
- Targeting of pathogens
  - Without collateral damage

Colostral Protective Factors Tailored for the Neonate

- Agents in colostrum
  - Alter the physiologic state of the gastrointestinal state
  - Transform from fetal physiology
    - To physiology appropriate to extrauterine life
- Growth factors in colostrum
  - Favor proliferation of commensal enteric bacteria
  - Inhibit pathogens
  - Trophic factors
    - Epithelial growth and development

Colostral Transfer
of Protective Factors

- GIt is the most likely portal of pathogens
  - Preventing luminal establishment of pathogens
  - Prevent proliferation of pathogens
  - Prevent invasion of pathogens
  - Protecting the neonate from sepsis

Antimicrobial Factors in Colostrum

- **Proteins**
  - Lactoferrin - bacteriostasis by Fe chelation
  - Lactoferricin - causing bacterial killing
  - Lysozymes – bacteriolysis
- MUCI - inhibits the binding of fimbriated *E coli*
- Lactadherdrin - binds viruses
- Oligosaccharides and glycoconjugates
  - Receptor analogues
  - Enteric pathogens and toxins
- Monoglycerides
- Fatty acids
  - Disrupt envelope viruses
  - Inactivate certain bacteria
  - Defend against *Giardia*

Antimicrobial Factors in Colostrum

- PAF-degrading enzyme
  - PAF is an important proinflammatory mediator
  - High levels in neonate
  - Protects mucosal cells from damage
- Erythropoietin
  - Protects against epithelium apoptosis
  - Trophic substance
- Epidermal Growth Factor (EGF)
  - Role in mucosal barrier function
  - Down-regulates apoptosis

Colostrum Substitutes

- Why measure IgG levels?
  - Only measurement available
  - Surrogate for of the establishment of this immune barrier
  - Surrogate for transfer of immune competence
  - Quantity vs. quality

Colostrum Substitutes

- IgG concentrate colostrum substitutes
  - Poor trade off
  - Only thing available
  - Not a true colostrum replacement

Colostrum Substitutes

- IgG quantity
  - Is not the aim of passive transfer
  - Misconception
    - Market of IgG based colostrum substitutes
  - Hyperimmune plasma is not a true substitute
    - Donor is stimulated – variety IgG (quality)
    - Contains many helpful factors other than IgG

Mother Nature's Wonder Elixir

- May not be appropriate for all foals
  - Critically ill foals
    - Poor perfusion
    - Hypoglycemia
    - Hypoxia
    - Other challenges
  - Feeding colostrum
    - More of a risk than a benefit
    - Considering referral – talk to clinic
    - Significant NG and secondary sepsis
    - On farm critical care - moderate volumes

Mother Nature's Wonder Elixir

- Foals not fed first few days of life
  - "Trophic" feeding
  - Small volumes of colostrum
    - 0.5-1% or 0.5 – 2 oz q4-6h
    - Fresh colostrum
    - Frozen colostrum
    - Fresh mare's milk
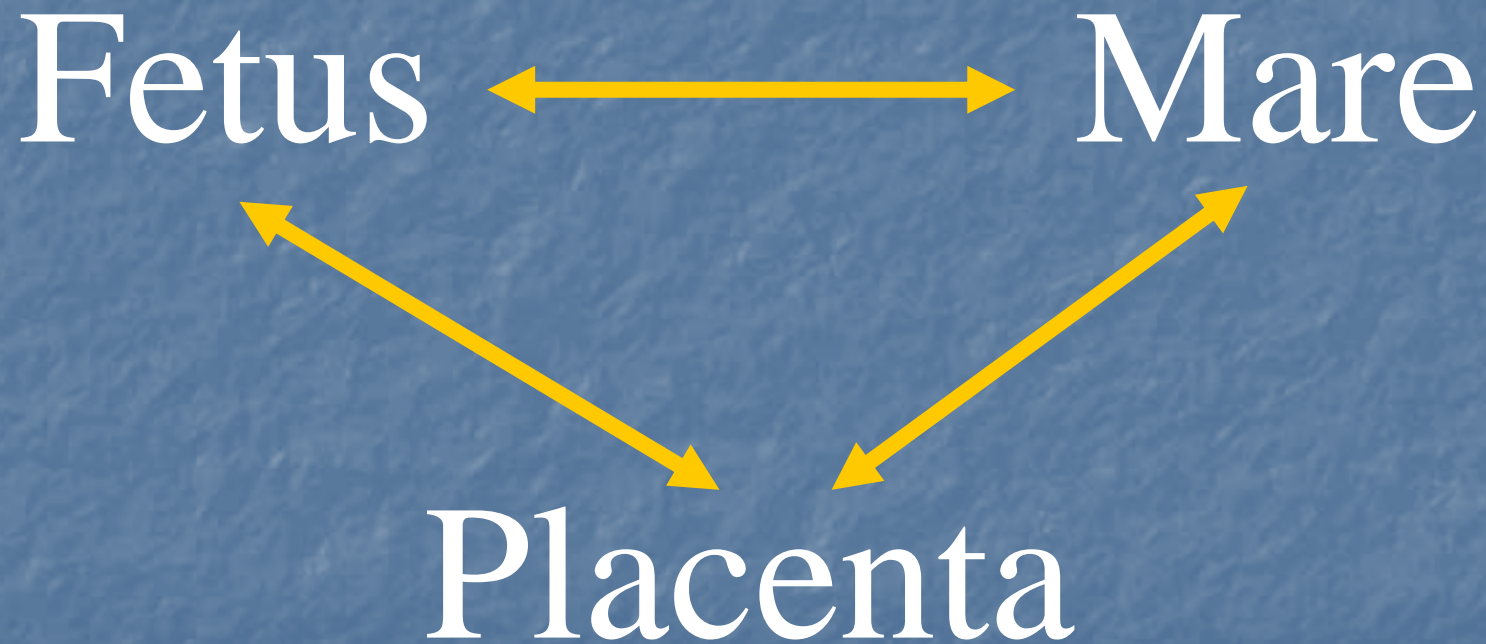
Timing of Birth

Prematurity

Postmaturity

Prematurity

- Average gestational length
  - 334 to 340 days
- Traditionally premature
  - < 320 days
- Each mare - own normal
  - Range 310 – 390 days
- Can have an apparently mature foal at 315 days
- Can have an apparently premature foal at 360 days

Coordination of maturation
Timing of foaling

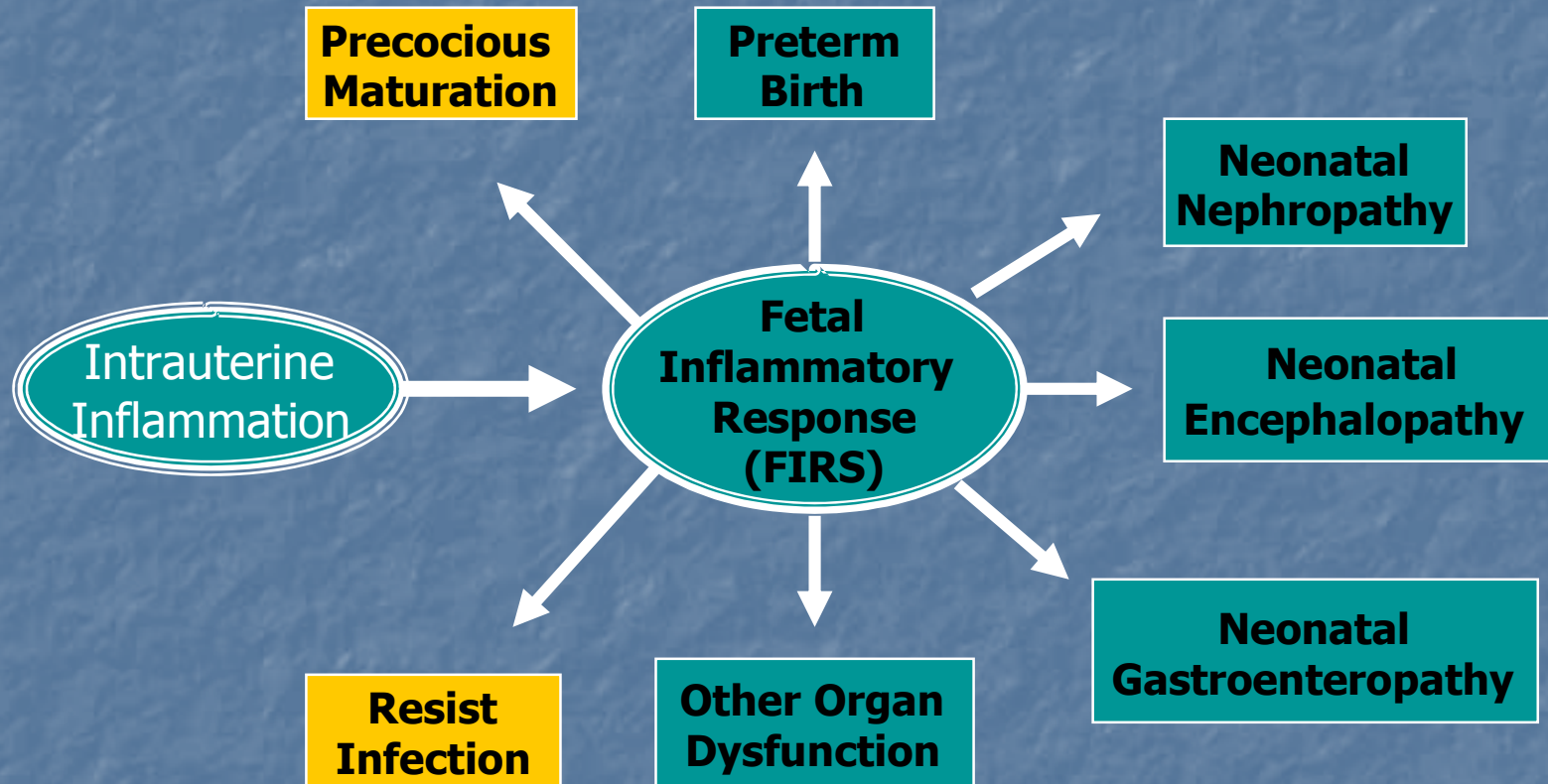Fetus ⟷ Mare

Placenta

Readiness for Birth

Readiness for Birth

Not ready

- Floppy ears
- Laxity
- Somnolence
- Weakness
- Hypotonia
- Low/normal WBC
- Low/normal fibrinogens
- Low presuckle IgG

Precocious maturation

- Ears up
- Contracture
- Alert
- Bright looking
- Good postural reflexes
- Leukocytosis
- Hyperfibrinogenemia
- High presuckle IgG

Role of Sepsis
in Premature Birth

- **Placentitis**
  - Maternal inflammatory response
  - Fetal exposure
    - Maternal inflammatory mediators
    - Maternal inflammatory cells
  - Fetal inflammatory response
    - Fetal inflammatory mediators
    - Fetal inflammatory cells

Role of Sepsis in Premature Birth

- Readiness for birth

- Variation in inflammatory response

- Rapid progression of inflammation

  - No adaptation of the fetus

- Chronic inflammation

  - Precocious maturation

- Maternal inflammation

- Fetal inflammation

Role of Sepsis
in Premature Birth

- **Inflammatory mediators role in preterm delivery**

  - **Intraamniotic IL-1β or TNFα**

    - Induce preterm labor (primates)

    - Increased fluid IL-8, PG, MMP9, WBC

    - Induce fetal membrane and lung inflammation

  - **Intraamniotic IL-6 or IL-8**

    - Not induce preterm labor (primates)

    - Increased fluid IL-8, PG, MMP9, WBC

    - Induce fetal membrane and lung inflammation

FOAL SEPSIS AND PREMATURITY

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SEPSIS

Recognition and early treatment of sepsis is of paramount importance. Sepsis is the biggest killer of neonatal foals. It is commonly involved in prematurity having a role in placentitis. All compromised foals have increased susceptibility to secondary infections.

Portals of entry of bacterial pathogens include the GI tract, the respiratory tract (secondary aspiration), the placenta (secondary to *in utero* placental infections) and the umbilicus. The umbilicus is overrated as a portal of entry. The gastrointestinal tract, through translocation of bacteria, is probably the most important portal of entry. Factors which predispose to sepsis include prematurity, hypoxic ischemic disease, hypothermia, failure of passive transfer, immature or suppressed immune response, stress, poor nutrition and poor husbandry. Once the pathogens enter the neonate's body the infection may localize resulting in pneumonia, enteritis, arthritis, osteoarthritis, meningitis, omphalitis or may remain generalized (septicemia).

Early signs of sepsis include loss of suckle, fever or hypothermia, lethargy, weakness and injected scleral or oral membranes. Other signs include tachycardia, tachypnea petechia of the oral, scleral, or aural membranes, hyperemia of the coronary bands (coronitis), linear dermal necrosis (LDN -- necrosis of the skin often over the hock in a linear pattern), either increased or decreased capillary refill time and finally shock. These signs are caused by over activation of the inflammatory response resulting in showers of inflammatory mediators. The inflammatory reaction can cause damage to the GI tract, lungs, CNS or kidneys. In the GI tract there may be a breach of the intestinal barrier and translocation of bacteria into the submucosa. In the lungs damage can be widespread and result in acute respiratory distress syndrome (ARDS) and severe respiratory failure, resulting in poor gas exchange. In the CNS there may be changes in vascular permeability interfering with normal blood brain barrier function and activation of cerebral inflammatory cascades. There can be decreased renal blood flow resulting in prerenal azotemia and later acute tubular necrosis resulting in renal failure. This may be mediated either by hypotension or damage to the microvasculature. All tissues may be affected by hypoxic ischemic damage secondary to hypotension, poor perfusion and poor oxygen deliver which is exacerbated by poor oxygen loading of the blood in the lungs. In all tissues occlusion of vessels because of adherence of platelets and neutrophils to damage endothelium and formation of microthrombi as a procoalulant response results in regional hypoxic ischemic damage, even if perfusion and regional oxygen delivery is returned through therapeutic interventions.

Early treatment is very important in supporting the compromised neonatal foal. Treatment should include plasma transfusion therapy (even if the IgG level is considered adequate) and appropriate antimicrobials. Antimicrobial choice should be based on likely sensitivity of pathogen (whether community or nosocomial pathogen), avoiding antimicrobials commonly used on the farm since the pathogen is more likely to be sensitive to these. Also care should be used to avoid antimicrobials with toxic effects involving compromised organ systems, such as aminoglycosides when renal compromise is suspected. Community acquired isolates from our practice during the last few foal seasons include: 22% *E coli* , 19% *Enterococcus spp*, 19% *Pantoea agglomerans* , 5% *Klebsiella*, 5% *Strep* and others (*Acinetobacter lwoffi*, *Aeromonas caviae*, Alpha *Strep* not Gp D, *Burkholderia cepacia*, *Comamonas testosterone*, CDC Enteric Gr 76, *Listeria monocytogenes*, *Mannheimia haemolytica* A, *Salmonella*, *Staph*). Thus, as we have found for the past decade, about 60% of the isolates are Gram-negative and 40% Gram-positive, emphasizing the need for initial broad spectrum antimicrobials. Nosocomial bacteria isolates from our NICU patients during the same period: 23% *Enterococcus*, 18% *E coli*, 11% *Enterobacter cloacae*, 9% *Acinetobacter baumannii*, 9% *Salmonella*, 7% *Pantoea agglomerans*, 7% *Pseudomonas aeruginosa*, 5% Coag neg *Staph*, 4% *Klebsiella pneumonia*, 4% *Strep* and others (CDC VE type 2, *Moraxella osloensis*, *Proteus vulgaris*). This represents 68% Gram-negative isolates and 32% Gram-positive isolates. These percentages are somewhat biased by a focal, limited *Salmonella* nosocomial outbreak.

Based on sensitivity patterns of our community acquired pathogens my first line therapy in ambulatory patients with evidence of controlled sepsis is a second generation cephalosporin (cefuroxime axetil 30 mg/kg/day PO divided BID/QID, Cefuroxime Na 50-100 mg/kg/day IV divided TID/QID) or IV TMS with or without a first generation cephalosporin. In the critically ill neonate (recumbent with evidence of uncontrolled community acquired sepsis) my first line therapy is high levels of a third generation cephalosporin (IV ceftiofur Na using much higher doses and frequency than commonly accepted; 10 mg/kg IV QID or continuous rate infusion using 1.5 mg/kg/hr). When faced with a nosocomial infection, again based on current sensitivity, I use penicillin and amikacin (K or Na Penicillin at 20,000-50,000 U/kg IV QID; amikacin in foals < 1 wk old at a dose of 30-35 mg/kg IV SID tailoring the dose to result in a 30 minute peak level of >60 μg/ml and a 23 hr trough < 2μg/ml) or ticarcillin with clavulanic acid (50 - 100 mg/kg IV QID or 2-4 mg/kg/hr IV as a continuous rate infusion). Further discussion of choices, pharmacokinetics and variations from adult therapy is beyond the scope of this article.

PASSIVE TRANSFER

While discussing treatment of sepsis a discussion of passive transfer is in order. A better understanding of passive transfer will aid us in understanding its roll in preventing and modulating sepsis. Rather than following the traditional view that the primary role of colostrum is to transfer IgG, I feel that the primary function of colostrum is the establishment of a healthy immune barrier between the luminal bacteria and the foal at the GI mucosa. Although colostrum is an important source of IgG, it contains many other biologically active proteins, immune modulators and pro and anti-inflammatory substances. All of these substances are important in insuring the development of an effective protective barrier targeting potential pathogens before their invasion and insuring that the fragile development of the gastrointestinal tract is not disrupted by inflammatory damage.

It was Paul Ehrlich in 1891 who first recognized the importance of colostral transfer of protective factors. Colostrum is tailored for the neonate who has yet to develop a complete compliment of immune functions. Certain agents in colostrum initiate or augment functions which are otherwise poorly expressed in the neonates. In fact, without some agents in colostrum, immune development will be delayed (e.g. maturation of equine neutrophils). Certain immune functions that are initially absent in neonates are replaced by factors in colostrum. In addition, defense agents in colostrum have enhanced survival in the gastrointestinal tract of the recipient compared to their plasma derived counterpart. Also, defense factors in colostrum protect without provoking inflammation and some agents inhibit inflammation both allowing targeting of pathogens without allowing the inflammatory reaction to disrupt the development of the neonate's gastrointestinal tract. There are also agents in colostrum that alter the physiologic and biochemical state of the gastrointestinal state from one suited to fetal life to one appropriate to extrauterine life. Finally and perhaps most importantly, growth factors in colostrum augment the proliferation of the commensal enteric bacteria. Since the gastrointestinal tract is the most likely portal of entry of pathogens, the action of colostrum in preventing luminal establishment, proliferation and invasion of pathogens is vital in protecting the neonate from sepsis.

Antimicrobial factors in colostrum include proteins such as lactoferrin (bacteriostasis by Fe chelation), lactoferricin (causing bacterial killing), lysozymes (bacteriolysis by degrading peptidoglycans), MUCI (inhibits the binding of S-fimbriated E coli to epithelial cells), lactadherdrin (binds viruses so prevents epithelial attachment), oligosaccharides and glycoconjugates (receptor analogues which inhibit binding of enteric pathogens and toxins to epithelial cells) and monoglycerides and fatty acids (disrupt envelope viruses, inactivate certain bacteria, defend against Giardia). Other important factors in colostrum include PAFacetylhydrolase (PAF-degrading enzyme; PAF is an important proinflammatory mediator in the GIt with high levels in the neonate; this enzyme protects mucosal cells from damage caused by PAF by degrading it), erythropoietin which protects against apoptosis of intestinal epithelium, epidermal growth factor which has been shown to play an important role in mucosal barrier function in developing intestine, and down-regulates apoptosis of intestinal epithelium.

Using IgG concentrates as a substitute for colostrum is a poor trade off. If it is the only thing available, it should be used but not with the expectation that it is a true colostrum replacement. When we measure IgG plasma levels as a reflection of passive transfer, what we a doing in essence is making the only measurement of the establishment of this immune barrier and transfer of immune competence available to us. There is no way to test to see if the enteric protective barrier has been established, to insure that protective and modulating substances are present and in place at the mucosal level resulting in an effective immune barrier. There are no simple techniques to see if the colostral substances have had their stimulating effect on the neonate's immune function or have stimulated the healthy maturation of the neonate's mucosal barrier. So we use the measurement of plasma IgG levels as a surrogate for these things. Transfer of a quantity of IgG is important

but not the most important part of passive transfer. It's not the quantity but the quality of IgG that's important. Having a large quantity of IgG targeted against influenza virus is not helpful in protecting the neonate against bacterial pathogens. But since we have no method to measure the quality of IgG transferred, we rely on quantity as a surrogate. It is unfortunate that we have largely lost sight of this and frequently teach that the surrogate, IgG quantity, is the aim of passive transfer. In fact a whole industry has grown out of this misconception and IgG concentrates are frequently marketed as colostrum substitutes. Even when hyperimmune plasma transfusion is used as a colostrum substitute, a significant quantity of IgG transferred will be directed against pathogens that aren't a threat to the neonate. But when the donor is stimulated to produce this unhelpful IgG, other, more useful antibodies will also be produced as well as immune modulating substances which may be important in the neonate who has not benefit from colostrum. I hope you will widen your view of passive transfer and think of it in broader terms than just transfer of IgG.

I would like to make it very clear that even if colostrum is Mother Nature's wonder elixir, it may not be appropriate for all foals. Giving large volumes of colostrum to critically ill foals with poor perfusion, hypoglycemia, hypoxia and other challenges is more of a risk of sepsis than a benefit in protecting against sepsis. Critical foals fed large volumes of colostrum before referral are more likely to suffer from significant Neonatal Gastroenteropathy and secondary sepsis resulting in a longer and more expensive hospital stay and more likely fatal outcome. If referral or intensive on the farm critical care is not in the foal's future, then moderate volumes of fresh colostrum may be the best course, giving the foal the best chance despite the possible drawbacks.

PREMATURITY

Prematurity is the result of a preterm birth. Most veterinary texts will define prematurity in the foal by a gestational length of less than 320 days. But in order to truly define a preterm birth, the normal gestational length must be known. The average gestational length of a mare is 334 to 340 days. We never deal with the "average" mare but with an individual mare. Each mare has decided herself what her normal gestational length is, despite what we think. This may vary from 315 days to more than 390 days. Thus a mare who normally carries a foal to 365 days may have a premature foal with a gestational length of 340 days and another which normally carry 315 days may have a term foal at 315 days gestation.

Foals which are born after their expected due date but are small and have the characteristics of being premature have been called dysmature. I believe the term dysmature is not useful because some of these foals are really premature but the mare has a longer than average gestation and others are a result of intrauterine growth restriction (IUGR) which is quite different although both are placental in origin. IUGR should be distinguished from postmaturity. A postmature foal is a post-term foal who has adequate axial skeletal size (usually large) for the gestational age but is thin due to emaciated. Postmature foals are foals retained too long *in utero*. Because of this relative placental insufficiency, they may have hypoxic or inflammatory insults. At least in theory, the longer they are retained, the more abnormal they become. Their continued skeletal growth may lead to dystocia. A good example of postmaturity is a foal born from a mare with fescue endophyte toxicity.

Clinical characteristics of prematurity include: low birth weight, small frame (may appear thin with poor muscle development), periarticular laxity, flexor laxity (occasional contracture), hypotonia (occasional hypertonia), high compliance to chest wall, low compliance lungs (respiratory distress secondary to fatigue), general muscle weakness (delayed standing), short, silky hair coat, domed forehead, poor ear cartilage development, weak suckle, poor thermoregulation, GI tract dysfunction, delayed maturation of renal function, entropion (secondary corneal ulcers) and poor glucose regulation.

Clinical characteristics of postmaturity: normal to high birth weight, large frame but thin with muscle wasting, flexor contraction (occasionally flexor laxity), hypertonia (occasional hypotonia), delayed time to standing (hyperreactive state and poor postural reflexes), long hair coat, fully erupted incisors, weak suckle, poor thermoregulation, GI tract dysfunction, delayed maturation of renal function and poor glucose regulation.

Often Neonatal Encephalopathy, Neonatal Nephropathy, Neonatal Gastroenteropathy and other organ maladaptation frequently accompany prematurity/IUGR/postmaturity as does neonatal septicemia. This is understandable as the etiology of all these problems is placental dysfunction.