A 4-year-old male castrated mixed breed dog (15 kg) is diagnosed with valvular endocarditis. The patient is febrile (104.2°F [40.1°C]) and severely hypoalbuminemic with an albumin of 1.3 g/dl [13 g/L](normal range, 2.5-4.0 g/dl[25.0-40.0 g/L]).

**Question 1:** Using the proposed modified Duke system, list 4 major and 4 minor criteria necessary for diagnosis of endocarditis in dogs and how a probable diagnosis is made using this system.

The Duke Criteria - Modified to classify dogs with possible or definite IE:

- **Major Criteria**
  1. Identification of a typical organism (eg, streptococci, staphylococci, or *Escherichia coli*) on MCB
  2. All 3 of 3, or at least 3 of 4, MCBs, with the first and last blood samples collected at least 1 hour apart
  3. Persistent positive MCB results for any microorganism when blood samples are drawn more than 12 hrs apart
  4. Positive findings for infectious endocarditis on echocardiogram

- **Minor Criteria:**
  1. Predisposing heart condition
  2. New or worsening heart murmur
  3. Fever (rectal temperature ≥ 39.4°C (≥103°F))
  4. Detection of vascular or embolic phenomena
  5. Immunologic phenomena: non-degenerate neutrophilic polyarthritis, glomerulonephritis, or immune-mediated hemolytic anemia
  6. Microbiologic phenomena: positive MCB not meeting major criteria, serologic evidence of infection with a typical organism, or detection of a typical organism by use of PCR technology

Probable diagnosis made with one of the following:
  1. positive echocardiographic findings and fulfillment of 1 minor criterion
  2. 1 major and 3 minor criteria,
  3. 5 minor criteria

**Reference:**

**Question 2:** What are the four most common infectious isolates noted in canine patients with endocarditis?

In Dr. Gordon Peddle and Dr Meg Sleeper’s 2007 review on Canine bacterial endocarditis the organisms most commonly recognized and identified as the causative agents of bacterial endocarditis in dogs included: Coagulase-positive *Staphylococcus* sp., *Streptococcus* sp., *Escherichia coli* sp., *Pseudomonas aeruginosa*, *Corynebacterium* sp., *Erysipelothrix rhusiopathiae*, and more recently *Bartonella* sp have been identified as causative agents in cases of endocarditis.
Additionally, a 2006 retrospective case series indicated that the most common infecting organisms in dogs were *streptococci* (most commonly *streptococcus canis*), gram-negative bacilli (most commonly *Escherichia coli*), *Bartonella* sp, and *Staphylococci*.

Reference:

Three days later your culture and sensitivity results are available.

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>ENTEROBACTER CLOACAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIKACIN</td>
<td>Sensitive (≤2 ug/ml)</td>
</tr>
<tr>
<td>AUGMENTIN</td>
<td>Resistant (≥32 ug/ml)</td>
</tr>
<tr>
<td>CARBENICILLIN</td>
<td>Resistant (128 ug/ml)</td>
</tr>
<tr>
<td>CEFTAZIDIME</td>
<td>Resistant (≥32 ug/ml)</td>
</tr>
<tr>
<td>CEFTIOFUR</td>
<td>Resistant (≥8 ug/ml)</td>
</tr>
<tr>
<td>CEPHALOTHIN</td>
<td>Resistant (≥32 ug/ml)</td>
</tr>
<tr>
<td>CHLORAMPHENICOL</td>
<td>Resistant (≥32 ug/ml)</td>
</tr>
<tr>
<td>CIPROFLOXACIN</td>
<td>Resistant (≥4 ug/ml)</td>
</tr>
<tr>
<td>ENROFLOXACIN</td>
<td>Intermediate (4 ug/ml)</td>
</tr>
<tr>
<td>GENTAMICIN</td>
<td>Sensitive (≤0.5 ug/ml)</td>
</tr>
<tr>
<td>NITROFURANTOIN</td>
<td>Intermediate (64 ug/ml)</td>
</tr>
<tr>
<td>PIPERACILLIN</td>
<td>Resistant (128 ug/ml)</td>
</tr>
<tr>
<td>TETRACYCLINE</td>
<td>Resistant (≥16 ug/ml)</td>
</tr>
<tr>
<td>TICARCILLIN</td>
<td>Resistant (128 ug/ml)</td>
</tr>
<tr>
<td>TOBRAMYCIN</td>
<td>Sensitive (≤0.5 ug/ml)</td>
</tr>
<tr>
<td>TRIBRISSEN</td>
<td>Sensitive (≤10 ug/ml)</td>
</tr>
<tr>
<td>CEFAZOLIN</td>
<td>Resistant (ug/ml)</td>
</tr>
<tr>
<td>CEFIXIME</td>
<td>Resistant (ug/ml)</td>
</tr>
<tr>
<td>CEFOTAXIME</td>
<td>Resistant (ug/ml)</td>
</tr>
<tr>
<td>CEFTRIAXONE</td>
<td>Resistant (ug/ml)</td>
</tr>
<tr>
<td>CEFUROXIME</td>
<td>Resistant (ug/ml)</td>
</tr>
<tr>
<td>DIFLOXACIN</td>
<td>Resistant (ug/ml)</td>
</tr>
<tr>
<td>IMIPENEM</td>
<td>Sensitive (ug/ml)</td>
</tr>
<tr>
<td>MARBOFLOXACIN</td>
<td>Resistant (ug/ml)</td>
</tr>
<tr>
<td>ORBIFLOXACIN</td>
<td>Resistant (ug/ml)</td>
</tr>
<tr>
<td>OFLOXACIN</td>
<td>Resistant (ug/ml)</td>
</tr>
<tr>
<td>CEFPODOXIME</td>
<td>Resistant (ug/ml)</td>
</tr>
</tbody>
</table>
**Question 3:** In the above sensitivity report, enrofloxacin is listed as having intermediate sensitivity. Describe what is meant when an organism has intermediate sensitivity. Give one instance in which a drug with intermediate sensitivity may be efficacious, and explain why.

- When an organism has intermediate sensitivity its growth is inhibited at concentrations that approach breakpoint MIC. The breakpoint MIC of a drug is the highest concentration that can be safely attained in blood using the recommended (labeled) dosing regimen. Organisms characterized by intermediate susceptibility are inhibited at concentrations that approach breakpoint and so should be used cautiously.

- One instance in which a drug with intermediate sensitivity may be efficacious is when that drug is concentrated in the part of the body that is infected (e.g. urine or in white blood cells) or when it is being applied topically.

Reference:

**Question 4:** For each drug below provide the mechanism of action and potential toxicities in dogs and cats:

- **Amikacin:**
  Mechanism of action:
  - aminoglycoside – bactericidal by acting on susceptible bacteria presumably by irreversibly binding to the 30S ribosomal subunit thereby inhibiting protein synthesis
  Toxicities:
  - Nephrotoxic – causes tubular necrosis likely by interference with phospholipid metabolism in the lysosomes of proximal renal tubular cells, resulting in leakage of proteolytic enzymes into the cytoplasm
  - Ototoxic – causes 8th cranial nerve toxicity and manifested by either auditory and/or vestibular symptoms

- **Enrofloxacin:**
  Mechanism of action:
  - fluoroquinolone – bactericidal by inhibiting bacterial DNA-gyrase (a type-II topoisomerase), thereby preventing DNA supercoiling and DNA synthesis
  Toxicities:
  - Ocular toxicity in cats - characterized by mydriasis, retinal degeneration and blindness
  - Articular cartilage toxicity - bubble-like changes in articular cartilage noted when the drug was given at 2-5 times recommend doses for 30 days, although clinical symptoms have only been seen at the 5X dose. Large and giant breed dogs may be in the rapid-growth phase for periods longer than 8 months of age, so longer than 8 months may be necessary to avoid cartilage damage

- **Ticarcillin**
  Mechanism of action:
  - Extended spectrum penicillin - bactericidal by inhibiting mucopeptide synthesis in the cell wall resulting in a defective barrier and an osmotically unstable spheroplast. Extended spectrum penicillin’s have similar spectrums of activity as the aminopenicillins but with additional activity against several gram-negative organisms of the family Enterobacteriaceae, including many strains of *Pseudomonas aeruginosa*
  Toxicities:
  - hypersensitivity
  - neurotoxicity (ataxia) in high doses or prolonged use in dogs

- **Trimethoprim-Sulfa:**
  Mechanism of action:
  - Potentiated sulfa drug - inhibits enzymes in the folic acid pathway, thereby inhibiting bacterial thymidine synthesis. The sulfonamide blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid (DFA), and trimethoprim blocks the conversion of DFA to tetrahydrofolic acid by inhibiting dihydrofolate reductase
  Toxicities:
- keratoconjunctivitis sicca
- acute neutrophilic hepatitis
- IMHA
- Acute hypersensitivity reactions manifesting as Type I (anaphylaxis), or Type III reaction (serum sickness)

- Chloramphenicol:
  Mechanism of action:
  - acts by binding to the 50S ribosomal subunit of susceptible bacteria, thereby preventing bacterial protein synthesis

  Toxicities:
  - bone marrow toxicity causing aplastic anemia

Reference:
- Plumb’s Veterinary Drug Handbook

Question 5: Imipenem is typically combined with cilastin. What is the purpose of cilastin?

- Cilastin is an inhibitor of dehydropeptidase I (DHP I). DHP 1 metabolizes imipenem on the brush borders of renal tubular cells. Therefore, DHP 1 inhibits the metabolism of Imipenem. This serves two functions: it allows higher urine levels and may also protect against proximal renal tubular necrosis that can occur when imipenem is used alone.

Reference:
- Plumb’s Veterinary Drug Handbook

Question 6: Define minimum inhibitory concentration:

- The MIC of an organism for a drug refers to the minimum amount of drug necessary to inhibit visible growth of an organism using standardized culturing methods as guided by the National Committee for Clinical Laboratory Standards (NCCLS) of the Center for Disease Control (CDC).

Reference:

Question 7: Define breakpoint:

- The breakpoint MIC of a drug is the highest concentration that can be safely attained in blood using the recommended (labeled) dosing regimen. Breakpoint MICs are the basis for determining the resistance or susceptibility of an organism to a drug. They should be the same for all laboratories because they are dependent on the microbe and the targeted animal species. The MIC<sub>BP</sub> is determined by at least three criteria: it will be below (or approximate) the peak PDC (maximum concentration; Cmax) that will be achieved using the recommended dose of the drug; it will be greater than the MIC of most organisms (ie, the MIC 90) included in the spectrum of the drug; and it must be correlated with clinical response to the selected antimicrobial. If the MIC of the organism is sufficiently lower than the MIC<sub>BP</sub>, the organism is considered susceptible (S). If the MIC of the organism equals or surpasses the MIC<sub>BP</sub>, the organism is considered resistant (R). Some laboratories also offer an "I" or "MS" (medium susceptibility), indicating that the MIC of the organisms is approaching the MIC<sub>BP</sub>.

Reference:

Question 8: Describe the difference between concentration- (dose) dependent and time-dependent antimicrobials and give an example of each:
• Time dependent
  The time-dependent antibiotics exert optimal bactericidal effect when drug concentrations are maintained above the minimum inhibitory concentration (MIC). Typically, concentrations are maintained at 2 to 4 times the MIC throughout the dosing interval. For these agents, higher concentrations do not result in greater kill of organisms.

  Examples: beta-lactams (penicillins, cephalosporins), clindamycin, macrolides (erythromycin)

• Dose dependent
  Concentration-dependent antibiotics achieve increasing bacterial kill with increasing levels of drug.

  Examples: Aminoglycosides and quinolones

Reference:

Question 9: List 4 strategies used by organisms to develop antimicrobial resistance:

1. Alteration of the antimicrobial’s target receptor molecule in the bacteria
2. Decreasing the accessibility of the antimicrobial to the target by altering entry of the antimicrobial into the cell or increasing removal of the antimicrobial from the cell
3. Destruction or inactivation of the antimicrobial
4. Synthesis by the bacteria of a new metabolic pathway that is not inhibited by the antimicrobial

Reference:

During rounds, three therapeutic options are considered for use in this patient: 25% human albumin solution; hydroxyethylstarch; and fresh frozen plasma.

Question 10: Describe two effects by which each of these agents would impact hemostasis.

25% Human Albumin Solution:
1. Decrease in platelet aggregation
2. Dilutional coagulopathy

Hydroxyethylstarch
1. Dilution of clotting factors
2. Inhibition of platelet function by coating platelets and decreasing adhesion
3. Decreasing activity of factor VIII:c and von Willebrand factor
4. Accelerating fibrinolysis

Fresh Frozen Plasma:
1. Provides ATIII, fibronectin, alpha-macroglobulins, antitrypsin
2. Provides coagulation factors

Reference:
Question 11: Formulate a justification for or against correcting this patient’s serum albumin concentration.

In addition to contributing 80% of colloid oncotic pressure and supporting intravascular volume, Albumin also carries endogenous and exogenous substances (free fatty acids, bile acids, bilirubin, porphyrins, ketosteroids, drugs such as penicillin, aspirin, and the barbiturates, histamine, and cations such as copper, calcium and zinc), is a mediator of coagulation, and serves as a free radical scavenger. Low albumin levels (<2.0 g/dl) have been correlated with increased mortality in humans, even when maintaining normal COP with colloid infusions. Therefore, a decrease in albumin will cause GI effects such as delayed gastric emptying, ileus, GI mucosal edema, and enteral feeding intolerance as well as other effects such as: delayed wound healing, interstitial edema, and increased morbidity and mortality. Based on this information and a significantly low albumin (1.3), there is substantial evidence to correct this patient’s albumin.

A decision is made to administer 20 ml/kg of fresh frozen plasma to this patient. Following the transfusion, serum albumin concentration is 1.5 g/dl [15 g/L] and coagulation parameters are within normal limits.

Question 12: Explain why this dose of fresh frozen plasma was ineffective at normalizing this patient’s serum albumin concentration.

This 15kg patient was administered a 20ml/kg dose of fresh frozen plasma which equals 300mls given. Fresh frozen plasma contains 0.025g of albumin per ml which means this patient received 7.5 g of Albumin. In order to determine the actual increase in serum albumin based on the amount give, the total 7.5g must be divided by the total volume of distribution of albumin. Albumin is contained within the extracellular spaces with 40% circulating and the remainder within the interstitium. 60% of the body weight equals the amount of water in the body and the extracellular space makes up 1/3 of this total body water. Therefore, 7.5gs was administered into 3.0 liters (extracellular space) or 0.25g/dl. If this increase in albumin is added to the current 1.3g/dl the newly measured Albumin equals 1.5g/dl. Based on these calculations it is evident that an ineffective dose of fresh frozen plasma was administered to substantially raise this patients serum albumin.

Calculations:

\[
\text{20ml/kg x 15kg = 300mls given}
\]
\[
\text{FFP has 0.025g alb/ml}
\]
\[
\text{300mls x 0.025g/ml = 7.5 g albumin given}
\]
\[
\text{60\% of body weight = water in body}
\]
\[
\text{2/3 intracellular, 1/3 extracellular (1/4 intravascular and ¼ interstitial)}
\]
\[
\text{Albumin primarily in extracellular spaces}
\]
\[
\text{0.6 x 15 kg = 9 x 0.333 = 3.0 liters of extracellular space}
\]
\[
\text{7.5g/3.0 = 2.5 g/L = 0.25g/dl}
\]
\[
\text{1.3g/dl + 0.25g/dl = 1.55g/dl}
\]

The following day, another clinician decides to normalize this patient’s serum [albumin].

Question 13: Calculate the amount (in grams) of albumin required to raise the current albumin concentration of 1.5 g/dl [15 g/L] to a desired value of 2.0 g/dl[20 g/L]. Show all calculations.
Amt (in g) of Albumin to raise current Alb from 1.5 g/dl to 2.0 g/dl

\[
\text{Albumin deficit (grams) } = 10 \times (\text{albumin desired - current albumin}) \times \text{kg} \times 0.3 \quad \text{(based on body wt?)}
\]
\[
X \, g = 10 \times 0.5g \times 15\text{kg} \times 0.3
\]
\[
22.5 \, \text{grams}
\]

**Question 14:** Concentrated 25% human serum albumin solution is the only product available in your practice. What volume of this solution needs to be administered to correct the albumin deficit calculated in the previous question?

\[
250\text{mg/ml} = 0.25g/ml
\]
\[
22.5g \times 0.25g/ml = 90\text{ml}
\]

During administration of 25% human albumin solution, the patient develops facial swelling, tachycardia, hypotension, and tachypnea.

**Question 15:** What type of hypersensitivity reaction is occurring?

This patient is having a Type I hypersensitivity reaction. Type I (anaphylactic, immediate) hypersensitivity reactions are classically described as those involving genetic predilection, antibody (IgE) production, and mast cell degranulation. A genetically programmed individual absorbing a complete antigen responds by producing a unique antibody (IgE). IgE avidly binds membrane receptors on tissue mast cells and blood basophils. This reaction occurs within minutes. The classic examples of diseases that involve type I hypersensitivity reactions in dogs and cats are urticaria, angioedema, anaphylaxis, atopy, food hypersensitivity, flea bite hypersensitivity and some drug eruptions. The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis). The reaction may cause a range of symptoms from minor inconvenience to death.

Reference:
- Scott DW, Miller WH, Griffin CE, Muller & Kirk’s Small Animal Dermatology, 5th ed, pg 496.

Appropriate therapy is instituted and the patient is discharged 4 days later. Two weeks following discharge, the same patient represents with azotemia, facial and limb edema, joint pain and proteinuria.

**Question 16:** A transfusion reaction to the exogenously-administered albumin product is suspected. What type of hypersensitivity reaction is likely to be present?

Type III (immune complex) hypersensitivity reactions are characterized by the deposition of circulating antigen-antibody complexes in blood vessel walls. These immune complexes (usually containing IgG or IgM) the fix complement, which attracts neutrophils. Proteolytic and hydrolytic enzymes released from the infiltrating neutrophils produce tissue damage. Type I hypersensitivity reactions and histamine release may be important in the initiation of immune complex deposition. Examples of type III hypersensitivity reactions in dogs and cats are systemic lupus erythematous, leukocytoclastic vasculitis, some drug eruptions and bacterial hypersensitivity.

Reference:
- Scott DW, Miller WH, Griffin CE, Muller & Kirk’s Small Animal Dermatology, 5th ed, pg 496.

**Question 17:** Pentoxifylline is being considered for this patient.

A) What is this agent used for?

The mechanisms for pentoxifylline's actions are not fully understood. The drug increases erythrocyte flexibility probably by inhibiting erythrocyte phosphodiesterase and decreases blood viscosity by reducing plasma fibrinogen and increasing fibrinolytic activity. Additionally, Pentoxifylline is postulated to reduce negative endotoxic effects of cytokine mediators via its phosphodiesterase inhibition.

B) How may this drug help this patient?
Pentoxifylline is used in dogs to treat immune-mediated conditions, enhance healing and reduce inflammation and for other conditions where improved microcirculation may be of benefit. For this patient it may promote improved circulation to reduce the facial and limb edema.

Reference:
- Plumb’s Veterinary Drug Handbook

**Question 18:** What other therapies should be considered in the treatment regime for this patient, considering the development of azotemia and proteinuria? Give justification for the treatments.

Treatment for immune-mediated glomerulonephritis includes: 1) treating underlying disease process, 2) treatments to reduction the magnitude of proteinuria (e.g., feeding a renal diet, administration of an ACE inhibitor), 3) treating uremia other complications of generalized renal failure or excessive proteinuria.

- **ACE inhibitors** such as Benazapril can be used for persistent proteinuria of glomerular origin. Angiotensin converting enzyme (ACE) inhibitors (e.g., enalapril, benazepril) reduce glomerular capillary hydrostatic pressure by decreasing postglomerular arteriolar resistance and thus reduce proteinuria. This beneficial effect must be balanced against their potential to worsen azotemia.

- **Anti-hypertensives** may be used in the management of hypertension. These include amlodipine, hydralazine, prazosin, and propranolol.

- **Aspirin** at a low dosage may selectively inhibit platelet cyclooxygenase without preventing the beneficial effects of prostacyclin formation (e.g., vasodilatation, inhibition of platelet aggregation).

- **Clopedigrol** is indicated for the reduction of thrombosis.

- **Omega-3 polyunsaturated fatty acids** (as found in fish oil) may suppress glomerular inflammation and coagulation by interfering with production of pro-inflammatory prostanoids. A diet with a low N6:N3 ratio of polyunsaturated fatty acids thus may be beneficial.

- **Immunosuppressives:** No studies in veterinary medicine are available to demonstrate effectiveness of any specific therapy for GN. Immunosuppressive drugs (e.g., corticosteroids, azathioprine, cyclophosphamide, chlorambucil, cyclosporine) have been variably recommended.

The patient develops severe respiratory distress in the 24 hours following admission. Thoracic radiographs are obtained.

**Question 19:** Please list 3 radiographic findings that suggest to you that this patient’s pulmonary problems are not primarily cardiogenic.

1. no evidence of pulmonary venous congestion
2. no evidence of cardiomegaly
3. lack of hilar pulmonary edema
4. no evidence of a dorsally displaced trachea to suggest atrial enlargement
5. no evidence of atrial enlargement

**Question 20:**

Please list 3 pulmonary and 3 non-pulmonary causes of ARDS.

**Pulmonary causes of ARDs**
1. pneumonia
2. pulmonary contusions
3. inhalation of noxious gases

Non-pulmonary causes of ARDs
1. sepsis
2. noncardiogenic pulmonary edema (electrocution)
3. SIRS
4. shock
5. anaphylaxis
6. polytrauma

Reference:

**Question 21:** Optimal fluid therapy including the use of colloids and diuretics in ARDS patients is controversial.

A. Give the Starling equation for transvascular fluid dynamics (describing fluid flux across a semi-permeable membrane).

\[ \text{Net filtration} = L_p S [\Delta \text{hydraulic pressure} - \Delta \text{oncotic pressure}] = L_p S [(P_{cap} - P_{if}) - s(\pi_{cap} - \pi_{if})] \]

B. Define each term and describe how each component influences fluid flux.

- \( L_p \) = permeability (porosity) of the capillary
- \( S \) = surface area available for fluid movement
- \( s \) = reflection coefficient for proteins across the capillary wall
- \( P_{cap} \) = hydrostatic pressure of plasma
- \( P_{if} \) = hydrostatic pressure of interstitial fluid
- \( \pi_{cap} \) = oncotic pressure (colloidal osmotic pressure) of plasma
- \( \pi_{if} \) = oncotic pressure (colloidal osmotic pressure) of interstitial fluid

C. Using the Starling equation variables, give an argument for conservative (less than maintenance rate, with or without diuretics) fluid support.

\[ \text{Net filtration} = L_p S [\Delta \text{hydraulic pressure} - \Delta \text{oncotic pressure}] = L_p S [(P_{cap} - P_{if}) - s(\pi_{cap} - \pi_{if})] \]

ARDS patients have an inflammatory condition which leads to altered permeability at the alveolar-capillary interface. The permeability (\( L_p \)) becomes increased. With in increased permeability the net filtration is increased meaning excessive or liberal fluid therapy may cause fluid to escape the intravascular space entering the alveolus and interstitium. Therefore, conservative fluids would be advocated to prevent this.

D. Using the Starling equation variables, give an argument for liberal fluid support.

\[ \text{Net filtration} = L_p S [\Delta \text{hydraulic pressure} - \Delta \text{oncotic pressure}] = L_p S [(P_{cap} - P_{if}) - s(\pi_{cap} - \pi_{if})] \]

In order to maintain optimal perfusion pressure we need to maintain the intravascular volume. In order to do this we want to support the hydrostatic pressure of plasma (\( P_{cap} \)) with liberal fluid support.