# Ampicillin–Sulbactam

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Despite increasing bacterial resistance worldwide, penicillin-based antimicrobial agents remain one of the most important classes of antibiotics used in dogs, cats, and humans.[1]

## PHARMACOLOGY & CLINICAL APPLICATIONS

**Ampicillin–sulbactam is a potentiated aminopenicillin that kills bacteria by blocking bacterial cell wall growth.**[2-4]

- For details, see ***Pharmacodynamics & Pharmacokinetics***.

**This combination agent is usually reserved for treating bacterial infections known to produce β-lactamase.**

- In humans, this agent is especially important in treating multidrug-resistant infections caused by *Acinetobacter baumannii*, an opportunistic gram-negative pathogen responsible for serious hospital-acquired infections.[2,5]

MIC = minimum inhibitory concentration
PCR = polymerase chain reaction

**In human medicine, increasing prevalence of bacterial resistance to ampicillin and amoxicillin–clavulanic acid has raised concerns.**[6-9]

- Use of ampicillin–sulbactam should be limited to cases in which a susceptible organism is strongly suspected or documented with susceptibility testing.
- When presumptive treatment is initiated, performing a culture is strongly recommended.
  - If the susceptibility of the isolated organism is resistant, ampicillin–sulbactam treatment should be discontinued.

**In veterinary medicine, extralabel use is likewise indicated only when a susceptible organism is strongly suspected or documented.**

- Routine extralabel use not recommended

**In dogs and cats, ampicillin–sulbactam may be a rational empiric choice or presumptive therapy for the following clinical situations involving specific suspected pathogens (see *Spectrum of Activity*, page 44):**

- Infections with penicillinase-producing anaerobes likely (eg, GI compromise)[10,11]

- Single therapy for penetrating skin injuries associated with cat bites, puncture wounds, and foreign bodies[12]
- Combination therapy for systemic infection (eg, cholangitis, aspiration pneumonia, septicemia)[13-16]
- Susceptible infections during hospitalization, with de-escalation to amoxicillin–clavulanic acid because of its similar spectrum of activity or to amoxicillin when clinical need for β-lactamase inhibition has been ruled out[17,18]
- Presumptive use in animals in which an infectious agent (eg, *Leptospira* spp) is suspected in association with acute kidney injury and/or hepatopathy[19]
  - Pending results of urine culture and leptospirosis testing (eg, urine PCR, serology)
  - Clears leptospiremic phase of leptospirosis
    - Patients with confirmed leptospirosis should be transitioned to doxycycline.

### In the United States, extralabel use of ampicillin–sulbactam in dogs and cats is limited to parenteral administration as extrapolated from human formulation.

- Extralabel doses (based on ampicillin component) as recommended[3]
  - For empiric therapy in critically ill dogs and cats: extralabel dosage, 15-30 mg/kg IV q6-8h[3]
    - For systemic infections, use in combination with a parenteral drug with gram-negative activity (eg, aminoglycoside, fluoroquinolone).
  - For infections susceptible to amoxicillin–clavulanic acid in patients unable to receive oral medication: extralabel dosage, 10-20 mg/kg IV or IM q8h[3]
- Available as a 2:1 ratio of ampicillin to sulbactam for parenteral administration in vials as crystalline powder for reconstitution[20]
  - 1.5 g (1 g ampicillin sodium, 0.5 g sulbactam sodium)
  - 3 g (2 g ampicillin sodium, 1 g sulbactam sodium)
  - 15 g (10 g ampicillin sodium, 5 g sulbactam sodium)
- Reconstituted ampicillin–sulbactam stability is concentration- and temperature-dependent.[20]
  - Concentration commonly used for IV administration is 30 mg/mL (20 mg/mL ampicillin, 10 mg/mL sulbactam; initially reconstituted in a small volume of sterile water to dissolve crystalline powder, followed by further dilution with 0.9% NaCl for final concentration for injection, which is stable at 4°C for 72 hours).[20]
  - Administer IV slowly, over ≈15 to 20 minutes.
  - Aminopenicillins are eliminated by the kidneys (including a significant portion excreted via tubular secretion).[21]
    - In some human patients with altered glomerular filtration rates due to renal azotemia, consideration should be given for dose adjustment.[21,22]
    - Although no known data are available for veterinary patients, some animals with severe renal dysfunction may require dose reduction.

## PHARMACODYNAMICS & PHARMACOKINETICS

### Ampicillin–sulbactam is a potentiated (ie, β-lactamase inhibitor) aminopenicillin with bactericidal and time-dependent activity.[23]

- For antibacterial drugs with time-dependent activity, bactericidal activity depends on the duration of drug exposure above the minimum inhibitory concentration (MIC).
  - Because bacterial killing is time-dependent, clinical success, especially in the treatment of gram-negative infections, depends on retaining drug concentrations above the MICs during the entire dosing interval.

### Ampicillin is a semisynthetic penicillin (ie, β-lactam antibiotic) that effectively kills bacteria by disrupting the bacterial cell wall.[2-4]

- Bacterial cell wall synthesis is inhibited through penicillin-binding proteins and by disrupting cell wall integrity via inhibition of the transpeptidation reaction responsible for bacterial cell wall cross-linking.

### Sulbactam is a semisynthetic β-lactamase inhibitor that irreversibly binds and inactivates a variety of β-lactamases.[2-4]

- Used in combination with β-lactam antimicrobials to target bacterial strains that would otherwise be resistant to nonpotentiated β-lactam antibiotics
- Alone, sulbactam has weak antibacterial activity.

### As an aminopenicillin, this combination has a short elimination half-life (healthy humans, 1 hour),[21] resulting in need for frequent administration.

### Overall, ampicillin–sulbactam is a relatively polar or hydrophilic drug combination.

- In humans, drug concentrations are achieved in tissue (eg, bone, muscle, skin) and body fluids (eg, sputum, peritoneal fluid).[1,5]

## ADVERSE EVENTS & PRECAUTIONS

### Adverse reactions include[3,4,12]

- Thrombophlebitis or allergic reactions (IV)
- Seizures (rapid IV infusion)
- Pain at injection site (IM)

### Other possible side effects include vomiting and diarrhea.

- Hepatocellular cholestasis has been reported in association with administration of ampicillin–sulbactam in humans[24,25]; this has not been reported in veterinary patients.
- Pregnancy and lactation
  - Penicillins are known to cross the placenta; however, ampicillin has been suggested as probably safe (class A) during pregnancy in dogs and cats, based on lack of toxicity or teratogenicity identified in other species.[26,27]
  - Little is known about the safety of sulbactam during pregnancy and whether it crosses the placenta.
  - Breast milk concentrations of ampicillin and sulbactam are considered low, and both antimicrobial agents are considered compatible with breastfeeding in humans.[3]

## SPECTRUM OF ACTIVITY[3,4]

- Susceptible gram-positive aerobes include *Staphylococcus* spp, *Streptococcus* spp, *Enterococcus faecalis*, and *Actinomyces* spp
  - Ineffective against methicillin-resistant *Staphylococcus* spp
- Susceptible gram-negative aerobes including β-lactamase–producing bacteria (ie, *Escherichia coli*, *Pasteurella* spp, *Klebsiella* spp, *Proteus* spp) and *Salmonella* spp
- Ineffective against bacterial strains containing type 1 β-lactamases, including *Citrobacter* spp, *Enterobacter* spp, *Serratia* spp, and *Pseudomonas* spp
- Also considered ineffective against *Pseudomonas aeruginosa* because of drug impermeability or drug efflux
- Susceptible anaerobes including *Clostridium* spp, *Bacteroides* spp, *Prevotella* spp, *Fusobacterium* spp, *Peptostreptococcus* spp, and *Propionibacterium* spp

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