Colistin Dosing Protocol

Infectious Diseases Section, VA Greater Los Angeles, March 2013

NOTE: because of the complexity of dosing, the limited therapeutic spectrum and high degree of toxicity, use of parenteral colistin at the VA Greater Los Angeles Healthcare System requires Infectious Diseases consultation.

Background

Colistin (Coly-Mycin M), also known as polymyxin E, is available for parenteral administration as a prodrug, colistin methanesulfonate (CMS). Colistin is a multicomponent polypeptide antibiotic, mainly used for treatment of multidrug resistant Gram negative bacteria, including *Pseudomonas aeruginosa, Acinetobacter baumannii*, *Klebsiella* species, *Enterobacter* species, *E.coli*, and *Citrobacter* species. However, *Pseudomonas mallei*, *Burkholderia cepacia*, *Proteus* species, *Providencia* species, *Serratia* species, *Edwardsiella* species, and *Brucella* species are all resistant to colistin. Colistin produces concentration dependent killing activity with moderate post antibiotic effect at high concentration (≥ 16x MIC, mostly not achievable in clinical practice). Extended interval regimens have a greater time of period in which the concentration falls below the MIC, therefore increasing the risk of treatment failure and resistance. Dosing regimens using shorter time intervals may be favored. Antimicrobial activity is best associated with AUC/MIC ratio. Colistin $C_{ss,\ avg}$ of 2.5mg/L corresponds to a ratio of $AUC_{(0\text{-}24)}$/MIC of 60 which is associated with an effect somewhere between stasis and 1-log kill in *Pseudomonas* and *A.baumannii* murine thigh and lung infection models.

CLSI recommends the following breakpoints:

- *P.aeruginosa*
  - ≤ 2ug/ml = susceptible
  - 4ug/ml = intermediate
  - 8ug/ml= resistant
- *Acinetobacter*
  - ≤ 2ug/ml = susceptible
  - ≥4ug/ml = Resistant
- Enterobacteriaceae- no recommendation

Colistin is best used as part of a highly active combination, especially when treating an infection caused by an organism with an MIC of >0.5 µg/ml.

Body size affects the volume of the central compartment for CMS. Therefore the suggested CMS loading dose is a function of body weight. However, body size does not affect the clearance of either CMS or colistin; therefore maintenance doses are not weight based.

The prodrug, CMS, is cleared predominantly by renal excretion. As CrCl declines, a progressively larger fraction of a dose of CMS is converted to colistin. Thus, dosage adjustment based on CrCl is necessary. Colistin is eliminated predominantly by the non-renal route in individuals with normal kidney function by a mechanism that is not yet fully understood. Both CMS and colistin are efficiently cleared during intermittent HD.

Dosing Guidelines:

The dose of CMS is expressed as colistin base activity (CBA). Each vial contains 150mg of colistin base activity.

Loading dose (**LD,** All patient categories)

LD of CBA (mg) =5.0 x body wt (kg)

*** Use the lower of ideal or actual body wt (kg)

*** Not to exceed 300mg

Maintenance dose: 1st dose should be given 24 hours after LD

- Not on renal replacement therapy:

  Daily dose of CBA (mg) = 2.5 x (1.5xCrcl+30)

  ***Dosing interval adjusted based on CrCl (ml/min/1.73m2):
  - CrCl<10ml/min/1.73m^2= q12h
  - CrCl: 10-70ml/min/1.73m^2 = q12-q8h
  - CrCl>70ml/min/1.73m^2= q8h
- Intermittent hemodialysis:
  - None HD day- **Daily dose of CBA** = 75mg; given as 37.5 mg q 12h
  - On days when dialysis is given an additional 30% of the daily maintenance dose is given after HD :
    - 1st dose = 37.5mg
    - Second dose (12 hours later) = 60 mg
- CRRT:
  - Daily dose =480mg; give as 160 mg q 8 h.

Administration

• IV infusion can be given over 30 minutes

• IM administration is not recommended because of severe pain at injection site

Toxicity Monitoring

• Nephrotoxicity:

– Relatively common (a recent study of higher dose colistin reported that ~48% of patients had a rise in serum creatinine of >50% of which 63% of levels remained elevated at the end of the study)

- Appears to be dose related and prolonged duration of treatment (>14days)

• Neurotoxicity:

- Much less common than nephrotoxicity , ~7% in earlier literatures
- Can manifest as dizziness, weakness, facial and peripheral paresthesia, vertigo, visual disturbances, confusion, ataxia, and neuromuscular blockage. Paresthesia is the main neurotoxic adverse event
- Typically reversible upon dose reduction or discontinuation

References

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