Optimizing Treatment for Gram-Negative Bacteremia

Alison Rydell, PharmD
PGY1 Pharmacy Resident
St. Luke's Hospital
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Objectives

1. Identify the most common causative organisms of Gram-negative bacteremia and current guideline recommendations
2. Evaluate when it may be appropriate to transition from IV to oral therapies
3. Describe appropriate oral therapies for Gram-negative bacteremia

Abbreviations

BA: bioavailability
BL: beta-lactam
BSI: bloodstream infection
CAE: chromosomally-mediated AmpC-producing Enterobacterales (*Enterobacter, Serratia, Citrobacter*, and *Morganella*)
CLABSI: central line-associated bloodstream infection
FQ: fluoroquinolones
GI: gastrointestinal
GNB: Gram-negative bacteremia
IA: intra-abdominal
IV: intravenous
MDR: multi-drug resistant
MIC: minimum inhibitory concentration
PO: *per* os, oral (by mouth)
SMX/TMP, S/T: sulfamethoxazole/trimethoprim
SSTI: skin and soft tissue infection
UTI: urinary tract infection

Epidemiology of Gram-negative bacteremia[1,2]

- Gram-negative bacilli cause 25-50% of all bloodstream infections
- Primary sources: urinary (51%), abdominal (11%), respiratory (11%)
- Microbiology: *Escherichia coli* (47.4%), *Klebsiella pneumoniae* (14.7%), *Pseudomonas aeruginosa* (9.2%), *Enterobacter* spp. (6.5%), *Proteus mirabilis* (4.2%)

Guideline-recommended treatment options[3]

Organism	Preferred	Alternatives
E. coli, K. pneumoniae, ESBL-negative	IV 3rd generation cephalosporin	Ciprofloxacin or aztreonam
E. coli, K. pneumoniae, ESBL-positive	Carbapenem	Ciprofloxacin or aztreonam
Enterobacter spp.	Carbapenem	Ciprofloxacin or cefepime*
Acinetobacter spp.	Ampicillin/sulbactam or carbapenem	-
P. aeruginosa	4th generation cephalosporin or carbapenem or piperacillin/tazobactam +/- aminoglycoside	-

*Cefepime is preferred when MIC $\leq$ 4

Guidance for treatment duration[3,4]

- Infectious Diseases Society of America
  - No consensus statement
  - Recommends 7-14 days for catheter-associated infections
- National Action Plan for Combating Antibiotic-Resistant Bacteria
  - No additional guidance and identifies this area as a need for further research

Inappropriate treatment duration impact[5]

- Inadequate duration: clinical failure, relapsing infection, development of resistance
- Excess duration: adverse effects from antibiotics, *C. difficile* infections, resistance in off-target pathogens

<u>What is the optimal treatment duration for Gram-negative bacteremia?</u>

Li, et al meta-analysis (2021)[6]

- Purpose: compare clinical outcomes of short courses versus long courses of antibiotics for uncomplicated Gram-negative bacteremia
- Six studies (2,689 patients) included
- Primary outcomes:
  - 30-day all-cause mortality
  - 30-day recurrent bacteremia
- Secondary outcomes:
  - Primary outcomes at 90 days
  - Adverse events
  - *C. difficile* infections
  - Emergence of resistance
- Study demographics

Study	Short-course (N)	Long-course (N)	Main pathogen	Main source
Von Dach (2021)	7 days (169)	14 days (165)	*E. coli* (74%)	Urinary (67%)
Yahav (2019)	7 days (306)	14 days (298)	*E. coli* (63%)	Urinary (68%)
Sousa (2018)	7-10 days (168)	>10 days (232)	*E. coli* (57%)	Urinary (52%)
Fabre (2019)	7-11 days (72)	>11 days (179)	*P. aeruginosa* (100%)	Urinary (30%)
Chotiprasitsakul (2018)	6-10 days (385)	11-16 days (385)	*E. coli* (47%)	Urinary (36%)
Park (2013)	7-10 days (170)	>10 days (170)	*Klebsiella* spp. (30%)	Central-line (62%)

- Inclusion and exclusion criteria
  - Inclusion: Gram-negative bacilli identified in at least one blood culture, uncomplicated infection
  - Exclusion: deep-seated infections (e.g. undrained abscess, endocarditis, osteomyelitis), polymicrobial infections, immunocompromised patients, *Brucella* or *Salmonella* infections, inappropriate antibiotic choice
- Median treatment durations

Study	Short-course Median Duration	Long-course Median Duration
Von Dach (2021)	7 days	14 days
Yahav (2019)	7 days	14 days
Sousa (2018)	10 days	14 days
Fabre (2019)	9 days	16 days
Chotiprasitsakul (2018)	8 days	15 days
Park (2013)	10 days	14 days

- Results

Outcome	Number of Patients	RR (95% CI)	P-value
30-day all-cause mortality	2,689	0.85 (0.65-1.13)	0.26
30-day recurrent bacteremia	2,689	1.07 (0.68-1.67)	0.78
90-day all-cause mortality	921	0.84 (0.57-1.24)	0.47
90-day recurrent bacteremia	1,316	0.98 (0.50-1.89)	0.77
Adverse events	933	1.14 (0.89-1.45)	0.62
C. difficile infections	2,043	0.86 (0.40-1.86)	0.61
Resistance development	1,374	1.19 (0.66-2.14)	0.12

Conclusions for optimal treatment duration

- For patients with uncomplicated Gram-negative bacteremia, it is reasonable to consider a shorter duration (7-10 days), as opposed to longer durations ($\geq$ 14 days)
- Consider a longer duration if:
    - Deep-seated infection
    - Immunocompromised patient
    - Polymicrobial infection
    - Unknown focus of infection
    - Source control not feasible

Can patients be transitioned to oral antibiotics?

Rationale for switching to oral therapy[7]

- Decreased hospital length of stay
- Decreased costs
- Less likelihood of line-associated complications (infections, phlebitis)

Considerations for switching to oral therapy[8]

- Clinically improving, source control, clinical efficacy data, drug bioavailability, dosing, drug interactions, adverse event profile

Current practice[9]

- Survey of 277 infectious disease specialists
- Transition from IV to PO:
    - 57% transition from IV to PO in all cases
    - 40% transition from IV to PO only for infections from certain sources
    - 3% treat with IV only
    - Willingness to transition according to treatment source: urine (92%), SSTI (90%), pneumonia (78%), IA (75%), line-associated (64%)
- Minimum duration of IV therapy: 5 days

Tamma, et al. retrospective trial (2019)[10]

- Study components
    - Objective: compare 30-day mortality rates for patients with early step-down from IV to PO vs. continued IV therapy for Gram-negative bacteremia
    - Study design: retrospective, propensity score-matched cohort
    - Inclusion: monomicrobial Enterobacterales bacteremia, source control, able to take other oral medications, clinical improvement by day 5

- Exclusion: oral antibiotics from day 1, inappropriate antibiotics within first 24 hours, less than 7 days or greater than 16 days of antibiotics
- Sample size: 2,161 (1,478 in propensity score-matched cohort)
- Intervention: transitioning to oral antibiotics at day 5 vs. continuing IV antibiotics
- Outcomes: 30-day all-cause mortality, 30-day recurrent bloodstream infection, length of hospitalization

- Cohort trends
  - Group that was transitioned to PO was less likely to require ICU level care, less likely to be immunocompromised or neutropenic, and less likely to receive combination antibiotics therapy for > 48 hours

- Infection sources

Source	Oral therapy (N=739) N (%)	IV therapy (N=739) N (%)
Urinary	295 (39.9)	299 (40.5)
Gastrointestinal	152 (20.6)	145 (19.6)
Catheter-associated	135 (18.3)	137 (18.5)
Biliary	103 (13.9)	107 (14.5)
Pulmonary	29 (3.9)	29 (3.9)
Skin and soft tissue	22 (3.0)	19 (2.6)

- Microbiology

Bacteria	Oral therapy (N=739) N (%)	IV therapy (N=739) N (%)
Escherichia coli	336 (45.5)	309 (41.8)
Klebsiella pneumoniae	237 (32.0)	268 (36.2)
Enterobacter spp.	91 (12.3)	82 (11.1)
Proteus mirabilis	25 (3.4)	40 (5.4)
Serratia marcescens	22 (3.0)	19 (2.6)
Citrobacter spp.	16 (2.2)	11 (1.5)
Klebsiella oxytoca	12 (1.6)	10 (1.3)

- Results
  - Median duration of total antibiotic therapy: 14 days

Outcome	Oral therapy (N=739)	IV therapy (N=739)	HR (95% CI)
30-day all-cause mortality	97 (13.1%)	99 (13.4%)	1.03 (0.82-1.30)
Recurrent BSI within 30 days	6 (0.8%)	4 (0.5%)	0.82 (0.33-2.01)
Median time to hospital discharge (days)	5 (IQR 3-8)	7 (IQR 4-14)	0.98 (0.91-1.00)

- Conclusions
  - Clinical outcomes are not worse for patients who transition to oral therapy
  - Transition to oral therapy is associated with shorter hospital length of stay

Transition to PO for GNB from urinary source

- Rieger, et al. (2017)[11]
    - Sample size: 241
    - Primary outcome: composite of clinical failure (escalation to IV from PO, readmission for same pathogen, change in antibiotic due to clinical worsening) within 30 days
    - Mediation duration of IV therapy: 4 days
    - Results:
        - Treatment failure in IV only: 4/106 (3.8%)
        - Treatment failure in IV/PO: 11/135 (8.2%)
        - p=0.19

- Thurber, et al. (2019)[12]
    - Sample size: 346
    - Primary outcome: composite of all-cause mortality and recurrent BSI within 21 days
    - Median duration of IV therapy: 3 days
    - Results:
        - Treatment failure in IV only: 2/82 (2.4%)
        - Treatment failure in IV/PO: 4/264 (1.5%)
        - HR 0.62 (95% CI 0.11-3.39), p=0.58
        - No deaths in either group

IV to PO transition conclusions

- Patients should be transitioned to PO antibiotics after 3-5 days of IV therapy
- Why?
    - Low rates of treatment failure with transition to oral antibiotics
    - Higher incidence of line-associated adverse effects with continued IV therapy

Which oral antibiotics are effective for treating Gram-negative bacteremia?

Oral therapy options[13]

- Fluoroquinolones: highest bioavailability ($\geq$ 95%)
    - Levofloxacin ~99%, ciprofloxacin ~70%
- Sulfamethoxazole/trimethoprim: moderate bioavailability (75-94%)
- Beta-lactams: lowest bioavailability (< 75%)

Bioavailability of oral beta-lactams[14]

Antibiotic	Bioavailability (%)	Protein binding (%)
Amoxicillin	74-92	20
Amoxicillin-clavulanate	60-85	20
Cephalexin	90-100	6-15
Cefaclor	52-95	25
Cefprozil	71-95	36
Cefuroxime	30-52	33-50
Cefdinir	21-25	60-70
Cefpodoxime	29-53	22-33

Proposed beta-lactam dosing for Gram-negative bacteremia[14]

Antibiotic	Dosing Regimen	Maximum MIC allowing for target obtainment	Highest frequency for wild-type MIC for *E. coli*
Amoxicillin	500 mg Q8H	0.5 mg/L	4 mg/L
	1000 mg Q8H	1 mg/L	4 mg/L
Amoxicillin-clavulanate	875 mg Q8H	0.5 mg/L	4 mg/L
Cephalexin	500 mg Q6H	2 mg/L	4 mg/L
	1000 mg Q6H	4 mg/L	4 mg/L
Cefaclor	500 mg Q6H	0.5 mg/L	1 mg/L
Cefpodoxime	400 mg Q12H	0.25 mg/L	0.5 mg/L

Kutob, et al. retrospective trial (2016)[13]

- Objective: identify risk factors for treatment failure in 362 patients who received oral antibiotics for GNB
- Antibiotics

Bioavailability	Antimicrobial Agent	N (%)
High (≥ 95%)	Levofloxacin	106 (29)
Moderate (75-94%)	Ciprofloxacin	151 (42)
	SMX/TMP	28 (8)
Low (< 75%)	Beta-lactam	77 (21)

- Microbiology

Bacteria	High BA (N=106)	Moderate BA (N=179)	Low BA (N=77)
Escherichia coli	68 (64)	115 (64)	60 (78)
Klebsiella spp.	14 (13)	25 (14)	10 (13)
Proteus mirabilis	7 (7)	9 (5)	4 (5)
Pseudomonas aeruginosa	1 (1)	12 (7)	0 (0)
CAE	13 (12)	13 (7)	2 (3)
Other	3 (3)	5 (3)	1 (1)

- Results
  - Treatment failure at 90 days: 27/362 (7.4%)

- Risk factors for treatment failure

Risk factor	HR (95% CI)	P-value
Diabetes	1.27 (0.58-2.71)	0.54
End-stage renal disease	1.95 (0.46-5.58)	0.32
Liver cirrhosis	6.52 (2.18-15.91)	0.002
Immunocompromised	3.15 (1.23-7.11)	0.02
Urinary source	0.56 (0.26-1.25)	0.15
***Pseudomonas* or CAE**	1.63 (0.48-4.25)	0.39
Moderate BA antibiotic	5.38 (1.53-34.04)	0.006
Low BA antibiotic	6.41 (1.65-42.03)	0.006

- Antibiotic route and duration

	High BA (N=106)	Moderate BA (N=179)	Low BA (N=77)
Duration of IV therapy, days (mean ± SD)	4.4 ± 2.8	4.8 ± 2.5	4.8 ± 2.2
Total duration of antibiotic therapy, days (mean ± SD)	13.2 ± 5.1	14.2 ± 6.1	13.9 ± 5.3

- Oral antibiotic regimens

BA	Antimicrobial agent	N	Most common oral regimens	N (%)
High	Levofloxacin	106	500 mg q24h 750 mg q24h	51 (48) 35 (33)
Moderate	Ciprofloxacin	151	500 mg q12h 750 mg q12h	127 (84) 11 (7)
	SMX/TMP	28	600/160 mg q12h	28 (100)
Low	Amoxicillin/clavulanate	30	875/125 mg q12h 500/125 mg q8h	21 (70) 9 (30)
	Amoxicillin	12	500 mg q8h	10 (83)
	Cephalexin	16	500 mg q6h	9 (56)
	Cefuroxime	8	500 mg q12h	8 (100)
	Cefdinir	7	300 mg q12h	7 (100)
	Cefaclor	3	250 mg q8h	3 (100)
	Cefpodoxime	1	200 mg q12h	1 (100)

- Conclusions:
    - Risk of treatment failure increases with lower bioavailability antibiotics
    - Oral antibiotics for GNB may not be appropriate for immunocompromised patients or those with liver impairment

Problems with fluoroquinolones[15]

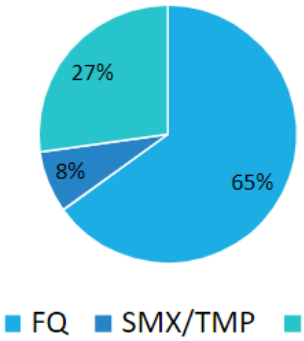
- Increasing rates of resistance
- Warnings and side effects:
    - *C. difficile* infections
    - Tendinitis and tendon rupture
    - Worsening of symptoms in patients with myasthenia gravis
    - Irreversible peripheral neuropathy
    - Anxiety, depression, altered mental status
    - QT prolongation

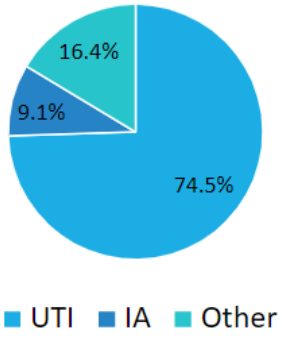
Punjabi, et al. meta-analysis (2019)[16]

- Purpose: compare oral therapies SMX/TMP, fluoroquinolones, and beta-lactams for GNB
- Eight studies (2,289 patients) included
- Primary outcomes:
    - All-cause mortality
    - Infection recurrence

- Study demographics

Study	Patient N and regimens	Infection source	Follow-up period (d)
Kutob (2016)	N=362 FQ=257, S/T=28, BL=77	UTI (70.2%)	90
Sessa (2018)	N=208 FQ=49, S/T=8, BL=151	UTI (77.8%) IA (16.3%)	30
Rieger (2018)	N=114 FQ=74, S/T=10, BL=30	UTI (100%)	30
Mercuro (2018)	N=224 FQ=140, BL=84	UTI (70.85%) IA (21%)	30
Fong (2018)	N=173 FQ=114, BL=59	UTI (57%) IA (22.5%)	90
Gumbleton (2018)	N=205 FQ=108, S/T=11, BL=86	UTI (80%) IA (11%)	30
Tamma (2019)	N=739 FQ=518, S/T=99, BL=122	UTI (40.2%) IA (20.1%) CLABSI (18.4%)	30
Thurber (2019)	N=264 FQ=229, S/T=21 BL=14	UTI (100%)	21





- Results
  - Median duration of IV therapy: 3-5 days
  - Total duration of antibiotic therapy (IV + PO): 13.6-16 days

Study	All-cause mortality (N, %)		Recurrence of infection (N, %)	
	FQ/SMX-TMP	**BL**	**FQ/SMX-TMP**	**BL**
Kutob (2016)	9/285 (3.2)	3/77 (3.9)	12/285 (4.2)	7/77 (9.1)
Sessa (2018)	0/57 (0)	0/151 (0)	3/57 (5.3)	14/151 (9.3)
Rieger (2018)	2/84 (2.4)	0/30 (0)	2/82 (2.4)	1/30 (3.3)
Mercuro (2018)	1/140 (0.7)	1/84 (0.1)	3/140 (2.1)	5/84 (5.9)
Fong (2018)	4/114 (3.5)	1/59 (1.7)	5/114 (4.4)	4/59 (6.8)
Gumbleton (2018)	1/119 (0.8)	2/86 (2.3)	0/119 (0)	3/86 (3.5)
Tamma (2019)	68/617 (11)	15/122 (15)	4/617 (0.6)	0/122 (0)
Thurber (2019)	0/250 (0)	0/14 (0)	4/250 (1.6)	0/14 (0)

- Conclusions:
    - Mortality rate and infection recurrence is low
    - Mortality rate and recurrence risk is lower with higher bioavailability antibiotics
    - Total durations for antibiotics with transition to PO is long (13-16 days)

Sutton, et al. retrospective trial (2020)[17]

- Objective: compare oral BL vs FQ or SMX/TMP for definitive treatment of GNB from urinary source
- Study design: retrospective cohort
- Inclusion: monomicrobial Enterobacterales bacteremia, received 1-5 days of IV antibiotics and transitioned to oral by day 6
- Exclusion: prior Enterobacterales bacteremia in previous 365 days, polymicrobial bacteremia, urologic abscess or prostatitis within 90 days of enrollment
- Sample: 4,089
- Outcomes: 30-day all-cause mortality, 30-day recurrent BSI
- Results:

	FQ, SMX/TMP (N=3134) N (%)	**BL (N=955) N (%)**	**aRD, % (95% CI)**	**aRR, % (95% CI)**
30 d composite	94 (3.0)	42 (4.4)	0.99 (-0.42 to 2.40)	1.31 (0.87 to 1.95)
Mortality	82 (2.6)	29 (3.0)	0.06 (-1.13 to 1.26)	1.02 (0.67 to 1.56)
Recurrent BSI	12 (0.4)	14 (1.5)	1.03 (0.24 to 1.82)	3.43 (0.42 to 27.90)
90 d composite	238 (7.6)	96 (10.1)	1.81 (-0.24 to 3.87)	1.23 (0.96 to 1.56)
Mortality	208 (6.6)	75 (7.9)	0.68 (-1.16 to 2.52)	1.10 (0.85 to 1.42)
Recurrent BSI	34 (1.1)	25 (2.6)	1.38 (0.30 to 2.47)	2.15 (0.92 to 5.01)

- Primary outcomes for BL regimens:

Antibiotic	**Patients N (%)**	**Recurrent BSI N (%)**	**Mortality N (%)**	**Dose (mg)**	**Patients N (%)**
Amoxicillin/ clavulanate	251 (26.3)	4/251 (1.6)	13/251 (5.2)	875/125 BID 500/125 BID 500/125 BID	161/251 (64.1) 46/251 (18.3) 28/251 (11.2)
Cephalexin	245 (25.7)	0 (0)	5/245 (2.0)	500 QID 500 BID 500 TID	115/245 (46.9) 57/245 (23.3) 47/245 (19.2)
Cefpodoxime	243 (25.4)	4/243 (1.6)	8/243 (3.3)	200 BID 400 BID	154/243 (63.4) 47/243 (19.3)
Amoxicillin	63 (6.6)	3/63 (4.8)	1/63 (1.6)	500 TID 500 BID	44/63 (69.8) 9/63 (14.3)
Cefdinir	35 (3.7)	1/35 (2.9)	0 (0)	300 BID	33/35 (94.3)

- Primary outcomes for FQ or SMX/TMP:

Antibiotic	Patients N (%)	Recurrent BSI N (%)	Mortality N (%)	Dose (mg)	Patients N (%)
Ciprofloxacin	2447 (78.1)	9/2447 (0.4)	61/2447 (2.5)	500 BID 500 daily 250 BID 750 BID	2003/2447 (81.9) 172/2447 (7.0) 130/2447 (5.3) 122/2447 (5.0)
Levofloxacin	374 (11.9)	0 (0)	13/374 (3.5)	750 daily 500 daily 250 daily	156/374 (41.7) 154/374 (41.2) 43/374 (11.5)
SMX/TMP	295 (9.4)	3/295 (1.0)	7/295 (2.4)	800/160 BID	259/295 (87.8)
Moxifloxacin	18 (0.6)	0 (0)	1/18 (5.6)	400 daily	18 (100)

- Conclusions: beta-lactams are not associated with higher mortality or increased risk of recurrence
- Strengths: large sample size, ability to follow-up, reporting of antibiotic regimens as they associated with outcomes
- Limitations: unable to assess adherence to oral antibiotics, no dosing guidance for oral antibiotics, no data collected for whether patients had indwelling catheters, limited by low event rate

Upcoming trials

- BALANCE Trial[18]
    - Study design: international randomized noninferiority trial
    - Intervention: 7 days vs. 14 days of antibiotic therapy for GNB
    - Primary outcome: all-cause mortality at 90 days
    - Estimated sample size: 3,622
    - Estimated completion date: March 2022
- INVEST Trial[19]
    - Study design: international randomized noninferiority trial
    - Intervention: early transition (within 72 hours) to FQ or SMX/TMP vs. continued IV therapy
    - Primary outcome: all-cause mortality at 30 days
    - Estimated sample size: 720
    - Estimated completion date: March 2025

Antibiotic duration summary

- Shorter courses (~7-10 days) are likely as effective as longer courses (~14 days)
- Consider extended course:
    - Immunocompromised patients
    - *Pseudomonas aeruginosa* bacteremia
    - No source control or deep-seated infection
- Ideal patient for short course:
    - Monomicrobial Enterobacterales bacteremia
    - Identifiable source with source control, if appropriate
    - Early clinical improvement

IV to PO summary

- More data needed to identify ideal total duration when switching to oral therapy
- Transition to oral after 3-5 days of IV therapy is likely appropriate

- Ideal candidate for early IV to oral transition:
    - Monomicrobial Enterobacterales bacteremia
    - Identifiable source and source control, if appropriate
    - Clinical improvement within 48 hours
    - No persistent bacteremia
    - Able to absorb oral medications

Oral antibiotics summary

- Higher bioavailability antibiotics, like levofloxacin, are the most effective
- More data is needed for sulfamethoxazole-trimethoprim
- Oral beta-lactams may be effective, but likely require longer durations
    - Should opt for higher bioavailability and higher doses

Assessment Questions

1. Which bacterium is the most common cause of Gram-negative bacteremia?
    a. *Pseudomonas aeruginosa*
    b. *Escherichia coli*
    c. *Klebsiella pneumoniae*
    d. *Proteus mirabilis*

2. Which oral antibiotic has the most evidence to support its use in the treatment of Gram-negative bacteremia?
    a. Levofloxacin
    b. Ciprofloxacin
    c. Sulfamethoxazole/trimethoprim
    d. Cefdinir

3. A patient presents with *E. coli* bacteremia secondary to cholecystitis. The culture and sensitivity report shows that the bacteria is susceptible to cefazolin, ceftriaxone, and levofloxacin. The patient has a past medical history of hyperlipidemia, hypertension, and prolonged QT syndrome. On day 2 of hospitalization, her gallbladder is removed. Her temperature returns to normal and her white blood cells are within normal limits. What is the most appropriate antibiotic regimen for this patient?
    a. Levofloxacin 750 mg PO x 14 days
    b. Piperacillin-tazobactam 3.375 g every 8 hours x 12 days
    c. Ceftriaxone 2 g IV daily x 7 days, then cefdinir 300 mg PO twice a day x 7 days
    d. Ceftriaxone 2 g IV daily x 5 days, then cephalexin 1000 mg PO Q6H x 9 days

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