

**Bon Secours Richmond
Pharmacy & Therapeutics Committees
Ceftriaxone Dosing Recommendation &
2 Gram Dosing DUE**

Recommendations:

- Patients with symptoms of CNS infections empirically, or evidence of CNS infections susceptible to ceftriaxone, should be given 2 gram doses of ceftriaxone at a dosing interval of every 12 hours. Patients with gonococcal endocarditis may also require twice daily dosing. Patients with endocarditis, febrile neutropenia, osteomyelitis, and Lyme disease should receive ceftriaxone 2 gram given daily.
- All other indications for ceftriaxone should be treated with **1 gram daily dosing**. Pharmacists will call the physician or leave a note for the physician recommending conversion to 1 gram daily unless the patient meets one of the above indications. If pneumococcal resistance is a concern Levaquin may be added and it covers atypical pathogens.

Review of the Literature

- According to the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group, **standard-dose β -lactam agents** provide an effective option against S pneumoniae **Community Acquired Pneumonia (CAP)** caused by either penicillin-susceptible isolates (ie, Minimum Inhibitory Concentrations (MICs) ≤ 0.06 $\mu\text{g/mL}$) or penicillin-intermediate isolates (ie, MIC range, 0.1 to 1 $\mu\text{g/mL}$). The dilemma about the continued efficacy of β -lactam agents arises only for those isolates with MICs of ≥ 2 $\mu\text{g/mL}$. Fortunately, the prevalence of S pneumoniae strains with MICs of > 2 $\mu\text{g/mL}$ remains uncommon.^{1,2}
 - It is important to utilize antibiogram data for each individual hospital. The breakpoints for Streptococcus pneumoniae were decreased in 2002, because the old breakpoints were set to ensure adequate coverage for central nervous system infections. Therefore, only current antibiogram data should be used when choosing antimicrobial therapy for S pneumoniae.

Cultures and Sensitivity for S. pneumoniae		
	2003	2004
SMH	N=20	N=13
Rocephin	85% (17/20)	92% (12/13)
Levaquin	100%	100%
Erythromycin	55%	54%
MRMC	N=33	N=26
Rocephin	88% (29/33)	92% (24/26)
Levaquin	100%	100%
Erythromycin	64%	50%

- **Nosocomial or healthcare acquired pneumonia (HAP)** occurs in patients who present with the following risk factors³:
 - Prior antimicrobial therapy in the preceding 3 months
 - Current hospitalization for at least 5 days
 - High frequency of antibiotic resistance in the community or in the specific hospital unit
 - Presence of risk factors for health-care related pneumonia
 - Hospitalization for at least 2 days in the preceding 90 days

- Residence in a nursing home or extended care facility
- Patients on home infusion therapy (including antibiotics)
- Chronic dialysis within 30 days
- Home wound care
- Family member with infection caused by a multi-drug resistant organism
- Patient on immunosuppressive therapy

The following decision tree should be utilized for the management of patients presenting with HAP⁴:

Early onset HAP (48 hrs after hospital admission), no prior antibiotics

- Nonpseudomonal third-generation cephalosporin (i.e. ceftriaxone 1 gram daily) or β -Lactam- β -lactamase inhibitor combination

Early onset HAP, prior antibiotics; or late-onset HAP, no prior antibiotics

- Aminoglycoside (pulse-dosing) or levofloxacin (Levaquin[®]) 750mg daily **plus** one of the following: ceftazidime (Fortaz[®]) or piperacillin-tazobactam (Zosyn[®])

Late-onset HAP, prior antibiotics

- Aminoglycoside or levofloxacin plus piperacillin-tazobactam or imipenem plus vancomycin

- **Febrile neutropenia** is defined by the following parameters: a single oral temperature of $\geq 38.3^{\circ}\text{C}$ (101°F) or a temperature of $\geq 38.0^{\circ}\text{C}$ (100.4°F) for $\geq 1\text{h}$ **and** a neutrophil count of $\leq 500\text{ cells/mm}^3$ or a count of $< 1000\text{ cells/mm}^3$ with a predicted decrease to $< 500\text{ cells/mm}^3$.⁵ The following decision tree should be utilized for empiric management of patients presenting with febrile neutropenia⁵:

Oral Route

- For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate

Monotherapy when vancomycin is not indicated

- Choose therapy with 1 of the following agents: ceftazidime or imipenem (Primaxin[®])

Two drugs without vancomycin

- Choose an aminoglycoside **plus** antipseudomonal penicillin, ceftazidime, or imipenem

Vancomycin plus 1 or 2 antibiotics, if criteria for use of vancomycin are met*

- Choose ceftazidime plus vancomycin with or without an aminoglycoside; imipenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin

* Inclusion of vancomycin in initial empirical therapy may be prudent for selected patients with the following clinical findings: (1) clinically suspected serious catheter-related infections (e.g., bacteremia, cellulitis), (2) known colonization with penicillin- and cephalosporin-resistant pneumococci or methicillin-resistant *S. aureus*, (3) positive results of blood culture for gram-positive bacteria before final identification and susceptibility testing, or (4) hypotension or other evidence of cardiovascular impairment.

- Ceftriaxone is highly protein bound and distributes throughout the body. High doses are used for meningitis in order to penetrate the central nervous system; otherwise concentrations resulting from 1 gram dosing should be adequate to treat susceptible organisms.^{6,7}
- Strategies to improve antimicrobial use include the following⁸:
 - Prompt initiation of appropriate empiric antimicrobial therapy
 - Using proper dosing and dosing regimens
 - Antimicrobial streamlining (de-escalating)- narrowing the spectrum of empiric antibiotic therapy once an organism has been identified
 - IV to PO switch therapy (Criteria include the following: medication has high oral bioavailability, patient has had at least 2 days of IV therapy, patient is taking other oral medications, and patient's condition is compatible with oral therapy.)

- Antibiotic control programs, including restricting the formulary
- Hallmark symptoms of **meningitis** include fever, headache, and stiff neck. Patient history, blood culture and lumbar puncture are needed to make a diagnosis of meningitis. Findings in the cerebral spinal fluid (CSF) that are characteristic for bacterial meningitis include a glucose concentration of 45 mg/dL or below, a protein concentration above 500 mg/dL, and a white blood cell count above 1000/mm³. When the causative bacteria is unknown, the recommendation for immunocompetent adults is to use a third-generation cephalosporin: ceftriaxone (2 g IV every 12 hours in adults) plus vancomycin (2 g/day IV in two or four divided doses in adults) until the organism is identified and its antibiotic susceptibility is determined. Coverage for *L monocytogenes* should be considered in patients who are immunocompromised.⁹
- When drug shortages require an automatic substitution to other therapy, all health care providers should be aware of the change in therapy. The order needs to be followed as written.
- Bon Secours cost data: \$21.32 per 1 gram vial; \$42.37 per 2 gram vial

Findings from DUE:

- 23 charts were retrospectively reviewed for the dates between 3/26/05 and 4/25/05. Patients were identified from Pyxis charge data.
- The mean patient age was 69 (max 93, min 19).
- 65% of patients were admitted through the emergency department and 35% were admitted directly from home or the physician's office.
- Average length of stay was 9 days (max 30, min 2).
- Indications for use included the following: CAP (17%), nosocomial pneumonia (13%), UTI (13%), pre-op prophylaxis (13%), COPD exacerbation (9%), urosepsis (9%), bacteremia (4%), r/o meningitis (4%), cellulitis (4%), tracheitis (4%), dental infection (4%), and febrile neutropenia (4%).
- Ceftriaxone dosing was appropriate in one patient (4%) who was being ruled out for meningitis. This patient was the only patient to receive every 12 hour dosing.
- Average duration of 2 gram ceftriaxone therapy was 5 days (5 doses). Patients were switched to oral therapy after an average of 5 days.
- The following physicians prescribed at least one dose of 2 gram ceftriaxone:

Prescribing Physician	Patients Prescribed 2 Gram Ceftriaxone (%)	Number of Doses Prescribed (%)
Hagan*	5 patients (22%)	23 (29%)
Gelrud	3 patients (13%)	4 (5%)
Gonzalez	3 patients (13%)	13 (16%)
Timmerman**	3 patients (13%)	4 (5%)
Ferguson***	2 patients (13%)	4 (5%)
Wong	1 patient (4%)	4 (5%)
Moore	1 patient (4%)	5 (6%)
Schwarz	1 patient (4%)	1 (1%)
Cooper	1 patient (4%)	1 (1%)
Janney	1 patient (4%)	11 (14%)
Bonner	1 patient (4%)	9 (11%)
Sheehan	1 patient (4%)	1 (1%)

Total	23 patients (100%)	80 (100%)
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* One of these patients was being empirically treated with 2 gram dosing for presumptive meningitis.

** All of these patients were to receive 2 gram cefotetan for pre-op prophylaxis as written by a surgeon.

*** One of these patients had an order for 1 gram ceftriaxone, but a 2 gram dose was pulled from Pyxis and returned.

- Four of the doses were written as 1 gram doses and the nurse mistakenly pulled a 2 gram vial from Pyxis. One of these was replaced in Pyxis before it was given. The other three were automatic substitutions for cefotetan as pre-op prophylaxis, in conjunction with metronidazole.
- The most common antibiotic that was used when converting to oral therapy was levofloxacin (43%).
- 74% of patients were receiving at least one other antibiotic during the course of ceftriaxone therapy.
- 52% of patients went home on at least one antibiotic.

References:

- 1.) Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance. *Arch Intern Med* 2000; 160:1399–1408.
- 2.) File TM Jr; Garau J; Blasi F; et al. Guidelines for empiric antimicrobial prescribing in community-acquired pneumonia. *File TM Jr - Chest* - 01-MAY-2004; 125(5): 1888-901.
- 3.) Craven DE. Healthcare-associated pneumonia in adults:management principles to improve outcomes. *Infect Dis Clin North Am* - 01-DEC-2004; 18(4): 939-62.
- 4.) Chastre J. Antimicrobial treatment of hospital-acquired pneumonia. *Infect Dis Clin North Am* - 01-DEC-2003; 17(4): 727-37.
- 5.) Hughes WT. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* - 15-MAR-2002; 34(6): 730-51.
- 6.) <http://home.mdconsult.com/das/drug/view/47369211-2/1/694/top>
- 7.) Sinner SW. Antimicrobial agents in the treatment of bacterial meningitis. *Infect Dis Clin North Am* - 01-SEP-2004; 18(3): 581-602.
- 8.) Niederman MS. Appropriate use of antimicrobial agents: challenges and strategies for improvement. *Crit Care Med* - 01-FEB-2003; 31(2): 608-16.
- 9.) Losh D. Central nervous system infections. *Clin Fam Pract*-2004 Mar ;6(1) ;1.