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EXPERT REVIEW

Treatment Options for Gram-Positive and Gram-Negative Bacteria: Focus on Ceftriaxone

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Abstract: Ceftriaxone is a third-generation of cephalosporins which is used for community acquired infections such as pneumonia and urinaly tract infections. It showed great advantage of once-daily administration based on pharmacological manner and need no renal impairment. It is stable for β-lactamases against first- or second- generations of cephalosporins. Ceftriaxone is also used for streptococcal endocarditis as alternative first-line therapeutic regimen and used for Sexually Transmited Disease (STD) such as syphilis and chancoroid. Due to its pharmacological advantage, Ceftriaxone is used for Outpatient Parenteral Antibiotic Therapy (OPAT) with sufficient clinical efficacy in the world. This review focused on therapeutic option or alternative first line therapy of Ceftriaxone and Ceftriaxone in OPAT. The reappraisal of 'traditional antibiotics', such as ceftriaxone, has triggered a review of adequate antibiotic treatment.

Keywords: ceftriaxone, alternative therapy, streptococcal endocarditis, Outpatient parenteral antibiotic therapy (OPAT), Home intravenous antibiotic therapy (HIAT)

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Introduction

The aminothiazol-cephalosporin ceftriaxone sodium (ceftriaxone) is a third-generation cephalosporin. The product name for this drug is Rocephin throughout the world, including the USA, Canada and Japan, but is Cefaxona in Mexico and Peru. This agent is used for the treatment of various community-acquired infections and is also used for the treatment of infections with *Neisseria gonorrhoeae* and *Salmonella typhi*. Ceftriaxone was developed by Roche in 1978; it has the advantages of only requiring a once-daily administration and can be used as an intravenous or intramuscular injection for outpatients in an appropriate pharmacological manner. It has been used extensively because of its improved stability against traditional β-lactamases, compared with first or second generations of cephalosporins. However, the recent spread of derepressed mutants, which hyper produce chromosomal β-lactamases and extended-spectrum β-lactamases (ESBLs), during the past decade has diminished the activity of all third-generation cephalosporins against Enterobacteriaceae, necessitating careful attention to sensitivity studies.

Outpatient management for the treatment of infectious diseases is increasing because of medical economics. The outpatient use of ceftriaxone is based on pharmacokinetics and pharmacodynamics theory. It is also justified for medical economic reasons because it can reduce the length of hospital stay. Home intravenous antibiotics therapy (HIAT) or outpatient parenteral antimicrobial therapy (OPAT) are possible using ceftriaxone because of its pharmacological characterization.

Ceftriaxone has a good tolerability profile, the most well-known adverse events being diarrhea, nausea, vomiting, hematopoietic disturbance, and rash. However, these are common adverse events for beta-lactam antibiotics. Ceftriaxone may cause biliary pseudolithiasis, notably at higher dosages and/or after long-term administration (more than 2 g/day for more than 28 days), although the incidence of pseudolithiasis is less than 0.1%.

The pharmacological and clinical aspects of ceftriaxone have been previously documented in previous reviews. The present review focuses on therapeutic 'options', including first-line alternative therapies, for ceftriaxone use and its use against infections in which the causative pathogens or their resistance patterns have changed over the past decade.

Mechanism of Action, Metabolism, and Pharmacokinetic Profile

Ceftriaxone is a third generation cephalosporin that inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), which in turn inhibits the final transpeptidation step of peptide glycan synthesis in bacteria. The bacteria eventually lyse because of the ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested. Ceftriaxone is more stable against traditional beta-lactamases, such as TEM-1, TEM-2 and SHV-1, than first- or second-generation cephalosporins. Ceftriaxone has the same spectrum and efficacy as cefotaxime. However, ceftazidime is categorized as a third-generation cephalosporin with activity against *Pseudomonas aeruginosa*.

The mean peak plasma concentrations (Cmax) are 82, 151 and 257 mg/L produced by intravenous ceftriaxone at doses of 0.5, 1, and 2 g, respectively, whereas the Cmax values are 38 and 76 mg/L for intramuscular ceftriaxone at doses of 0.5 and 1 g, respectively, after two to three hours. The mean plasma concentrations after intravenous ceftriaxone administration (2 g) varied from 12 to 20 mg/L. The repeated once-daily intravenous administration of ceftriaxone (2 g) increases the mean Cmax by 8%. Furthermore, the repeated intramuscular administration of ceftriaxone (1 g) increases the drug accumulation by 11%. Ceftriaxone is widely distributed throughout the body fluids and tissues including the gallbladder, lungs, bone, bile, and cerebrospinal fluid (with higher concentrations present during active meningitis). The distribution volume of ceftriaxone ranges from 5.8 to 15.5 L. Ceftriaxone preferentially localizes in the bile, and the mean concentrations are over 153 mg/L at one hour and over 44 mg/L at 3 hours after the intravenous administration of 1 g of ceftriaxone in healthy volunteers. Dose attenuation is not needed in patients with renal impairment. Overall, 45 to 60% of a 0.5 to 3 g dose is excreted in the urine of healthy subjects within 48 hours. The remainder is secreted in the bile and the feces as microbiologically inactive compounds. The total plasma clearance of ceftriaxone is dose dominant. Ceftriaxone increases from mean

values of 0.6 to 1.0 L/h after a 0.5-g intravenous dose to 1.18 and 1.29 L/h after a 2-g intravenous dose. The mean elimination half-life (t 1/2) of ceftriaxone is five to nine hours in healthy adults and 12–16 hours in patients with mild-to-severe renal impairment, which is considerably longer than that for other cephalosporins (0.6 to 4.4 hours). The t 1/2 of ceftriaxone does not vary according to the dose size, frequency, or route of administration. The protein-binding rate is relatively high (85% to 95%). Drug excretion of ceftriaxone is in the urine (33% to 67% as unchanged drug) or feces (as inactive drug). No adjustments are needed for patients with renal or hepatic impairments. These characteristics illustrate the advantages of ceftriaxone. Nevertheless, cefotaxime, rather than ceftriaxone, is recommended for the antibiotic treatment of neonates with hyper bilirubinemia.[1–4]

General Indications for Ceftriaxone

Ceftriaxone is recommended for common community-acquired pneumonia, meningitis, genitourinary infections, and infections with *Salmonella typhi*. Additionally, it is also recommended for infective endocarditis or sexually transmitted diseases. The labeled or non-labeled use of ceftriaxone in the United States of America is shown in Table 1 A. The indications for ceftriaxone were determined based on the MIC of the pathogen and the drug transition. Common dosages of ceftriaxone are shown in Table 1B.

Ceftriaxone is also used for the treatment of sexually transmitted diseases (STDs) and zoonosis. Ceftriaxone is administered once daily and is suitable for antibiotic therapy on an outpatient basis. Patients who repeatedly suffer from STDs may have unfavorable drug compliance, because once-daily treatment is well-suited for patients with STDs. A single intramuscular dose of ceftriaxone (250 mg) has produced bacteriological eradication rates of more than 95% among adult patients with confirmed, uncomplicated infections with *Neisseria gonorrhoeae* in randomized clinical trials. Single-dose intramuscular ceftriaxone (125 mg) is a first-line antimicrobial therapy for gonococcal pharyngitis and cervical, urethral and anorectal infections. However, such infections can be difficult to differentiate from infections with *Chlamydia trachomatis*, for which combined therapy with azithromycin (AZM) or doxycycline (DOXY) is generally recommended.[5]

Gram-Positive Pathogens

Staphylococci, including MSSA, MRSA, and coagulase-negative staphylococci

Methicillin-susceptible *Staphylococcus aureus* (MSSA) is susceptible to avariety of beta-lactam antibiotics. Ceftriaxone has a good activity against MSSA, with approximately 100% of all strains susceptible to this drug in vitro.[6] However, a reduced susceptibility (77%–100%) has been previously reported.[7]

According to a previous report comparing ceftriaxone with other cephalosporins, ceftriaxone had a better activity than ceftazidime (15% to 90% susceptibility) against MSSA but was less active than cefepime (97% to 100% susceptibility).[7] Ceftriaxone also has good activity against coagulase negative staphylococci (CNS) in vitro. However, the correlation between its activity and clinical efficacy remains unclear. Generally, a glycopeptide, such as vancomycin, is recommended for the treatment of disseminated infections with CNS strains. Similar to other traditional beta-lactam antibiotics, ceftriaxone is inactive against methicillin-resistant *Staphylococcus aureus* (MRSA) (see Table 2).[6–9]

Streptococcus spp., including viridans streptococci and beta-hemolytic streptococci

β-hemolytic group streptococci remain highly susceptible to ceftriaxone (98%–100%), while viridans streptococci tend to be less susceptible (69%–84%).[10–12] The activity of ceftriaxone against these bacteria was similar to that of cefepime and greater than that of ceftazidime. Ceftriaxone has also good activity against each strain (Table 2).

Streptococcus pneumoniae

Ceftriaxone has good activity against *S. pneumoniae*. The incidence of reduced susceptibility to ceftriaxone among *S. pneumoniae* varies markedly according to geographical region. Although the incidence of intermediate resistance to ceftriaxone varies from 1% to 30%, depending on the region, the incidence of complete resistance to ceftriaxone remains at under 5% worldwide. In 2008, the Clinical Laboratory Standards Institute (CLSI) in the United States (M100-S18) determined two different break points

Table 1A. Labeled or unlabelled use of ceftriaxone in USA.

Infectious disease	Dose	Route		Duration
Septic arthritis	1–2 g	iv	Once daily	
Brain abscess	2 g	iv	Every 12 hours	
Cavernous venous thrombosis	2 g	iv	Once daily with VCM or LZD	
Chancroid	250 mg	im	As single dose	
Prophylaxis for meningococcal disease	250 mg	im	As single dose	
Cholecystitis (mild-moderate)	1–2 g	iv	Every 12–24 hours	
Gonococcal infections: uncomplicated urithritis	**125–250 mg**	**im**	**As single dose**	
Disseminated infections	1 g	iv or im	Once daily	
Endocarditis	1–2 g	iv or im	Every 24 hours	
Acute epidymitis	250 mg	im	As single dose with DOXY	
Prostatitis	125–250 mg	im or iv	As single dose with DOXY	
Infective endocarditis: Native valve	**2 g**	**iv**	**Once daily**	**2–4 weeks**
Prothetic valve	**2 g**	**iv**	**Once daily**	**6 weeks**
Intra-abdomninal infection (complicated, community-acquired)	**1–2 g**	**iv**	**Every 12–24 hours with metronidazole**	**4–7 days**
Lyme disease	2 g	iv	Once daily	14–28 days
Mastoiditis (hospitalized)	2 g	iv	Once daily	
Meningitis (selected organisms, check MICs)	**2 g**	**iv**	**Every 12 hours**	**7–14 days**
Orbital cellulitis	2 g	iv	Once daily	
PID (Pelvic Inflammatory Disease)	**250 mg**	**im**	**As single dose**	
Community acquired pneumonia	**1–2 g**	**iv**	**Once daily**	
Pyelonephritis (acute, uncomplicated)	**1–2 g**	**iv**	**Once daily**	
Septic/toxic shock/necrotizing fasciitis	2 g	iv	Once daily with CLDM for toxic shock	
STD prophylaxis in sexual assult victims	**125 mg**	**im**	**As single dose**	
Surgical priphylaxis	**1 g**	**iv**	**As single dose 30 min to 2 h before surgery**	
Cholecystomy	**1–2 g**	**iv**	**Every 12–24 hours**	
Syphilis	1 g	im or iv	Once daily	8–10 days
Typhid fever	2 g	iv	Once daily	14 days
Whipple's disease	2 g	iv	Once daily	10–14 days + for 1 year

Note: Labeled use; Unlabeled use.

for meningitis or non-meningitis (CLSI M100-S18).[13] The indications for treatment with ceftriaxone are based on the susceptibility to penicillin G. According to the M100-S18 determined by the CLSI in 2008, non-meningitic pneumococcal infections, including pneumonia, should be treated with an intravenous high-dose amino-penicillin, penicillin G, or ceftriaxone for penicillin-susceptible or resistant strains. Notably, ceftriaxone is an alternative regimen for non-meningitic infections, such as pneumonia, caused by penicillin-intermediate *S. pneumoniae* (PISP) (PCG MIC ≥ 4 mg/L) or penicillin-resistant *S. pneumoniae* (PRSP) (PCG MIC ≥ 8 mg/L) strains. The breakpoint of *S. pneumoniae* in meningitis is very different from that in cases of non-meningitis. Ceftriaxone is an alternative regimen for the treatment of penicillin-susceptible (PCG MIC <0.1 mg/L) pneumococcal meningitis and is the preferred, or first-line, regimen for penicillin G-reduced susceptibility (PCG MIC, 0.1 to 1.0 mg/L) pneumococcal meningitis. Vancomycin plus ceftriaxone or cefotaxime is recommended for penicillin G-resistant (PCG MIC ≥ 2 mg/L) or ceftriaxone-resistant (ceftriaxone MIC ≥ 1 mg/L) pneumococcal meningitis.

Table 1B. Usual doe of Ceftriaxone.

Patients	Dose	Administration	Maximum dose
Adults	1–2 g	Every 12–24 hours	4 g/day (meningitis)
Neonates <7 days	50 mg/kg/day	Once a daily	
Neonates >7 days Bw <2000 g	50 mg/kg/day	Once a daily	
Neonates >7 days Bw >2000 g	50–75 mg/kg/day	Once a daily	
Infants and children	50–75 mg/kg/day	Devided every 12–24 hours	4 g/day

Note: *Use cefotaxime in place of ceftriaxone in hyperbilirubinemic neonates.

Ceftriaxone is also indicated for the treatment of acute otitis media, endophthalmitis, and orbital cellulitis caused by *S. pneumoniae.* The activity of ceftriaxone is shown in Table 2.[6]

Actinobacteria (*Nocardia, Actinomyces*)

Infections caused by *Nocardia* spp., *Actinomyces* spp., and *Streptomyces* spp. are categorized as actinomycosis. These pathogens are Gram-positive branchial bacteria that were previously considered to be mycetes. Ceftriaxone has been reported to have a limited antimicrobial activity against Actinomyces.[14] On the other hand, ceftriaxone is regarded as an alternative regimen because its antimicrobial activity against *Nocardia* spp. varies.[15,16]

Other Gram-positive pathogens

Ceftriaxone is inactive against most Gram-positive rod strains. *Clostridium* spp., including *C. difficile* and *C. perfringens*, are resistant to ceftriaxone. *Listeria monocytogenes* is a well-known food borne pathogen that can cause septicemia in third-trimester pregnant women and meningitis in elderly persons or patients with cellular immunodeficiencies. Ceftriaxone combined with vancomycin is the empiric treatment for adult community-acquired meningitis thought to be caused by *S. pneumoniae* or *Neisseria meningitidis*. High-dose ampicillin is added for the treatment of *L. monocytogenes*, which is fundamentally resistant to ceftriaxone. All Enterococci strains are spontaneously resistant to all cephalosporins, including ceftriaxone.

Gram-Negative Bacteria

Enterobacteriaceae

Previously, ceftriaxone had a good activity against Enterobacteriaceae, such as *Escherichia coli* or *Proteus mirabilis*. Now, its activity against Enterobacteriaceae has become more variable than it has been over the last one or two decades, since newly resistant strains, including ESBLs, have begun to spread all over the world. The activity of ceftriaxone against these strains differs according to geographic region,

Table 2. In vitro antimicrobial susceptibility of ceftriaxone and ceftazidime and cefepime against Gram-positive bacterias since 2000.

Organism	n	Ceftriaxone			Ceftazidime		Cefepime		Reference
		MIC_{50} (mg/L)	MIC_{90} (mg/L)	S (%)	MIC_{90} (mg/L)	S (%)	MIC_{90} (mg/L)	S (%)	
Staphylococcus aureus (MSSA)	22389	4	4	99.9	8	99.4	4	99.8	6
Staphylococcus epidermidis	321	>4	>4	60	NS		>32	70.8	9
Viridans group streptococci	1887	≦0.25	1	92.1	NS		1	91	6
Viridans group streptococci (PCN-R)	27	4	32	4	NS		>16	0	10
β-haemolytic streptococi	4598	≦0.25	≦0.25	99.9	NS		≦0.12	99.9	6
Streptococcus pneumoniae	10260	≦0.25		94.9	NS		1	99.6	6

Note: $MIC_{50/90}$, minimum inhibitory concentrations required to inhibit the groth of 50% or 90% of strains, respectively.

with the lowest susceptibility rates clearly restricted to South America and Asia.[17] In 2010, a newly emerged form of resistance involving the New Delhi metallo-beta-lactamase (NDM-1) enzyme appeared in India and spread throughout the world.[18] Consequently, antimicrobial activities against Enterobacteriaceae have begun to change (Table 3).

In 2010, the CLSI determined new performance standards for susceptibility testing against Enterobacteriaceae. They revised the previous M100-S19 and developed the present M100-S20.[19] One of the main modifications was to set breakpoints for Enterobacteriaceae that were much lower than those used in the M100-S19. Previously, the breakpoints for ceftriaxone against Enterobacteriaceae were set as follows: susceptible MIC, ≦8; intermediate MIC, 16 to 32; resistant, ≥64. In the new M100-S20, the following breakpoints were defined: susceptible MIC, ≦1; intermediate MIC, 2; resistant, ≥4. The M100-S20 was quickly revised once again to create the M100-S21 in 2011. The breakpoints for cefazolin, a first-generation cephalosporin, against Enterobacteriaceae were updated with new dosage regimens, such as intravenous cefazolin (2 g) every 8 hours (Table 4).

Although the change seems drastic, some previous reports[7,20,21] of in-vitro susceptibility have indicated that ceftriaxone has sufficient level of activity against *E. coli*. These reports showed that the MIC90 of *E. coli* without ESBLs is approximately less than MIC < 1 according to the CLSI M100-S20 in clinical situations. However, this change warrants attention in clinico-epidemiological data of antimicrobial susceptibility according to the M100-S19 standards set forth by the CLSI.

The in vitro activity of cefazolin against 162 isolates of *E. coli* decreased from 87.7% to 3.1%, according to the M100-S19 and the M100-S20.[22] The activity changed from 87.7% to 63.5% according to the M100-S19 and the M100-S21. Meanwhile, the in vitro activity of ceftriaxone against the same 162 isolates of *E. coli* was approximately more than 95% according to the CLSI M100-S19 or the M100-S20 and M100-S21(Table 5).

The in vitro activity of ceftriaxone against 84 isolates of *Enterobacter cloacae* decreased from 92.9% to 69.0% according to the M100-S19 and the M100-S20. Thus, since the CLSI changed the breakpoint for Enterobacteriaceae in 2011, the in vitro activity of ceftriaxone may have changed for some pathogens.

Some Enterobacteriaceae produce class C AmpC beta-lactamases including CMY-2, P99, ACT-1, and DHA-1. These proteins are usually encoded by the *bla* gene on the bacterial chromosome. A plasmid-related AmpC also exists. The production of chromosomal AmpC in Enterobacteriaceae, such as *Klebsiella* species, is usually at a suppressed level, but production can be induced by first- or second-generation cephalosporins, such as cefoxitin.[23] According to relevant reports, the frequency of resistance induction by ceftriaxone is lower than that induced by cefoxitin or imipenem.[24]

Ceftriaxone might be recommended as a definitive therapy for Enterobacteriaceae if the bacteria seem to be susceptible to first or second-generation cephalosporins because the number of strains producing classical beta-lactamases against first or second-generation cephalosporins is increasing.

Previous data showed that ceftriaxone has good activity against both *Salmonella* spp. and *Shigella* spp.[25] Although resistance to third-generation cephalosporins among *Salmonella* spp. has been reported in parts of Europe, Africa, South America and Asia, a large study conducted in the US showed that only 0.07% of 4008 *Salmonella* spp. were resistant to ceftriaxone. Most resistance is derived from ESBL or AmpC beta lactamases.[26–28] On the other hand, *Salmonella* spp. resistant to fluoroquinolone and nalidixic acid have spread widely throughout the world. In the United Kingdom, more than 20% of *Salmonella Typhi* or *Salmonella paratyphi* is resistant to ciprofloxacin.[29,30]

Morganella morganii is found in the environment and in the intestinal tracts of humans, mammals, and reptiles as normal flora and is a rare cause of severe invasive disease. It accounts for less than 1% of nosocomial infections. *M. morganii* is usually an opportunistic pathogen in hospitalized patients, particularly those receiving antibiotic therapy. Ceftriaxone has a good activity against non-ESBL *Morganella morganii* strains (more than 90%).[31] However, the number of ESBL-positive strains is increasing, similar to other Enterobacteriaceae.

Helicobacter cinaedi is a rare pathogenin humans, occurring mostly in immunocompromised patients as bacteremia with or without soft tissue infections, with

Table 3. In vitro antimicrobial susceptibility of ceftriaxone and ceftazidime and cefepime against Gram-negative bacterias since 2000 (partly before 2000).

Organism	n	Ceftriaxone			Ceftazidime		Cefepime		Reference
		MIC_{50} (mg/L)	MIC_{90}(mg/L)	S (%)	MIC_{90} (mg/L)	S (%)	MIC_{90} (mg/L)	S (%)	
Enterobacteriacae (non-ESBL)									
Citrobacter spp.*	1110	≤0.25–32	0.5–>32	40–94	0.5–>16	30–94	≤0.12–>16	70–100	4
C. frendii	85	≤1	32	82.4	NS		≤1	100	9
Enterobacter spp.*	3331	≤0.25–4	8–>256	46–90	8–>256	48–90	0.25–8	90–100	4
E. cloacae	424	≤1	64	75.5	NS		≤1	99.80%	9
E. aerogenes	90	≤1	32	82.4	NS		≤1	92.90%	9
Escherichia coli	3930	≤1	≤1	93	NS		≤1	96.60%	9
E. coli (Japan)	162	0.063	0.25	97.5	0.5	98	0.125	98	22
K. pneumoniae	1128	≤1	≤1	95.5	NS		≤1	98	9
K. oxytoca	272	≤1	≤1	91.2	NS		≤1	99.6	9
Morganella Morganii	3981			91.9					31
P. mirabilis	288	≤1	≤1	98.3	NS		≤1	100	9
S. marcescens	251	≤1	≤1	94.8	NS		≤1	99.6	9
Other Gram-negative bacteria									
Acinetobacter spp.	1226	6–>32	32–>256	9–94	16–>256	19–100	6–48	41–97	4
Capnocytophaga canis	96	0.12	1		1		NS		35
*Haemophilus influenzae**	9946	≤0.004–≤0.015	0.008–0.03	100					4
H. influenzae	672	≤0.06	≤0.06	99.9	NS		≤0.25	100	9
H. influenzae (pediatric population in Japan)	824	0.02	0.25		NS		ND		30
*Moraxella catarrhalis**	3953	0.06–0.5	0.5–1	100					4
M. catarrhalis	62	0.25	2	96.8					39
Neisseria gonorrhoeae	17450			100					48
Neisseria meningitidis (Africa)	137	<0.002	<0.002	100					58
Pseudomonas aeruginosa	1476	32	>64	22.2	NS	NS	4	75.2	9
Yersinia enterocolitica	184			100		83			118

Note: $MIC_{50/90}$, minimum inhibitory concentrations required to inhibit the groth of 50% or 90% of strains, respectively.

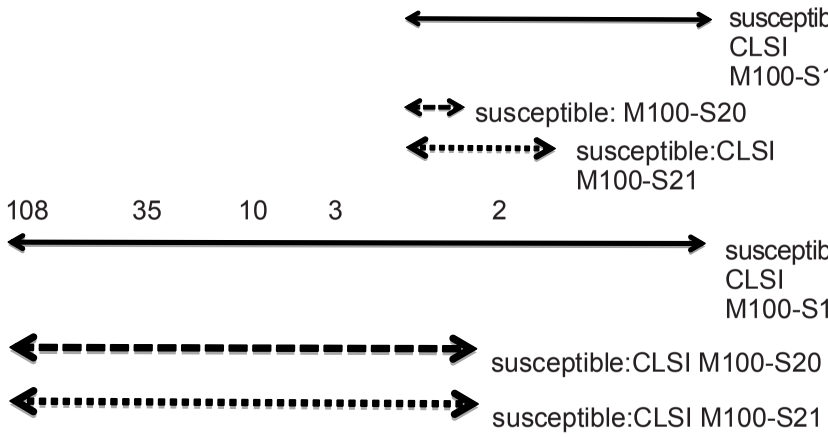
Table 4. CLSI M100-S19 and M100-S20, S21.

	M100-S19			M100-S20 (revised in 2010)			M100-S21 (revised in 2011)*		
	Susceptible	**Intermediate**	**Resistant**	**Susceptible**	**Intermediate**	**Resistant**	**Susceptible**	**Intermediate**	**Resistant**
Cefazolin	≦8	16	≧32	≦1	2	≧4	≦2	4	8
Cefoitaxime	≦8	16–32	≧64	≦1	2	≧4	≦1	2	≧4
Ceftizoxime	≦8	16–32	≧64	≦1	2	≧4	≦1	2	≧4
Ceftriaxone	≦8	16–32	≧64	≦1	2	≧4	≦1	2	≧4

Note: *M100-S21: Recommded dose of cefazolin is at least 2 g every 8 hour.

Table 5. Changes of susceptibility distribution: 162 clinical isolates of *Escherichia coli* adopted measures of CLSI M100-S19 and M100-S20, S21.

MIC (μg/mL)																
	≤0.063	0.125	0.25	0.5	1.00	2.00	4	8	16	32	64	>64	MIC50	MIC90	CLSI	Susceptible (%)
Strains					5	98	24	15	4	3	6	7			M100-S19	87.7
Cefazolin													2	16	M100-S20	3.1
															M100-S21	63.5
Strains(n)	108	35	10	3		2						4				
															M100-S19	97.5
Ceftriaxone													≤0.063	0.25	M100-S20	96.2
															M100-S21	96.2



Note: To adopt measure of CLSI M100-S19 and S20, S21 against 162 clinical isolates of *E. coli* in Japan.[22]

a high potential for recurrence. No clear treatment guidelines are available regarding the choice or duration of antibiotic therapy. The use of ceftriaxone has been previously reported.[32] Ceftriaxone is supposedly active against *H. cinaedi*. The MIC 50 and MIC 90 values for ceftriaxone are 4 mg/L and 8 mg/L, respectively.[33] However, the in vitro activity and clinical efficacy remain unclear. *Serratia* spp. used to have an susceptibility of 90% when third-generation cephalosporins were first approved. Susceptibility has since decreased, with resistance in approximately 40% of the strains reported from North America. At present, the use of ceftriaxone against *Serratia marcescens* is not recommended. Thus, the susceptibility of Enterobacteriaceae to ceftriaxone may have changed to some degree according to the CLSI M100-S20 and M100-S21.

Other-GNRs

Haemophilus influenzae is an important pathogen for pediatric bacterial meningitis and pneumonia. The *H. influenzae* type B (Hib)-vaccine is administered in most developed countries and was approved as an inoculation vaccine in Japan in 2009. However, the vaccine is not administered for all indicators, similar to the situation in developing countries. *H. influenza* remains a common pathogen for pediatric infections throughout the world. BLNAR (beta-lactamase-negative ABPC-resistant), BLNAS (beta-lactamase-negative ABPC-susceptible), or BLPAR (beta-lactamase-positive ABPC-resistant) strains of *H. influenzae* are approximately 100% susceptible to ceftriaxone, and *H. influenzae* BLNAR-strains are widely spread throughout Japan.[34]

Capnocytophaga canimorsus is responsible for dog bite-related infections. The antibiotic susceptibility of 96 isolates of *Capnocytophaga* sp. was assessed. Ceftriaxone exhibited a good activity in vitro. (MIC 90, 1 mg/L; n = 96).[35] Ceftriaxone also exhibited a good activity against *Pasturella multocida* (MIC 90, 0.12 mg/L; n = 20).[36] Ceftriaxone is active against *Acinetobacter* spp. to a small degree. Its MIC varies, and antibiotic therapy with ceftriaxone is not recommended against *Acinetobacter* spp. Ceftriaxone has no activity and no clinical efficacy against *Pseudomonas aeruginosa*. The CLSI M100-S21, which was revised in 2011, indicated that ceftriaxone is no longer available and that its indications for use against *P. aeruginosa* are limited. The CLSI deleted ceftriaxone from its interpretive criteria for infections with *P. aeruginosa*. Ceftriaxone has no activity against *Stenotrophomonas maltophilia*[37] or *Achromobacter xylosoxidans*.[38]

Gram-negative coccus

Moraxella catarrhalis is a common pathogen causing adult or elderly pneumonia or otitis media. Ceftriaxone is highly active against *M. catarrhalis* (over 92.9%) but fluoroquinolone-resistant *M. catarrhalis* has been reported.[39,40]

Ceftriaxone is also active against *Neisseria* spp. Against a total of 403 strains of *N. gonorrhoeae*, the MIC 90 values for ceftriaxone ranged from 0.001 to 0.125 mg/L. These strains included penicillinase-producing strains and ciprofloxacin- and tetracycline-resistant strains.[41–47] The Gonococcal Antimicrobial Surveillance Programme (GASP) by the World Health Organization (WHO) South East Asian Region (SEAR) has published similar data intermittently.[48] Considerable concern has been expressed following the appearance and spread of gonococci that are not susceptible to later generations of cephalosporins in the WHO's Western Pacific Region. The recognition of such strains followed the documentation of treatment failure using several oral third-generation cephalosporins.[49–51] Surveillance of gonococcal susceptibility to 'third-generation' cephalosporins has emphasized the assessment of ceftriaxone susceptibility because of its widespread use throughout both regions. Consequently, the reported MIC data were based mostly on an assessment of the in vitro susceptibility of gonococcal isolates to injectable ceftriaxone. A large number of countries including Australia, Fiji, India, Japan,[49] Hong Kong, Korea, Laos, Malaysia, New Zealand, Papua New Guinea, the Philippines, Singapore, Thailand, Tonga and Vietnam have reported no or very low proportions of strains with altered ceftriaxone susceptibility when large numbers of strains were tested. However, Brunei, China, Myanmar and Mongolia all reported much larger proportions of ceftriaxone 'resistant' or 'less susceptible' gonococci strains.[52–56]

Neisseria meningitidis causes community-acquired meningitis. This pathogen is highly dominant in the Sub-Saharan 'meningitis belt' area. A certificate of vaccination is required to enter Saudi

Arabia. Resistance to penicillins has been reported. Eighty percent of the *N. meningitis* strains isolated from 44 patients with meningitis were resistant to PCG in North Eastern Nigeria. In contrast, no resistance to ceftriaxone has been reported.[57] Among 693 isolates from Africa, no cases of ceftriaxone resistance were found.[58] In another study that included developed countries, no ceftriaxone-resistant strains were found.[59,60] Ceftriaxone-resistant *N. meningitidis* strains have been rarely documented in Japan and India over the past decade.[61,62]

Therapeutic options: Ceftriaxone

Ceftriaxone is generally used for the treatment of many community-acquired infections, such as pneumonia, meningitis, urinary tract infections, and acute otitis media. Ceftriaxone is also used as an alternative therapy for the treatment of some infectious diseases because of antibiotic allergies or the pharmacological advantage of its once-daily administration.

Ceftriaxone for streptococcal endocarditis

Streptococcal endocarditis represents the second most common cause of infectious endocarditis, following *Staphylococcus* spp., and accounts for approximately 30% of all cases of infectious endocarditis.[63] Of particular note, Streptococcal spp. are the most frequent causes of subacute infectious endocarditis. The American Heart Association (AHA) guidelines recommend the use of penicillin G or ceftriaxone monotherapy for four weeks for cases with native valve involvement and for six weeks in cases with prosthetic valve involvement at a penicillin G MIC $\leq$ 0.12 mg/mL.[64] In addition, for similar *Streptococcus* spp.- derived infections, combination therapy with ceftriaxone plus gentamicin is recommended, similar to penicillin G, even under conditions of $0.12 < \text{MIC} < 0.5$. Although no clinical studies comparing these two drugs have been made, both penicillin G monotherapy and ceftriaxone monotherapy achieved microbiological cure rates of more than 98% when administered for four weeks in cases infected with penicillin G-sensitive viridans streptococci or *Streptococcus bovis*, leading to the general recognition that these two drugs have equivalent therapeutic effects.[65,66] The clinical efficacy is also considered to be the same as that of a penicillin G regimen because some clinical case series have reported clinical cure rates of 83%–100%. Ceftriaxone is an alternative first-line regimen for the treatment of streptococcal endocarditis. Ceftriaxone, rather than penicillin G, is indicated for patients with a penicillin allergy, renal dysfunction, or social or economical problems such as an adversity to hospital admission or a home care setting[67–74] (Table 6).

Ceftriaxone for enterococcal endocarditis

Generally, Enterococci are spontaneously resistant to first to fourth generations of cephalosporins. The synergistic bacterial activity of double beta-lactam antibiotics against *Enterococcus faecalis* strains both in vivo and in vitro has been previously documented.[75,76] Imipenem (IPM) plus ampicillin (ABPC) or ceftriaxone plus ABPC is recommended for the treatment of infective endocarditis caused by *E. faecalis* resistant to VCM, penicillins, and aminoglycosides according to the AHA guidelines.[64,77] However, clinical data for 'double beta-lactam therapy' is extremely limited and has an insufficient evidence level. At present, linezolid, quinupristin-dalfopristin or daptomycin may have taken the place of these agents and has resolved this clinical problem.[78]

Ceftriaxone for disseminated infections with MSSA, including endocarditis and bacteremia

Oxacillin (or cloxacillin) and cefazolin (CEZ) are the recommended first-line antibiotics. Recently, Paul et al reported 498 cases of MSSA bacteremia. Treatment of MSSA bacteremia with cefazolin was not significantly different from treatment with cloxacillin, while treatment with other beta-lactams, including second- and third-generation cephalosporins including ceftriaxone, might be associated with a higher mortality. With ceftriaxone, the odds ratio was 2.24, compared with cloxacillin or CEZ ($P = 0.008$). MSSA bacteremia or disseminated infection was an indication for treatment with oxacillin (or cloxacillin) or CEZ. Indeed, ceftriaxone exhibited a good activity against MSSA, but it should be avoided for severe MSSA infections.[79] McKissic et al. reported 98 cases of MSSA bacteremia treated with several types of antibiotics include ceftriaxone. Forty-five of the 98 cases were treated with ceftriaxone.

Table 6. Ceftriaxone for streptococcal endocarditis.

Cases	Age (years)	Clinical cure (%)	Operation (%)	OPAT	Reference
29	55 (16–84)	100	34.5		67
32	n.d.	83	n.d.	✓	68
59	59 (19–87)	100	17		69
52	61 (18–80)	88	17		70
30	63 (30–83)	96	n.d.	✓	71
61	52 (18–87)	95.7	27.5		72
37	55 (17–76)	100	10	✓	73
18	68 (35–83)	89	11	✓	74

Abbreviation: n.d., not described; OPAT, Outpatient Parenteral Antimicrobial Therapy.

No significant differences in the microbiological and clinical cure rates were reported.[80] Melissa et al described 400 cases of MSSA infections, ie, osteomyelitis and bacteremia, that were treated with ceftriaxone using outpatient parenteral antibiotic therapy (OPAT) and reported a high (95.4%) clinical efficacy.[81]

Cephalosporins, such as ceftriaxone or cefepime, were active against MSSA in vitro, but their indications are limited. Their use may be considered in patients with a stable condition or for maintenance therapy because of socio-economic reasons.

Ceftriaxone for MSSA osteomyelitis without other infection(s)

Epidemiological results showed that 40% of spondylitis cases were complicated with infective endocarditis. Thus, osteomyelitis must be suspected as a possible complication of bacteremia. Infective endocarditis must be discriminated from osteomyelitis caused by MSSA. Long-term therapy lasting more than six weeks is needed for osteomyelitis caused by MSSA. CEZ or oxacillin (cloxacillin) is preferred as the initial therapy. The clinical efficacy of ceftriaxone against osteomyelitis caused by MSSA has been reported. Seventeen out of 22 patients were cured. Clinical failure was associated with chronic osteomyelitis and the continued presence of necrotic bone or infected hardware.[82]

Ceftriaxone for soft tissue infections caused by MSSA or *Streptococcus* spp.

Long-term antibiotic therapy is needed for skin and soft tissue infections caused by MSSA or *Streptococcus* spp. CEZ is recognized as an appropriate treatment regimen. Some clinical studies have shown an equivalent clinical efficacy between CEZ and ceftriaxone.[83–85] In 1996, Brown et al enrolled 194 patients with severe skin and soft tissue infections. Ninety-six of the 194 patients were treated with intravenous ceftriaxone (2 g), and 98 patients were treated with intravenous CEZ (2 g). No statistical differences in the patients backgrounds or clinical outcomes were reported.[86] In 2002, Grayson et al showed no significant differences among 116 adult patients with moderate to severe cellulitis who were treated with different antibiotics.[87] In addition, an economical advantage has been shown for outpatient antibiotic treatment with ceftriaxone. Once-daily intravenous ceftriaxone is indicated for skin and soft tissue infections without other infections. Infective endocarditis and abscess or bacteremia must be discriminated at the initial visit.

Periorbital and orbital cellulitis are critical infectious diseases in the field of ophthalmology. The major causative pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*. Ceftriaxone combined with oxacillin (or vancomycin) and metronidazole is recommended as an empirical therapy.[88]

Ceftriaxone for *Nocardia* infections

Nocardia asteroides complex (*N. asteroides sensu stricto*, *N. farcinica, N. nova*) is responsible for more than 90% of all cases of *Nocardia* pneumonia. Sulfamethoxazole-trimethoprim (TMP-SMX) are the recommended first-line agents for the treatment of disseminated infections with *Nocardia* and have a subtotal activity against almost all *Nocardia* spp. *N. asteroides sensu stricto* is the second most common pathogen causing nocardiosis in Japan. In contrast, *N. asteroides sensu stricto* is a rare

causative pathogen of nocardiosis in Belgium. Thus, the distribution of this pathogen varies markedly according to geographical region.[15,89,90] Ceftriaxone or carbapenems are alternative agents because their activities vary notably for *N. farcinica*, the most common strain causing nocardiosis. Stanley W. Chapman et al, who authorized 'Up to date', recommended the use of TMP-SMX plus amikacin sulfate (AMK) combined with ceftriaxone or imipenem (IPM/CS) for the treatment of pulmonary nocardiosis with meningitis or brain abscess.[91] The in vitro confirmation of drug susceptibility for *Nocardia* spp. is still not common in microbiological laboratories. Ceftriaxone has considerable variations in its activity against *Nocardia* spp., compared with the susceptibility of *Nocardia* spp. to IPM/CS. The indications for each alternative antibiotic need to be considered with caution in cases with drug allergies or hematopoietic dysfunction as a result of TMP-SMX.[16,91–95] The antimicrobial susceptibility of common *Nocardia* spp. is shown in Table 7.[96]

Ceftriaxone for *Actinomyces* infections and Whipple's disease

Actinomyces israeli is an anaerobic bacteria and common human pathogen of *Actinomyces* spp. The prolonged use of an intra-uterine device (IUD) and bisphosphonate use are considered to increase the risk of infections, which are generally treated with AMPC or PCG. Ceftriaxone is an alternative regimen with limited but anecdotal clinical success.[97,98]

Whipple's disease is caused by *Tropheryma whipplei*, an Actinobacteria; the full genome sequence of *T. whipplei* was identified in 2003. Previously, the most common symptom of classic Whipple's disease was chronic weight loss and diarrhea with intestinal malabsorption. Now, endocarditis and neurologic manifestations have been described. Tetracycline has long been regarded as a first-line regimen, but a high frequency (28%) of recurrence after treatment with this agent has been described. The recommended first-line parenteral antibiotic regimen is 1 g of Streptomycin plus 12 million U per day of penicillin G or 2 g of Ceftriaxone once daily for fourteen days. Oral sulfamethoxazole-trimethoprim was administered for one year following parenteral antibiotics.[99,100]

Ceftriaxone for typhoidal/non-typhoidal *Salmonella* bacteremia

Bacteremia caused by non-Typhi *Salmonella*, such as *Salmonella enteritidis*, can be treated intravenously using 1–2 g of ceftriaxone for fourteen days as an alternative regimen. However, the number of fluoroquinolone or nalidixic acid and third-generation cephalosporin-resistant non-typhoidal strains is increasing in Asia much more quickly than in the United States.[101,102] Non-typhoidal *Salmonella* bacteremia causes endovascular infection, which can lead to mycotic aneurysm. Ceftriaxone is also indicated for the treatment of typhoid fever caused by *Salmonella* typhi or *Salmonella paratyphi* as a first-line alternative to fluoroquinolone. However, multi-drug resistant strains, including nalidixic acid-resistant strains, have spread widely throughout South-east Asia, Mexico, Africa, and Arabian countries. Thus, the antimicrobial susceptibility of the strain must be confirmed. Of note, fluoroquinolone should be avoided as an initial therapy for typhoid fever in patients from areas with a high incidence of fluoroquinolone resistance, such as South -Asia. 2 to 3 g of intravenous ceftriaxone once daily for fourteen days is recommended.[103,104] Short duration antibiotic therapy is closely associated with recurrence. In pediatric patients, fluoroquinolone should not be used, and once daily treatment with 100 mg/kg of ceftriaxone for ten to fourteen days is preferred.[105]

Ceftriaxone for *Campylobacter* bacteremia

Campylobacter fetus can be isolated from blood cultures. In contrast, *Campylobacter jejuni* infection

Table 7. Antimicrobial susceptibility of Nocardia species (% isolates susceptibles).

Antibiotics	Regimen	*N. asteroides*	*N. farcinica*	*N. nova*	*N. brasiliensis*	*N. transvalensis*
TMP-SMX	1st-line	91–100	89–100	89–100	100	88
CTRX	Alternative	94–100	0–73	100	88–100	50
IPM/CS	Alternative	77–98	64–100	100	20–30	90
AMK	Alternative	100	100	100	100	82

is localized and causes enteroinvasive diarrhea. Fifty-three percent of all cases of *Campylobacter* bacteremia are caused by *C. fetus*. The rate of fluoroquinolone resistance has been reported to be 32%. Empirical treatment of *C. fetus* bacteremia with fluoroquinolone was associated with an unfavorable outcome.[106] Ana et al reviewed 71 episodes of *Campylobacter* bacteremia and reported a mortality rate of 16.4%. Ceftriaxone (18.2%) and ciprofloxacin (CPFX;20.2%) were the most commonly used agents.[107] As the antimicrobial activity varies considerably, the indications for the use of ceftriaxone for the treatment of *Campylobacter* bacteremia depend on the confirmation of susceptibility to this agent.

Ceftriaxone for *Helicobacter cinaedi* infections

Infections with *Helicobacter cinaedi* may present with various clinical manifestations, such as gastroenteritis, meningitis in neonates, localized pain, rash, cellulitis or bacteremia. No clear recommendations are available concerning the choice or duration of antibiotic therapy. Many antibiotic agents, alone or in combination, have been successfully used, such as penicillin, ampicillin, cefazolin, erythromycin, ciprofloxacin, aminoglycosides, tetracyclines and rifampicin.

The reported duration of antibiotic therapy for *H. cinaedi* bacteremia ranges from ten days to twelve weeks, depending on the underlying disease. Ceftriaxone was used in some reports, with good efficacy.[32,108–110] Ceftriaxone is indicated for the treatment of *H. cinaedi* bacteremia upon confirmation of antibiotic susceptibility.

Ceftriaxone for *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*

Yersinia enterocolitica and *Yersinia pseudotuberculosis* are gram-negative coccobacillus strains. They are associated with a variety of symptoms and are responsible for digestive diseases, including enterocolitis and mesenteric lymphadenitis, as well as extradigestive manifestations, including respiratory tract and urinary tract infections, osteoarticular infection, erythema nodosum and endocarditis.[111] Iron overload or hemochromatosis, such as beta-thalassemia increase the risk of infection.[112] Optimal treatment strategies for infections with *Yersinia enterocolitica* remain unclear.[113] In patients with septicemia or severe disease, intravenous ceftriaxone (2 g per day in adults or 100 mg/kg per day in one or two divided doses in children, to a maximum dose of 4 g per day) combined with gentamicin (5 mg/kg per day in one to three divided doses) is recommended.[114–117] Antibiotic susceptibility is also shown in Table 3.[118]

Ceftriaxone for chancroid

Chancroid arising from infection with *Haemophilus ducreyi* is a major cause of genital ulcer disease (GUD) worldwide. At an STD clinic in Paris, 3% of all patients with genital ulcers were due to chancroid. On the other hand, chancroid is the most common cause of GUD in Sub-Saharan Africa, India, South-eastern Asia, and Caribbean coastal areas. Male to female transmission ranges from 3:1 to 25:1. Commercial sex workers were important vectors of transmission worldwide. Crack cocaine abuse is associated with outbreaks. The ulcer may appear four to seven days after sexual contact. Ceftriaxone administered as a single 250-mg intramuscular injection has been associated with cure rates for chancroid as high as 98%.[119] However, limited data suggest that this regimen may not be as effective in Kenya, where failure rates as high as 35% have been described.[120] Failure was more common among persons co-infected with HIV.[121]

Ceftriaxone for syphilis

Penicillin G has been the absolute first-line regimen for the treatment of syphilis for more than five decades. Ceftriaxone, azithromycin (AZM) or doxycycline (DOXY) are recognized as alternative regimens. However, AZM-resistant syphilis has been reported. Although clinical studies are limited, ceftriaxone is an alternative regimen for primary or secondary, late latent syphilis in immunocompetent patients.[122,123] The use of ceftriaxone for the treatment of syphilis has increased significantly in recent years, from 31.3% in 2003 to 68.4% in 2008. However, therapeutic failures after the intravascular or intramuscular injection of ceftriaxone (2 g) for fourteen days were reported in 23% of cases with neurosyphilis or AZM-resistant syphilis.[124–129] In addition, the optimal dose and therapeutic duration of ceftriaxone remains unknown. The dose reportedly ranges from 1 g to 3 g, while the duration ranges from 3 to 21 days.[130] Ceftriaxone is indicated for patients with penicillin allergies, but physicians must be

aware of the possibility of therapeutic failure in response to third-generation cephalosporins, include ceftriaxone.

Ceftriaxone for gonococcal infections

Ceftriaxone is a first-line regimen for gonococcal infections. Patients with urethro-genital infections by *Neisseria gonorrhoeae* are often co-infected with *Chlamydia trachomatis*. For uncomplicated urethritisor infection of the cervix, rectum, or pharynx, a single 250-mg dose of intramuscular ceftriaxone with a single oral dose of 1 g of AZM or DOXY (100 mg) orally twice a day for seven days is recommended. According to an MMWR report, the GISP (Gonococcal Isolate Surveillance Project) showed a very low incidence of *N. gonorrhoeae* strains with reduced susceptibility to ceftriaxone. The number of isolates of *N. gonorrhoeae* with a reduced susceptibility to ceftriaxone has been very small. Only four isolates were found between 1987 and 2008. Treatment failure after the administration of oral cephalosporin has been reported in Asian countries. However, antibiotic treatment using intravenous or intramuscular ceftriaxone may not be responsible for treatment failure. A single intramuscular dose (1 g) of ceftriaxone is recommended for the treatment of gonococcal conjunctivitis. The intravenous administration (2 g) of ceftriaxone every 12 hours is recommended for patients with disseminated gonococcal infections, such as endocarditis or meningitis.[131]

Ceftriaxone for infections with *Streptococcus suis*

Streptococcus suis is mostly derived from pigs and can cause severe systemic infection, such as meningitis or streptococcal toxic shock syndrome (STSS),[132] in humans. *S. suis* can also be derived from wild boars, horses, dogs, cats and birds. Thirty-five serotypes have been identified, with serotype 2 being the most common pathogen involved in infections by *S. suis*.[133–135]

Infected pigs have been found all over the world including Asia, Europe, Australia and America. *S. suis* is recognized as being susceptible to penicillin G, ceftriaxone, and vancomycin. Penicillin resistance has been reported in a human case as well as in pig isolates.[136] As 384 *S. suis* strains from infected pigs were reportedly susceptible to penicillin (MIC 90, 0.13 mg/mL),[137] susceptibility to ceftriaxone seems reasonable. The intravenous administration (2 g) of ceftriaxone every 12 hours with or without vancomycin is a reasonable empiric treatment for *S. suis* meningitis. The cure rate after treatment with penicillin G or ceftriaxone was 97%.[133] The reported mortality rates range from 7 to 13%, but a mortality rate of 18% in an outbreak of over 200 cases was reported in China.[138]

Ceftriaxone for the treatment of dog and cat bites: *Capnocytophaga canimorsus*, and *Pasteurella multocida* meningitis

Infections with *Capnocytophaga canimorsus* mostly occur after dog or cat bites and can cause severe bacteremia, meningitis, or osteomyelitis in immunocompromised and immunocompetent hosts, resulting in a mortality rate of 13%. Of note, meningitis caused by infection with *Capnocytophaga canimorsus*, which was previously known as dysgonic fermenter-2 (DF-2), results in a severe disease course. Disseminated intravascular coagulopathy is observed in severely infected patients without splenic function. In contrast, *Capnocytophaga ochracea* (DF-1) is derived from the human oral cavity. Its virulence is lower than that of *C. canimorsus*. Ampicillin and clavulanic acid are the recommended first-line regimens.[139] Ceftriaxone is an alternative regimen that can be used for patients with meningitis.[140]

Pasturella multocida is the most common pathogen isolated from cat-bite patients. Meningitis arising from infection with *P. multocida* is rare. Ampicillin and clavulanic acid or PCG are the recommended first-line regimens, and third-generation cephalosporins, including ceftriaxone, are also effective.[141] However, the indications for ceftriaxone are limited.[142,143]

Ceftriaxone for leptospirosis and lyme disease

Human leptospirosis is a concern in individuals in contact with dogs, rats, cats, guinea pigs, rabbits, bats, or hamsters. The causative organism is usually transmitted to humans by contact with urine from the host animal. The causative organisms can survive in water or soil for weeks or months under favorable conditions. The mortality rate of Weil syndrome (icteric leptospirosis) is 5–10%. The once daily intravenous administration (1 g) of ceftriaxone for seven days is an alternative first-line therapy for leptospirosis, after

penicillin G. The efficacy of ceftriaxone is equal to that of penicillin G.[144]

Lyme disease is caused by *Borrelia burgdorferi* and is transmitted by ticks. Intravenous ceftriaxone (2 g) is used as a first-line treatment for carditis, meningitis, and encephalitis and as an alternative regimen for facial nerve paralysis and arthritis.[145]

Tolerability and safety

Ceftriaxone rarely causes adverse events. These events are typically mild to moderate in severity, and patients experiencing adverse events generally recover immediately. A lower incidence of adverse events has been reported in outpatient parenteral antimicrobial therapy settings. Diarrhea was the most common adverse event associated with ceftriaxone use in previous clinical trials, with an incidence ranging from 1% to 15%. Nausea and vomiting had an incidence of less than 4%, and nausea or abdominal pain had an incidence of less than 2%. *Clostridium difficile* infection (CDI) is associated with the use of a broad spectrum of antibiotics including ceftriaxone. Other systemic events associated with ceftriaxone use include rash in ≤6% of patients and candidiasis (oral or vaginal) in about 4% of patients. Pruritus, headache, and dizziness occur in ≤3% of patients. These adverse events are shared by a broad spectrum of antibiotics. Hematopoietic disturbances, such as agranulocytosis or thrombocytopenia, are also adverse events commonly associated with the use of beta-lactam antibiotics, including penicillin, cephalosporins, and carbapenems.

Ceftriaxone-related agranulocytosis is correlated with the total dose and duration of therapy. Agranulocytosis occurs at a total ceftriaxone dose of 51 ± 29 g after 21 days (8–25 days) of treatment, according to a previous report.[146] Ceftriaxone-related thrombocytopenia is considered to resemble idiopathic thrombocytopenia, and has been reported to occur after an average total dose of 26 g (20–32 g) over a mean duration of 11.5 days (8–13 days).[147]

Ceftriaxone causes biliary pseudolithiasis in about 1% of patients because it tends to bind to calcium. Forty-six percent of cases with ceftriaxone-related biliary pseudolithiasis are children. In adults, biliary pseudolithiasis may occur 4–22 days after the start of high-dose (more than 2 g/day) ceftriaxone therapy, at a cumulative dose of approximately 28 g, and may resolve 3–63 days after the discontinuation of therapy.[148–150]

Previous studies have shown that biliary pseudolithiasis, which was diagnosed by abdominal ultrasonography, was observed in 12 to 43% of adolescents and children and 21% and 25% of adults treated with intravenous ceftriaxone.[4] Three of 29 patients with streptococcal endocarditis treatment with intravenous ceftriaxone developed biliary pseudolithiasis. The duration of ceftriaxone therapy was 28 days in all three patients, and the cumulative dose was 56 g.[67] The duration of resolution varied from 2 to 150 days after the end of antibiotic treatment.[4]

Ceftriaxone may cause pain at the injection site following intramuscular administration and phlebitis following intravenous injection. In clinical trials, the incidence of these events ranged from 0 to 45%. Treatment with 1% lidocaine has been shown to reduce the severity and duration of pain associated with intramuscular injections of ceftriaxone (250 mg to 1 g), compared with water, in healthy volunteers (aged 14 to 55 years) in randomized, single- or double-blinded trials. Ceftriaxone has a low nephrotoxicity, and dose adjustment in patients with renal impairment is not necessary.[1]

Place in therapy

Generally, a once daily administration that has been pharmacologically proven to be effective is a great advantage for an antibiotics. Most aminoglycosides and fluoroquinolones, other than ciprofloxacin, as well as azithromycin are well-known examples of such antibiotics. In contrast, ceftriaxone and ertapenem are the only two beta-lactam antibiotics that allow once-daily administration, either at home or in an outpatient clinic, with a sufficient clinical efficacy. Accordingly, ceftriaxone is widely used for home intravenous antibiotics therapy (HIAT)[151] or for 33%–42% of cases treated with outpatient parenteral antimicrobial therapy (OPAT) in the USA,[152–154] 14.7% of the cases treated in another study,[155] and 22.1% of elderly patients treated in Italy.[156]

Two ceftriaxone delivery models are commonly used: i) an outpatient or infusion center, or OPAT model; and ii) a visiting nurse or self-administration model, or HIAT model. The basic premise for performing such treatments is to ensure the stability of patients or to alleviate the burden of social problems, such as end-stage cancer. OPAT has several key elements, and the indications for such treatment must

be discussed among multiple medical practitioners after consideration of the patients' needs.

Ceftriaxone is used for community-acquired pneumonia[157–159] and skin and soft tissue infections, with a 98.4% efficacy when administered as HIAT or OPAT.[160] Streptococcal or staphylococcal endocarditis can be treated on an outpatient basis, usually with once-daily ceftriaxone. Most reports have documented microbiological and clinical cure rates of 83%–100%.[67,161]

Among 400 cases with MSSA infections, including bacteremia, osteomyelitis, endocarditis, and skin and soft tissue infections, a good efficacy (95.4%) was obtained using ceftriaxone administered as OPAT. In addition, cephalosporins, such as ceftriaxone, are associated with a much lower number of adverse events than vancomycin.[162]

The treatment of osteomyelitis requires a long duration of antibiotic therapy. Ceftriaxone continues to exhibit a sufficient clinical efficacy when used for long periods.[163] Four hundred and fifty-four patients with staphylococcal osteomyelitis were treated using OPAT. These patients were followed for more than ten years. The relative risk for recurrence was 0.8 for the ceftriaxone-treated group, compared with 2.5 for the vancomycin-treated group.[164] Seaton et al documented 114 cases of nurse-led OPAT management for uncomplicated cellulitis using the once-daily intravenous administration of ceftriaxone (1 g). This study reduced the need for a physician review from 100% to 19% with a similar clinical outcome in a series with 230 control cases (97% vs. 99%).[165] Thus, OPAT is expected to provide a sufficient clinical efficacy when used according to appropriate patient selection criteria.

OPAT can improve the cost-effectiveness of treatment where required, since health care insurance systems differ from one country to another. In Sheffield (UK), 334 cases treated using OPAT over a 13-year period were analyzed to determine the cost-benefit. One hundred and ninety-eight cases were treated for soft tissue infections with sepsis, while the other 136 cases were treated for other reasons including infections of the central nervous system. One hundred and ninety-seven of the 198 (99.5%) patients with soft tissue infections with sepsis were treated with ceftriaxone. The re-admission rate was 6.3%. Most of the patients were satisfied with OPAT. The cured or improved rate was 87% (291/334). The cured or improved rate among the patients with skin or soft tissue infections with sepsis was 92% (182/198). The cost of OPAT was equal to 41% of the inpatient cost for the treatment of an infectious disease. Thus, OPAT was cost-effective when compared with equivalent inpatient care in the UK health care setting.[166]

In Canada, 140 cases of OPAT therapy were assessed, and 11% of the patients were treated with ceftriaxone. The most common infectious diseases were bone or joint infections. The mean cost per treatment course of OPAT was CDN$ 1910, while the cost to the Ministry of Health was CDN$ 6326.[167] In contrast, the daily costs were lower than those for inpatient-only care ($278 vs. $478). However, another report showed no significant difference between the total mean cost for OPAT and inpatient-only care in Asia.[152] The clinical and economic efficacy of OPAT or HIAT using ceftriaxone requires further validation.

Conclusion

Ceftriaxone is recognized as a 'traditional' antibiotic, similar to PCG. Indeed, the development of new antibiotics is decelerating, but the spread of multi-drug-resistant pathogens has accelerated throughout the world over the past decade. Although new fifth-generations of cephalosporins, such as ceftaroline are now available,[20] ceftriaxone continues to have an important place in the treatment of many infectious diseases. Of note, ceftriaxone is becoming a first-line alternative regimen for the treatment of streptococcal endocarditis.

The reappraisal of 'traditional antibiotics', such as ceftriaxone, has triggered a review of adequate antibiotic treatment. In addition, the use of them requires no developmental costs and no clinical experiments. No new adverse events will be observed. Such topics of study can be considered as 'antibiotic-ecology.'

Disclosures

The authors report no conflicts of interest and confirm that they have permission to reproduce any copyrighted material.

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