

**Recommendations:**

The physicians present at the P&T Committee meeting, Dr. Crews and Dr. Threat, requested that Invanz be added to formulary. Infectious disease physicians and pharmacy recommend its usage be limited. Broad usage of Invanz will increase resistance to the carbapenems (Primaxin, Merrem) which are used in severe life threatening infections. Treatment with Invanz is recommended for the following conditions:

- Diabetic foot infections
- Mild to moderate community acquired intra-abdominal infections
- Inpatients requiring continuation of therapy as outpatients with an extended spectrum antibiotic such as ceftriaxone has failed or is not active against the bacterial isolates
- ED patients with medication compliance issues being discharged where a single dose of an extended spectrum antibiotic with antianaerobic activity is required
- Infections following bite wounds

*For further details please see the information below including IDSA Guidelines on Treatment of Diabetic Foot Infections, Complicated Intra-abdominal Infections, and Management of Skin and Soft-Tissue Infections.*

**Findings:**

- Community acquired pneumonia:
  - Patient outcomes for Invanz 1 g daily versus ceftriaxone 1 g daily are comparable, but Invanz cost \$47.72 per day versus \$3.71 for ceftriaxone.
  - Ertapenem was as effective as ceftriaxone in two clinical studies enrolling a total of 866 patients with community-acquired pneumonia. Patients were treated with either ertapenem or ceftriaxone, both at doses of 1 g intravenous or intramuscularly once daily. A switch to oral amoxicillin/clavulanate was allowed after a minimum of 3 days of parenteral therapy. Clinical assessment was available for 76% of patients. Microbiologic assessment was available for 41% of patients. The median duration of therapy was 12 days (4 days parenteral). Oral therapy was administered to 88% of patients. For the first study the primary efficacy parameter was the clinical success rate among clinically evaluable patients. Success rates were 92.3% (168/182) for ertapenem and 91% (183/201) for ceftriaxone at 7 to 14 days. In the second study the primary efficacy parameter was the clinical success rate in microbiologically evaluable patients. Success rates were 91% (91/100) for ertapenem and 91.8% (45/49) for ceftriaxone 7 to 14 days posttherapy.
- Complicated Urinary Tract Infections
  - Treatment outcomes are comparable to ceftriaxone, but Invanz cost 12.8 times more (\$47.47 versus \$3.71 per day)
  - Ertapenem was also as effective as ceftriaxone in two clinical studies enrolling a total of 850 patients with complicated urinary tract infections. Patients received either ertapenem or ceftriaxone at a dose of 1 g once daily. After a minimum of 3 days of parenteral therapy, patients could be switched to oral ciprofloxacin therapy. Assessment was available for 256 of 473 ertapenem-treated patients and 224 of 377 ceftriaxone-treated patients. The median duration of parenteral therapy was 4 days. A follow-up oral agent was administered to 96% of patients.

Response Rates for Ertapenem and Ceftriaxone in Complicated Urinary Tract Infections		
	Cure Rates	
Assessment	Ertapenem 1 g daily	Ceftriaxone 1 g daily
Overall bacteriologic eradication	89.4%	91.1%
Modified intent-to-treat bacteriologic eradication	90.1%	89%
Bacteriologic eradication - pyelonephritis patients	91.3%	93.4%
Bacteriologic eradication - other patients*	87.6%	89%
E. coli bacteremia eradication	92.1%	92.3%

\* included catheter-related infections or lower tract infections with urologic abnormalities

- Complicated Intra-abdominal Infections:
  - Invanz is not recommended for the treatment of hospital acquired intra-abdominal infections by Infectious Diseases Society of America or the Surgical Infection Society
  - Antimicrobial trials have generally been designed to demonstrate therapeutic equivalence, and have not been powered adequately to demonstrate superiority. Further, most patients entered into those trials have had community-acquired infections such as perforate appendicitis and have not been severely ill. Since all antimicrobial regimens appear to be of approximately equal efficacy for less severely ill patients with community-acquired infections, agents that are less toxic, less expensive, and have a narrower spectrum of activity would be preferable for these patients.

- The expanded gram-negative bacterial spectrum of some agents shown to be effective in clinical trials is not advantageous for patients with community-acquired infections, and unnecessary use of such agents may contribute to the emergence of antimicrobial resistance. In particular, agents that are used to treat nosocomial infections in the ICU should not be routinely used to treat community-acquired infections.
- Ertapenem is not active against Pseudomonas aeruginosa or Acinetobacter species
- Quinolones and metronidazole have high oral bioavailability and may be used orally.
- Antibiotic agents used for treatment are not recommended to be used for surgical prophylaxis.
- **In patients treated for complicated intra-abdominal infections death occurred in 4.7% (15/316) of patients receiving ertapenem and 2.6% (8/307) of patients receiving comparator drug.**
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Guidelines for the Selection of Anti-infective Agents for Complicated Intra-Abdominal Infections Journal of Clinical Infectious Disease 2003:37						
	Mild-Moderate Infections / Community Acquired	Half-Life (hours)	Cost Per Day	High-Severity Infections	Half-Life (hours)	Cost Per Day
Beta Lactam / Beta Lactamase Inhibitor	Ampicillin / Sulbactam 3 gm Q6h (Unasyn is not recommended in Richmond due to reduced E. Coli susceptibility)	1	\$35.16	Piperacillin/tazobactam	1	\$55.04
	Ticarcillin / Calvulanic Acid 3.1 q6h	1	\$39.95			
Carbapemems	Ertapenem	4	<b>\$47.47</b>	Imipenem/cilastatin 500 mg q6h	1	\$101.27
				Meropenem 1 gm Q8h (non formulary)	1	\$100.98
Combination Regimens						
	Cefazolin 2 gm q 6h plus metronidazole 1000 mg q12h or	2 6-14	<b>\$14</b>	Third generation Cephalosporins plus metronidazole Rocephin 1 gm plus metronidazole 1000 mg q12h	7-9 6-14	\$8.71
	Ciprofloxacin 400 mg q12h plus metronidazole 1000 q12h	4 6-14	<b>\$10.28</b>	Ciprofloxacin 400 mg q12h plus metronidazole 1000 q12h	4 6-14	\$10.28
	Levofloxacin 750 mg q24 plus metronidazole 1000 q12h	6 6-14	\$17.96			
Monobactam Based				Aztreonam 2 gm q6 plus metronidazole 1000 mg q12h	2 6-14	\$185

Cefoxitin and Cefotetan are not recommended for treatment.

- **Seizures occurred in 0.5% of Invanz study patients studied within 14 days of therapy, most commonly in patient with CNS disorders (brain lesions or history of seizure) and/or comprised renal function. The rate in piperacillin/tazobactam treated patients was 0.3% and 0% for ceftriaxone.**

Cost Comparison Chart		
	Usual Dose	Cost per day
<b>Azithromycin</b>	500 mg daily	\$11.49
<b>Cefoxitin</b>	2 gm q6h	\$46.64
<b>Cefriaxone</b>	1 gm q24h	\$3.71
<b>Ciprofloxacin</b>	400 mg q12h	\$5.28
<b>Ertapenem (Invanz)</b>	1gm daily	\$47.47
<b>Imipenem</b>	500mg q6h	\$101.27
<b>Levaquin</b>	750 mg q24h	\$12.95
<b>Metronidazole</b>	500 mg q6h	\$5.00
<b>Timentin</b>	3.1 gm q6h	\$39.92
<b>Zosyn</b>	3.375gm q6h	\$55.04

### **Findings from Guidelines for the Selection of Anti-infective Agents for Complicated Intra-abdominal Infections:**

- Complicated intra abdominal infections extend beyond the hollow viscus of origin into the peritoneal space and are associated either with abscess formation or with peritonitis.
- Susceptibility profiles for *Bacteroides fragilis* group isolates demonstrate substantial resistance to clindamycin, cefotetan, cefoxitin, and quinolones, and these agents should not be used alone empirically in contexts in which *B. fragilis* is likely to be encountered.
- For patient with community-acquired infections of mild to moderate severity, agents that have a narrower spectrum of activity and that are not commonly used for nosocomial infections, such as ampicillin/sulbactam, ceftazidime plus metronidazole, ticarcillin/clavulanate, ertapenem, and quinolones plus metronidazole, are preferable to agents that have broader coverage against gram-negative organisms and /or greater risk or toxicity.
- Patients with more-severe infections, as defined by accepted physiologic scoring systems, or patients deemed to have immunosuppression resulting either from medical therapy or from acute or chronic disease, might benefit from regimens with a broader spectrum of activity against facultative and aerobic gram-negative organisms.
- Health care-associated infections: Postoperative (nosocomial) infections are caused by more-resistant flora, which may include *Pseudomonas aeruginosa*, *Enterobacter* species, *Proteus* species, methicillin-resistant *Staphylococcus aureus*, enterococci, and *Candida* species.
- Bowel injuries due to penetrating, blunt, or iatrogenic trauma that are repaired within 12 hours and intraoperative contamination of the operative field by enteric contents under other circumstances should be treated with antibiotics for less than or equal to 24 hours. (Infectious Diseases Society of America or the Surgical Infection Society)
- For acute perforations of the stomach, duodenum, and proximal jejunum the absence of antacid therapy or malignancy, therapy is also considered prophylactic.
- Acute appendicitis without evidence of gangrene, perforation, abscess, or peritonitis requires only prophylactic administration of inexpensive regimens active against facultative and obligate anaerobes.
- Acute cholecystitis is often an inflammatory but noninfective disease.
  - Coverage against anaerobes is warranted in treatment of patients with previous bile duct-bowel anastomosis.
- Infections occurring during the course of acute necrotizing pancreatitis are due to microbial flora similar to that found in infections resulting from colonic perforations. Antibiotic choices appropriate for other types of intra-abdominal infection are considered appropriate for the empirical treatment of infected necrotizing pancreatitis.
  - If a patient with diagnosed infection has previously been treated with an antibiotic, then patient should be treated as if he/she has a health care-associated infection.
- Infections derived from the stomach, duodenum, biliary system, and proximal small bowel can be caused by gram-positive and gram-negative aerobic and facultative organisms.
- Infections derived from distal small-bowel perforations can be caused by gram-negative facultative and aerobic organisms with variable density.
- Colon-derived intra-abdominal infections can be caused by facultative and obligate anaerobic organisms. Streptococci and enterococci are also commonly present. By far the most common gram-negative facultative organism is *Escherichia coli*.
- In particular, agents that are used to treat nosocomial infections in the ICU should not be routinely used to treat community-acquired infections.
- Prolonged preoperative length of stay and prolonged (> 2days) preoperative antimicrobial therapy are significant predictors of antimicrobial failure leading to recurrent infection and suggest that organisms resistant to the empirical antimicrobial regimen may be responsible for infections. Such patient should be treated for nosocomial infection.
- If infections occurring after elective or emergent operations, a more resistant flora is routinely encountered.
- *Candida albicans* or other fungi are isolated from approximately 20% of patients with acute perforations of the GI tract. Even when fungi are recovered, antifungal agents are unnecessary, unless the patient has recently received immunosuppressive therapy for neoplasm, transplantation, or inflammatory disease or has postoperative or recurrent intra-abdominal infection.
  - Anti-infective therapy for *Candida* should be withheld until the infecting species is identified. If *C. albicans* is found, fluconazole is an appropriate choice.
- Antimicrobial therapy for enterococci should be given when enterococci are recovered from patients with health care-associated infections.

- Diabetic Foot Infections from IDSA Guidelines on Diagnosis and Treatment of Diabetic Foot Infections (2004)
  - Anaerobic gram-positive cocci (especially *Staphylococcus aureus*) are the predominant pathogens in diabetic foot infections.
  - Patients who have chronic wounds or who have recently received antibiotic therapy may also be infected with gram-negative rods, and those with foot ischemia or gangrene may have obligate anaerobic pathogens.
  - Select an empirical antibiotic regimen on the basis of the severity of the infection and the likely etiologic agent(s). Therapy aimed solely at aerobic gram-positive cocci may be sufficient for mild-moderate infections in patient who have not recently received antibiotic therapy.
  - Broad-spectrum empirical therapy is not routinely required, but is indicated for severe infections, pending culture results and susceptibility.
  - Definitive therapy should be based on both the cultures and susceptibility data and the clinical response to the empirical regimen.
  - The distinction between moderate and severe infections has less to do with the status of the foot than with the patient to whom it is attached.
  - The majority of mild and many moderate infections can be treated with agents with a relatively narrow spectrum. Although anaerobic organisms are isolated from many severe infections, they are infrequent in mild to moderate infections, and there is little evidence to support the need for anti-anaerobic therapy in most infections.

**Table 3. Pathogens associated with various clinical foot-infection syndromes.**

Foot-infection syndrome	Pathogens
Cellulitis without an open skin wound	$\beta$ -Hemolytic streptococcus <sup>a</sup> and <i>Staphylococcus aureus</i>
Infected ulcer and antibiotic naive <sup>b</sup>	<i>S. aureus</i> and $\beta$ -hemolytic streptococcus <sup>a</sup>
Infected ulcer that is chronic or was previously treated with antibiotic therapy <sup>c</sup>	<i>S. aureus</i> , $\beta$ -hemolytic streptococcus, and Enterobacteriaceae
Ulcer that is macerated because of soaking <sup>c</sup>	<i>Pseudomonas aeruginosa</i> (often in combination with other organisms)
Long duration nonhealing wounds with prolonged, broad-spectrum antibiotic therapy <sup>c,d</sup>	Aerobic gram-positive cocci ( <i>S. aureus</i> , coagulase-negative staphylococci, and enterococci), diphtheroids, Enterobacteriaceae, <i>Pseudomonas</i> species, nonfermentative gram-negative rods, and, possibly, fungi
“Fetid foot”: extensive necrosis or gangrene, malodorous <sup>c</sup>	Mixed aerobic gram-positive cocci, including enterococci, Enterobacteriaceae, nonfermentative gram-negative rods, and obligate anaerobes

<sup>a</sup> Groups A, B, C, and G.

<sup>b</sup> Often monomicrobial.

<sup>c</sup> Usually polymicrobial.

<sup>d</sup> Antibiotic-resistant species (e.g., methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, or extended-spectrum  $\beta$ -lactamase producing gram-negative rods) are common.

**Table 8. Suggested empirical antibiotic regimens, based on clinical severity, for diabetic foot infections.**

Route and agent(s)	Mild	Moderate	Severe
Advised route	Oral for most	Oral or parenteral, based on clinical situation and agent(s) selected	Intravenous, at least initially
Dicloxacillin	Yes	...	...
Clindamycin	Yes	...	...
Cephalexin	Yes	...	...
Trimethoprim-sulfamethoxazole	Yes	Yes	...
Amoxicillin/clavulanate	Yes	Yes	...
Levofloxacin	Yes	Yes	...
Cefoxitin	...	Yes	...
Ceftriaxone	...	Yes	...
Ampicillin/sulbactam	...	Yes	...
Linezolid <sup>a</sup> (with or without aztreonam)	...	Yes	...
Daptomycin <sup>a</sup> (with or without aztreonam)	...	Yes	...
Ertapenem	...	Yes	...
Cefuroxime with or without metronidazole	...	Yes	...
Ticarcillin/clavulanate	...	Yes	...
Piperacillin/tazobactam	...	Yes	Yes
Levofloxacin or ciprofloxacin with clindamycin	...	Yes	Yes
Imipenem-cilastatin	...	...	Yes
Vancomycin <sup>a</sup> and ceftazidime (with or without metronidazole)	...	...	Yes

**NOTE.** Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have US Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid is currently specifically approved for diabetic foot infections.

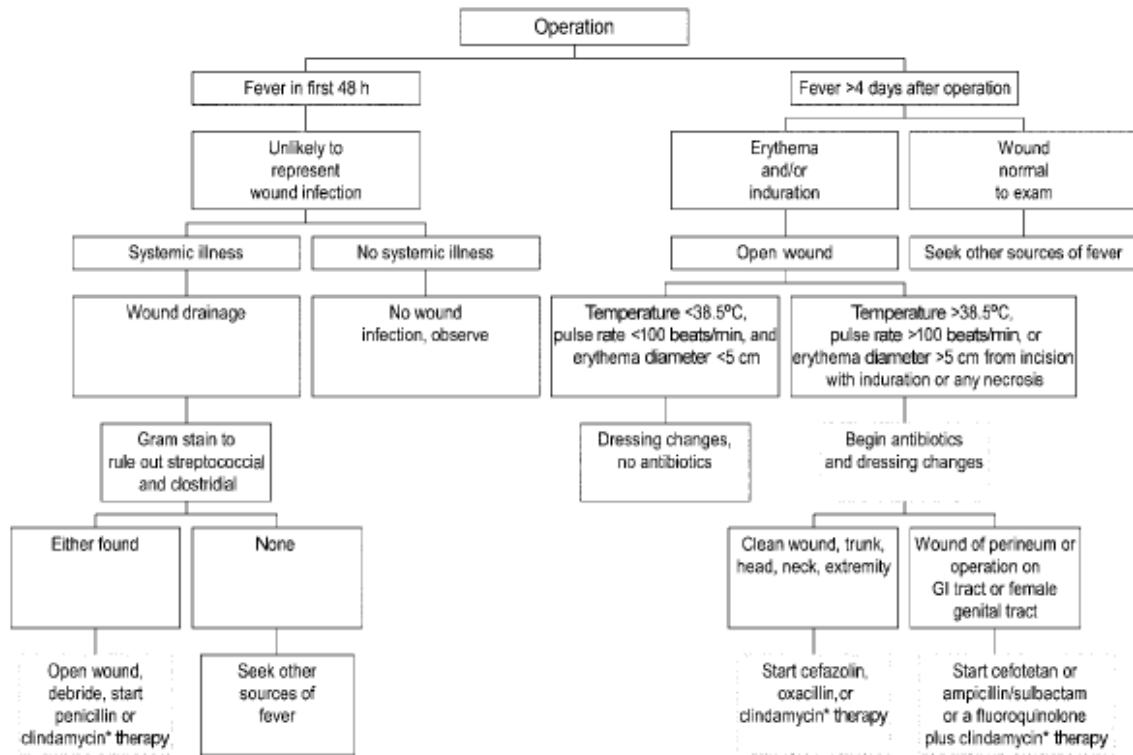
<sup>a</sup> For patients in whom methicillin-resistant *S. aureus* infection is proven or likely.

**Table 6. Clinical classification of a diabetic foot infection.**

Clinical manifestations of infection	Infection severity	PEDIS grade <sup>a</sup>
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
Presence of $\geq 2$ manifestations of inflammation (purulence, or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema extends $\leq 2$ cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness.	Mild	2
Infection (as above) in a patient who is systemically well and metabolically stable but which has $\geq 1$ of the following characteristics: cellulitis extending $> 2$ cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint or bone	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)	Severe	4

**NOTE.** Definitions of terms can be found in footnotes to table 4. Foot ischemia may increase the severity of any infection, and the presence of critical ischemia often makes the infection severe. PEDIS, perfusion, extent/size, depth/tissue loss, infection, and sensation.

<sup>a</sup> International Consensus on the Diabetic Foot [23].



**Figure 1.** Algorithm for the management and treatment of surgical site infections. \*For patients with type 1 (anaphylaxis or hives) allergy to  $\beta$ -lactam antibiotics. Where the rate of infection with methicillin-resistant *Staphylococcus aureus* infection is high, consider vancomycin, daptomycin, or linezolid, pending results of culture and susceptibility tests. Adapted and modified with permission from [154]. GI, gastrointestinal.

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