EMPIRIC ANTIBIOTIC USE IN CRITICALLY ILL PATIENTS

SUMMARY
Inappropriate empiric antibiotic therapy is widespread and associated with increased mortality in critically ill patients. Initial antibiotic selection must account for a variety of host, microbiologic, and pharmacologic factors. Institution-specific data, such as susceptibility patterns, must also be considered. Tailoring antimicrobial therapy based upon culture and sensitivity results will help to reduce costs, decrease the incidence of superinfection, and minimize the development of resistance.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Direct empiric antimicrobial selection at the most likely source of infection based upon clinical and microbiological data.**
    - **Perform a risk assessment for the presence of multi-drug resistant organisms by reviewing the patient's prior microbiologic data and antimicrobial use.**
    - **Consider initiating antifungal therapy in patients at risk (see "Management of Candida Infections in Surgical Patients" guideline).**
  - **Select combination therapy with agents from different classes for initial gram-negative coverage to increase the likelihood of susceptibility.**
- **Level 3**
  - **Perform focused diagnostic tests and procedures according to the "Fever Assessment Guidelines".**
  - **For patients with severe sepsis, initiate empiric antimicrobial agents within one hour.**
  - **Tailor antibiotics based on culture and susceptibility results.**
    - **For gram-negative infections, there is insufficient evidence to support routine combination therapy to achieve synergy or prevent resistance.**
    - **In the absence of a clear survival advantage to combination gram-negative coverage, the decision to tailor antibiotic administration to monotherapy should be based on patient-specific factors.**

INTRODUCTION

Inappropriate empiric antibiotic therapy is widespread and associated with increased mortality in critically ill patients. Although published consensus statements can provide general concepts by which to guide empiric antibiotic selection, they are limited by a failure to incorporate local pathogen susceptibility patterns. There is considerable variability in the frequency of infections, spectrum of potential pathogens, and susceptibility patterns between different ICU's as well as subsets of patients within the same ICU.

Several factors must be considered when selecting empiric antimicrobial therapy:

- Patient-specific factors
  - Presumed source of infection (i.e., blood, sputum, urine, intra-abdominal)
  - Presence of co-morbid conditions (i.e., recent surgery or trauma, chronic illness)
  - Previous antibiotic administration history
- Microbiological factors
  - Identification of the most likely pathogens and their unit-specific susceptibility patterns
- Pharmacologic factors
  - Potential drug toxicity (i.e. aminoglycosides)
  - Bioavailability
  - Distribution to the site of infection

Any empiric antibiotic regimen should be reassessed and tailored as soon as culture and sensitivity results become available. This practice serves to reduce costs, decrease the incidence of superinfection and minimize the development of antimicrobial resistance. The empiric use of vancomycin deserves special consideration. Widespread antimicrobial therapy with this agent has contributed to a significant increase in vancomycin-resistant enterococcal (VRE) infections. The potential transfer of resistance to more virulent organisms such as *Staphylococcus aureus* and *Staphylococcus epidermidis* poses a significant public health threat. As a result, the Centers for Disease Control (CDC) has published recommendations for the prudent use of vancomycin in a document addressing the prevention and control of resistance (1).

LITERATURE REVIEW

Early Appropriate Antimicrobial Therapy

A recent focus regarding antimicrobial therapy emphasizes the importance of early initiation of appropriate antibiotic therapy. Delays in effective antimicrobial coverage are associated with a detrimental impact on patient morbidity and mortality, with an increased risk of sepsis, higher costs, and increased ventilator days for patients with ventilator-associated pneumonia (VAP) (2). Tailoring of antibiotics once cultures are available may not compensate for initial inadequate therapy (Class II).

In a prospective, cohort study of critically ill patients, the relationship between inappropriate empiric antimicrobial therapy and outcome was evaluated (3). Multivariate analysis demonstrated that inadequate antimicrobial treatment of nosocomial infections was a risk factor for hospital mortality (adjusted OR 4.22; $p<0.001$). VAP and bloodstream infections accounted for 89% of inadequately treated nosocomial infections. The most common gram positive and gram-negative organisms associated with inadequately treated VAP were oxacillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*, respectively. *Candida* species were the most common organisms responsible for inadequate treatment of bloodstream infections (Class II).

Combination therapy does increase the likelihood of appropriate therapy for multi-drug resistant (MDR) pathogens. Therefore, initial coverage should include agents from different classes. Gram-negative coverage typically involves a β-lactam, fluoroquinolone or aminoglycoside. Quinolones demonstrate better lung penetration and less renal toxicity as compared to aminoglycosides. However, there is evidence supporting a trend towards increased survival with aminoglycoside-containing regimens (4) (Class II).

For patients with severe sepsis, it is recommended that intravenous antibiotic therapy be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained (5) (Class III).

Risk Factors for Multi-drug Resistant (MDR) Pathogens

When selecting empiric antimicrobial therapy, an assessment for risk of infection with MDR organisms must be made. Risk factors include admission following recent hospitalization or residency in a healthcare-associated facility. Additionally, patients who develop symptoms after five days of hospitalization and/or mechanical ventilation are also at risk for MDR pathogens.

Trouillet and colleagues noted a series of variables increasing the risk for MDR VAP. These include a duration of mechanical ventilation greater than seven days, prior antibiotic use, and broad-spectrum antimicrobial therapy, specifically, third-generation cephalosporins, fluoroquinolones and carbapenems (6) (Class II).

Combination versus monotherapy

Combination therapy has been advocated to achieve synergy against *Pseudomonas aeruginosa* and to prevent the emergence of multi-drug strains. However, this practice remains controversial. Synergy has been demonstrated to be valuable in neutropenic or bacteremic patients (7) (Class II). A meta-analysis of prospective, randomized trials comparing the treatment of sepsis with β-lactam monotherapy or with a β-lactam and aminoglycoside combination regimen failed to demonstrate a significant benefit for

combination therapy (8) (Class II). Of the 7,586 patients evaluated, 1,200 had sepsis from VAP or hospital-associated pneumonia (HAP). No advantage was found with combination therapy for the treatment of *Pseudomonas aeruginosa*. Combination therapy did not prevent the development of MDR strains and the use of aminoglycosides resulted in higher rates of nephrotoxicity. A summary of studies addressing this issue is provided in the table below.

Author	Hilf et al. (7)	Leibovici et al. (9)
Study Design	Prospective, multicenter study of consecutive patients (Class II)	Prospective, observational (Class II)
Population	*P. aeruginosa* bacteremia including neutropenic patients (27%)	Gram (-) bacteremia (single organism) including neutropenic patients
Comparison(s)	Combination (β-lactam + AG) vs. monotherapy	Combination (β-lactam + AG) vs. monotherapy (β-lactam or AG) Comparisons were made for appropriate empiric & definitive therapy
Results	200 patients 93% received anti-pseudomonal therapy 70% received combination therapy No correlation between results of *in vitro* susceptibility & synergy testing and outcome were found **Mortality: Combo (27%) vs. mono (47%); p=0.023**	2165 patients **Mortality (Empiric therapy)** **Combo (19%) vs. β-lactam (17%); p=NS.** **Combo (19%) vs. AG (24%); p<0.01** **Mortality (Definitive therapy)** **Combo (15%) vs.β-lactam (13%); p=NS** **Combo (15%) vs.AG (23%); p<0.01** **Mortality (β-lactam vs AG)** **Higher mortality in all strata with AG except UTI**
Author's Conclusions	The use of combination therapy rather than monotherapy for bacteremia caused by *P. aeruginosa* is associated with improved survival.	Mortality rates for non-neutropenic patients treated with combination therapy and those given a single β-lactam were similar. Treatment with an AG as a single agent was associated with a higher mortality than treatment with a β-lactam (except in patients w/ UTI).

Author	Siegman-Igra, et al. (10)	Crabtree, et al. (11)
Study Design	Retrospective (Class III)	Prospective, observational (Class II)
Population	*P. aeruginosa* bacteremia including neutropenic patients (11%)	Surgical patients with gram (-) infection including general surgery, trauma & transplant patients
Comparison(s)	Combo=fluoroquinolone OR 3rd generation cephalosporin OR imipenem-cilastatin + AG Monotherapy= fluoroquinolone OR 3rd generation cephalosporin OR imipenem-cilastatin	AG containing regimen vs. no AG
Results	123 patients (57 with appropriate definitive therapy & available for analysis) Urinary & respiratory tract most common sources. **Mortality: Combo (13%) vs. mono (14%); p=NS**	258 episodes 25.6% received AG Patients in AG group were more likely to be on HD Pneumonia was most common site of infection AG group hadmore *Pseudomonal* infections In the no AG group, quinolones & cephalosporins were most commonly used When combo therapy was used, the most common regimen was a penicillin + AG **Mortality: AG (25.8%) vs. no AG (13.5%); p=0.02**
Author's Conclusions	Monotherapy with a quinolone, cephalosporin, or imipenem-cilastatin is as effective as combination therapy.	Patients with gram (-) infections treated with AGs had a higher mortality

It is difficult to determine whether or not the administration of combination gram-negative antimicrobial therapy is associated with a mortality benefit. This is not only due to a lack of well-designed trials, but also a lack of homogeneity across trials and the presence of conflicting results. Patient populations ranged from those with pure bacteremias due to *P. aeruginosa* to all infections with any gram-negative organism. Additionally, neutropenic patients were included to varying degrees and a broad range of age groups were evaluated. Although aminoglycosides were consistently evaluated as the "second" antimicrobial agent, this was not the case for the "first" agent. Traditionally, combination therapy is

thought of as the addition of an aminoglycoside to a β-lactam agent; however, the literature addressing this issue encompasses several classes of β-lactams (penicillins, cephalosporins, and carbapenems) as well as fluoroquinolones. Until there is a well-designed trial evaluating a homogenous population with specific antimicrobial agents, this issue will remain unresolved. The decision to tailor to monotherapy should therefore be based on patient-specific factors and clinical judgment.

Specific Infections

Pneumonia

Wunderink and colleagues retrospectively reviewed two prospective, randomized, double-blind studies comparing **linezolid** to **vancomycin** for the treatment of nosocomial MRSA pneumonia (12) (Class III). Clinical cure was defined as resolution of initial symptoms with radiologic studies indicating improvement or lack of progression. Over 1000 patients were enrolled, of which 160 had a respiratory culture positive for MRSA. Clinical cure rates were 59% (36/61) and 36% (22/62) for linezolid and vancomycin, respectively ($p < 0.01$). Given the relatively small number of patients and subjective nature of a key end point, this analysis does not conclusively demonstrate that linezolid is superior to vancomycin for the treatment of MRSA pneumonia. However, it should be considered when an alternative to vancomycin is needed.

Inhaled polymyxin has been advocated as a therapeutic option for MDR *Pseudomonas aeruginosa* nosocomial pneumonia. In a case report of three patients, Hamer described an improvement in patient condition using colistin in conjunction with ceftazidime, aztreonam or gentamicin (13) (Class III). Given the limited data, colistin merits further investigation and may be considered when more conventional treatment options are limited.

Bacteremia

An emerging issue is the use of **tigecycline** for the management of bloodstream infections. Several reported cases highlight the development of bacteremia in patients receiving the drug for other indications (14). This agent has a large volume of distribution and undergoes rapid and extensive transfer from the bloodstream to the tissues. Due to time-dependent pharmacodynamics, it is important that serum concentrations are maintained above the MIC. The authors explain that the development of bacteremia may have resulted from inadequate serum concentrations and caution using tigecycline in patients with bloodstream infections caused by organisms with an MIC $\geq$1 mg/L (Class III).

Intra-abdominal Infection

It is important to remember that definitive management of intra-abdominal infections is source control and antimicrobial therapy is purely adjunctive. Key considerations for the selection empiric antimicrobial therapy in critically ill patients are highlighted in a review of this topic (15). Briefly, determination of the most likely infecting pathogens is dependent upon the classification of primary, secondary, or tertiary peritonitis. The source of contamination should also be considered. For example, infections arising from the upper gastrointestinal tract can be managed with an agent with aerobic, as opposed to aerobic and anaerobic, activity.

Following the publication of the above review, **tigecycline** was approved for use in the management of complicated intra-abdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis (*vancomycin-susceptible isolates only), *MSSA, MRSA* and selected anaerobes (16). With this indication, the product information states that caution should be exercised when considering tigecycline monotherapy in patients with complicated intra-abdominal infections secondary to clinically apparent intestinal perforation. In phase 3 studies, six patients treated with tigecycline and two patients treated with imipenem-cilastatin that presented with intestinal perforations developed sepsis/septic shock. The six tigecycline patients had higher APACHE II scores (median=13) than the imipenem-cilastatin patients (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established. The following literature provides additional information on this topic.

The results of two phase 3, multicenter, double-blind, randomized trials comparing the efficacy and safety of tigecycline and imipenem-cilastatin in patients with complicated intra-abdominal infections were summarized in a pooled analysis (17). Entry criteria included adult patients requiring surgery to treat a complicated intra-abdominal infection. There were several criteria for exclusion, including preoperative suspicion of spontaneous bacterial peritonitis, simple cholecystitis, gangrenous cholecystitis without rupture, simple appendicitis, acute suppurative cholangitis, pancreatic abscess or infected necrotizing pancreatitis; APACHE II score >30; significant hepatic or renal disease; current intra-abdominal infection known to be caused by bacterial isolate(s) not susceptible to either study drug (e.g., *P aeruginosa* and *P mirabilis*); surgical procedure requiring that fascia or deep muscular layers be left open or planned abdominal reexploration.

Patients were randomized to receive tigecycline 100mg, followed by 50mg IV Q12H or imipenem-cilastatin 500mg IV Q6H (or appropriate adjusted doses based on weight and renal function). The primary endpoint was clinical response at the test-of-cure visit for the modified intention to treat and microbiologically evaluable population. Secondary analyses evaluated bacteriologic response at the test-of-cure visit by patient and isolate.

Complicated appendicitis was the most common diagnosis, accounting for approximately 50% of infections in both groups. The mean APACHE II score in both groups was 6. Although a number of study populations were evaluated at the test-of-cure visit, there was no significant difference in clinical cure rates between tigecycline (80.2%) and imipenem-cilastatin (81.5%) ($p<0.0001$ for noninferiority). Additionally, there were no significant differences for either of the secondary endpoints between groups.

Table 1: Empiric Antibiotic Selection

****Antibiotics should be tailored when susceptibilities become available****		
Organism	**Antibiotic**	**Alternative**
Gram-positive organisms		
Staphylococci aureus	Cefazolin or Vancomycin	Linezolid
Coagulase-negative staphylococci	Vancomycin	Linezolid
S. pneumoniae	Ceftriaxone	Moxifloxacin
Enterococcus faecalis	Ampicillin +/- Gentamicin	Vancomycin +/- Gentamicin
Enterococcus faecium	Linezolid	Quinupristin/dalfopristin
Gram-negative organisms		
***S**erratia**	Piperacillin/tazobactam / Gentamicin	β-lactam / Ciprofloxacin or Ciprofloxacin / Aminoglycoside
***P**seudomonas aeruginosa**	Piperacillin/tazobactam / Tobramycin	
***A**cinetobacter**	Cefepime / Gentamicin	
***C**itrobacter**	Cefepime / Gentamicin	
***E**nterobacter**	Piperacillin/tazobactam / Gentamicin	
E. coli (non-ESBL isolate)	Cefazolin	Gentamicin
Klebsiella (non-ESBL isolate)	Cefazolin	Gentamicin or Quinolone
Haemophilus influenzae	Azithromycin	Cefuroxime
E. coli or Klebsiella (ESBL producer)	Meropenem	
Stenotrophomonas maltophilia	Trimethoprim/sulfamethoxazole	Ticarcillin/clavulanic acid

**** The "SPACE" pneumonic can be used to remember gram-negative organisms that should be double-covered until susceptibility results are available.***

Table 2: CDC RECOMMENDATIONS FOR PRUDENT VANCOMYCIN USE (1)
SITUATIONS IN WHICH THE USE OF VANCOMYCIN IS APPROPRIATE OR ACCEPTABLE
• For treatment of serious infections caused by beta-lactam-resistant gram-positive microorganisms. Vancomycin may be less bactericidal than beta-lactam agents for beta-lactam susceptible staphylococci. • For treatment of infections caused by gram-positive microorganisms in patients who have serious allergies to beta-lactam antimicrobials. • When antibiotic-associated colitis fails to respond to metronidazole therapy or is severe and potentially life-threatening. • Prophylaxis, as recommended by the American Heart Association, for endocarditis following certain procedures in patients at high risk for endocarditis. • Prophylaxis for major surgical procedures involving implantation of prosthetic materials or devices at institutions that have a high rate of infections caused by MRSA or MRSE. A single dose of vancomycin administered immediately before surgery is sufficient unless the procedure lasts greater than 6 hours, in which case the dose should be repeated. Prophylaxis should be discontinued after a maximum of two doses.
SITUATIONS IN WHICH THE USE OF VANCOMYCIN SHOULD BE DISCOURAGED
• Routine surgical prophylaxis other than in a patient who has a life-threatening allergy to beta-lactam antibiotics. • Empiric antimicrobial therapy for a febrile neutropenic patient, unless initial evidence indicates that the patient has an infection caused by gram-positive microorganisms and the prevalence of infections caused by MRSA in the hospital is substantial. • Treatment in response to a single blood culture positive for coagulase-negative staphylococcus, if other blood cultures taken during the same time frame are negative. • Continued empiric use for presumed infections in patients whose cultures are negative for beta-lactam-resistant gram-positive microorganisms. • Systemic or local prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters. • Selective decontamination of the digestive tract. • Eradication of MRSA colonization. • Primary treatment of antibiotic-associated colitis. • Routine prophylaxis for patients on continuous ambulatory peritoneal dialysis or hemodialysis. • Treatment (chosen for dosing convenience) of infections caused by beta-lactam sensitive gram-positive microorganisms in patients who have renal failure. • Use of vancomycin solution for topical application or irrigation.

Table 3: Antimicrobial Dosing Guidelines			
Drug	**Normal Renal Function (CrCl >50 mL/min)**	**Renal Dysfunction (CrCl 10-50 mL/min)**	**Renal Failure (CrCl <10 mL/min)**
Amikacin (*Calculator available on www.surgicalcriticalcare.net*)			
• Conventional dosing (once daily dosing not recommended)	7.5mg/kg IV Q8H *Obtain peak and trough with 3rd dose*	7.5mg/kg IV Q12-24H *Obtain peak and trough with 3rd dose*	7.5mg/kg IV x 1 dose *Subsequent doses based on levels*
Cefazolin	1-2gm IV Q8H	1gm IV Q12H	1gm IV Q 24H
Cefepime	1gm IV Q6H	1gm IV Q8-12H	1gm IV Q24H
Cefuroxime	1.5gm IV Q8H	1.5gm IV Q8-12H	1.5gm IV Q24H
Colistin (aerosolized)	150mg aerosolized Q12H	No adjustment necessary	No adjustment necessary
Ciprofloxacin	400mg IV Q8H	400mg IV Q12-24H	400mg IV Q24H
Clindamycin	600-900mg IV Q8H	No adjustment necessary	No adjustment necessary
Gentamicin (*Calculator available on www.surgicalcriticalcare.net*)			
• High-dose, extended interval	7mg/kg IV Q24H *Obtain level 12 hours after dose*	Not recommended	Not recommended
• Conventional dosing	2.5mg/kg IV Q8H *Obtain peak and trough with 3rd dose*	2.5mg/kg IV Q12-24H *Obtain peak and trough with 3rd dose*	2.5mg/kg IV x 1 dose *Subsequent doses based on levels*
Linezolid	600mg IV Q12H	No adjustment necessary	No adjustment necessary
Metronidazole	500mg IV Q8H	No adjustment necessary	500mg IV Q12H
Meropenem	500mg IV Q6H	500mg IV Q6-8H	500mg IV Q12H
Tobramycin (*Calculator available on www.surgicalcriticalcare.net*)			
• High-dose, extended interval	7mg/kg IV Q24H *Obtain level 12 hours after dose*	Not recommended	Not recommended
• Conventional	2.5mg/kg IV Q8H *Obtain peak and trough with 3rd dose*	2.5mg/kg IV Q12-24H *Obtain peak and trough with 3rd dose*	2.5mg/kg IV x 1 dose *Subsequent doses based on levels*
Vancomycin (*Calculator available on www.surgicalcriticalcare.net*)			
• Conventional dosing (once daily dosing not recommended)	15mg/kg IV Q8H *Obtain trough prior to 3rd dose*	15mg/kg IV Q12-24H *Obtain trough prior to 3rd dose*	15mg/kg IV x 1 dose *Subsequent doses based on levels*

Burn Patients (note: only applies to >20% TBSA in the initial hypermetabolic phase of injury)			
Cefazolin	1-2gm IV Q6H	1gm IV Q8H	1gm IV Q12H
Gentamicin/Tobramycin (*Calculator available on www.surgicalcriticalcare.net*)			
• Conventional dosing (once daily dosing not recommended)	2.5-3mg/kg IV Q8H *Obtain peak and trough with 3rd dose*	2.5-3mg/kg IV Q12-24H *Obtain peak and trough with 3rd dose*	2.5-3mg/kg IV x 1 dose *Subsequent doses based on levels*
Piperacillin/tazobactam	**CrCl >40 mL/min**	**CrCl 20-40 mL/min**	**CrCl <20 mL/min**
• Pneumonia	4.5gm IV Q6H	3.375gm IV Q6H	2.25gm IV Q6H
• Other infections	3.375gm IV Q6H	2.25gm IV Q6H	2.25gm IV Q8H
Vancomycin	15mg/kg IV Q6H *Obtain trough prior to 3rd dose*	15mg/kg IV Q8-12H *Obtain trough prior to 3rd dose*	15mg/kg IV x 1 dose *Subsequent doses based on levels*

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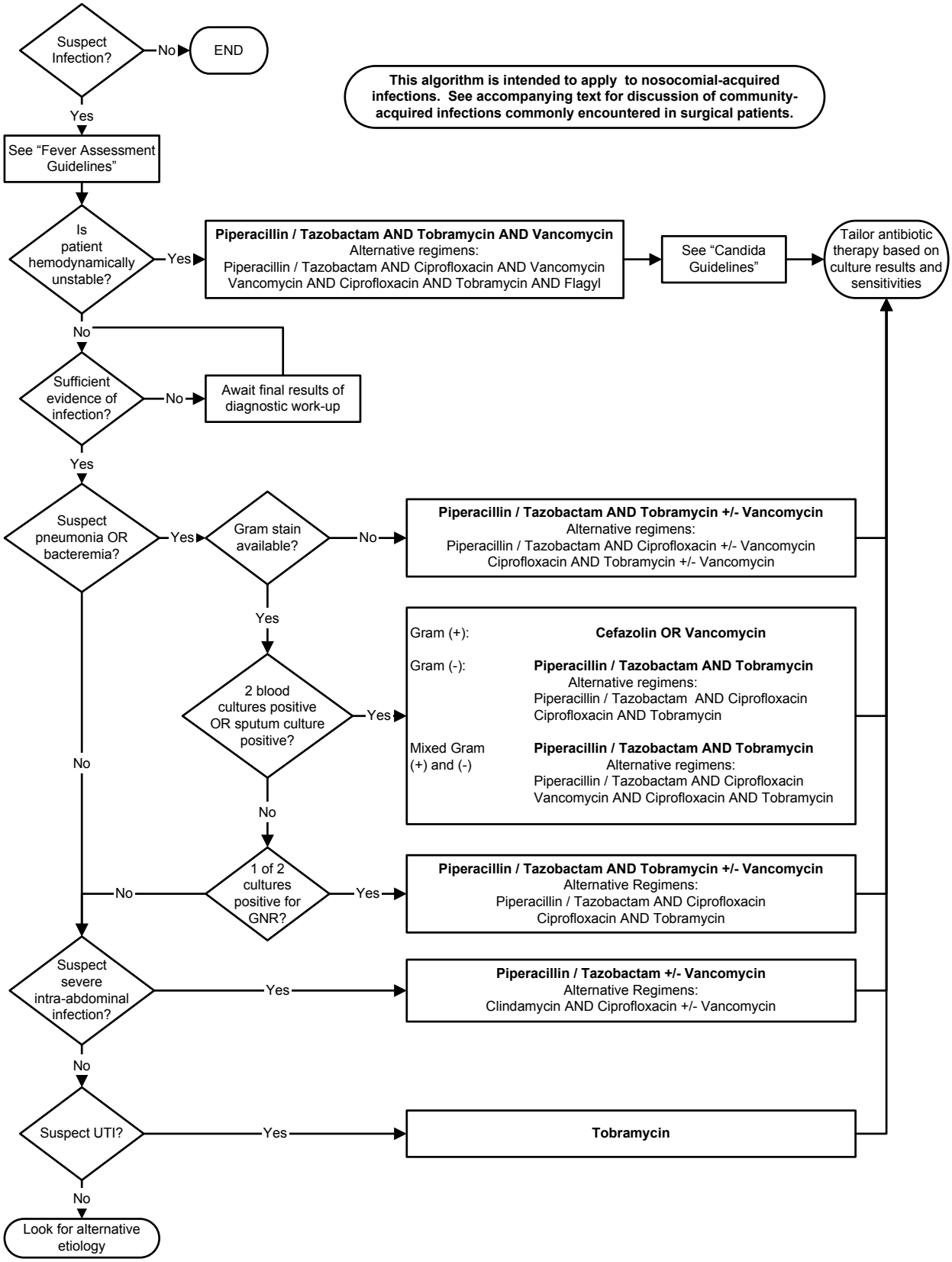
Suspect Infection?
No
END
Yes
This algorithm is intended to apply to nosocomial-acquired infections. See accompanying text for discussion of community-acquired infections commonly encountered in surgical patients.
See "Fever Assessment Guidelines"
Is patient hemodynamically unstable?
Yes
Piperacillin / Tazobactam AND Tobramycin AND Vancomycin
Alternative regimens:
Piperacillin / Tazobactam AND Ciprofloxacin AND Vancomycin
Vancomycin AND Ciprofloxacin AND Tobramycin AND Flagyl
See "Candida Guidelines"
Tailor antibiotic therapy based on culture results and sensitivities
No
Sufficient evidence of infection?
No
Await final results of diagnostic work-up
Yes
Suspect pneumonia OR bacteremia?
Yes
Gram stain available?
No
Piperacillin / Tazobactam AND Tobramycin +/- Vancomycin
Alternative regimens:
Piperacillin / Tazobactam AND Ciprofloxacin +/- Vancomycin
Ciprofloxacin AND Tobramycin +/- Vancomycin
Yes
2 blood cultures positive OR sputum culture positive?
Yes
Gram (+): Cefazolin OR Vancomycin
Gram (-): Piperacillin / Tazobactam AND Tobramycin
Alternative regimens:
Piperacillin / Tazobactam AND Ciprofloxacin
Ciprofloxacin AND Tobramycin
Mixed Gram (+) and (-): Piperacillin / Tazobactam AND Tobramycin
Alternative regimens:
Piperacillin / Tazobactam AND Ciprofloxacin
Vancomycin AND Ciprofloxacin AND Tobramycin
No
No
1 of 2 cultures positive for GNR?
Yes
Piperacillin / Tazobactam AND Tobramycin +/- Vancomycin
Alternative Regimens:
Piperacillin / Tazobactam AND Ciprofloxacin
Ciprofloxacin AND Tobramycin
No
Suspect severe intra-abdominal infection?
Yes
Piperacillin / Tazobactam +/- Vancomycin
Alternative Regimens:
Clindamycin AND Ciprofloxacin +/- Vancomycin
No
Suspect UTI?
Yes
Tobramycin
No
Look for alternative etiology