Antibiotic Timeout Implementation Guide for SSTOP (Self-Stewardship Time Out Project)

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Overview:

This document is intended to serve as a guide for implementation of antibiotic timeouts as a component of an antimicrobial stewardship program, as initially implemented at the VA Greater Los Angeles Healthcare System (VA GLA). It will serve as a "how to" guide that briefly addresses the rationale for an antibiotic time out follow by elaboration on the essential staff and core elements needed to replicate the intervention. This guide will provide practical information and examples on the tools and approach used, along with guidance for building support for the intervention, educational resources (messages, presentation outline, and reminders) and suggested approaches for outcome measurement.

Background:

Appropriate prescribing of antibiotics is a critical challenge for both patient safety and public health. Several studies have estimated that up to 50% of antimicrobial usage is inappropriate in a myriad of different healthcare settings[1-4]. Inappropriate antimicrobial therapy leads to increases in resistance among infecting organisms[5, 6], in adverse events (in particular, *Clostridium difficile*-associated colitis)[7], and in healthcare costs[8]. The increases in resistance brought on by inappropriate antimicrobial use are particularly troubling, as there is currently a dearth of new agents in development to combat infection caused by multidrug-resistant organisms[9]; we have now reached a point where there are infections that cannot be effectively treated by currently available antibiotics[10].

Antimicrobial stewardship has been proposed as a crucial component of our strategy to combat antimicrobial resistance[11]. Antimicrobial stewardship can be defined broadly as a program or series of interventions to monitor and direct antimicrobial use at a healthcare institution, thus providing a standard, evidence-based approach to judicious antimicrobial use[12]. Unfortunately, best practices in antimicrobial stewardship remain unclear. The Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS) all recognize that significant knowledge gaps remain in the literature with regard to implementation of antimicrobial stewardship; a joint statement by these societies identifies patient-centered outcomes research as a key need in determining the most effective deployment of antimicrobial stewardship interventions in varied healthcare settings[13]. A Cochrane review of interventions to improve antibiotic prescribing practices for hospital inpatients found that restrictive interventions (i.e. limiting access to antimicrobial therapy through formulary or approval policies) had a significantly greater impact on prescribing outcomes at 1 and 6 months post-intervention as compared to persuasive measures (dissemination of educational resources and/or outreach, reminders, or audit-feedback), but there were no significant differences at 12 or 24 months[14]. There is evidence that persuasive post-prescription review can work[15], but more trials with robust design and well-defined outcome measures are needed[16]. In Great Britain, post-prescription review has recently been made a highlight of the Great Britain National Health Service's new antimicrobial stewardship program entitled "Start Smart, Then Focus," where the "Focus" stage encourages clinical review and stewardship decision-making 48 hours into an antibiotic course, highlighting 5 potential choices: stop antibiotics altogether, switch from

intravenous to oral therapy, narrow spectrum of therapy, continue and re-review in 24 hours, or transition to outpatient parenteral therapy[17]. One advantage of persuasive interventions such as these, as compared to restrictive measures is that they may not only be as effective as restrictive measures in the long run, but they also may avoid incurring the ill will of providers.

Principles of SSTOP:

While promoting knowledge of the principles of appropriate antibiotic use, application of local epidemiology and resistance patterns, and application of local epidemiology and resistance patterns are important in developing a facility-specific antibiotic time out program, such programs also benefit from better understanding of how providers make decisions with regard to antimicrobial therapy. A fundamental theory in cognitive psychology called dual process theory posits that there are two systems involved in human decision-making: a "system 1" that relies on intuitive associations and heuristics and is rapid, requiring little cognitive effort, and a "system 2" that is much more deliberate, analytic, and deductive but requires much greater cognitive effort[18]. Much of medical care is done under the auspices of system 1 thinking[19], and, in particular, many healthcare providers, particularly trainees, rely on heuristics when prescribing antimicrobial therapy[20]. The program we implemented at VLA GLA was based on the principle that if providers who are taking care of patients who are receiving broad-spectrum antimicrobial therapy are given prompts to think deeper about their patient and are provided an aggregated clinical display of infection-related clinical parameters and ready access to educational resources that ease the cognitive effort associated with system 2 thinking, they will be "nudged" to make better decisions with regard to modifying antimicrobial therapy. Our concept was that an effective post-antibiotic prescription review requires the disruption of the normal flow of clinical activities combined with prompts that promote critical thinking while providing offsetting advantages to providers (e.g., respecting their autonomy by avoiding restrictive interventions). The nature of the intervention was intended to disrupt normal inertial processes and compel providers to actively consider choices other than merely continuing previously initiated therapy.

It is with this perspective that we developed and implemented an intervention at VA GLA in which providers who have patients who are receiving either of the two most commonly-prescribed broad-spectrum antimicrobial agents, vancomycin and piperacillin-tazobactam, are able to obtain automatic approval of continuation of these medications by completing an "antibiotic timeout" 48-72 hours into therapy. The concept of the antibiotic timeout was borrowed from the surgical literature, where it was demonstrated that formal pauses at critical time periods prior to and following surgery to review checklists pertaining to patient safety was associated with decreased post-operative complications and mortality[21]. The time frame of 48-72 hours into the course of therapy of broad-spectrum antibiotics was chosen as a particularly crucial time frame for modification of antimicrobial therapy, as it is a time when microbiologic data frequently becomes available and an assessment as to whether the clinical status of the patient has improved with initially-prescribed therapy[22].

As fully implemented at VA GLA, the antibiotic timeout intervention consisted of three primary components:

a) an electronic antimicrobial dashboard that aggregates data potentially useful in antimicrobial decision-making into a user-friendly report,

b) a templated note built into the electronic medical record that guides providers through a logical

decision tree that provides them with patient-specific clinical information and ready access to local guidelines on antimicrobial prescription, documents that a timeout has taken place, and by hospital policy provides the basis for automatic approval of continuation of antimicrobial therapy if so indicated, and

c) an educational program consisting of the dissemination of guidelines for antimicrobial use (distributed via links to guidelines built into the approval template and the stewardship program website), flyers, posters and other advertising and promotional material, lectures, and social marketing.

Prior to timeout implementation, continuation of vancomycin and piperacillin-tazobactam past 72 hours required approval by the infectious diseases pharmacist, fellow, or attending. With introduction of the antibiotic timeout, the need for approval by infectious diseases was waived, and approval of continuation was automatically given if documentation of the timeout process indicated that the antibiotic in question was to be continued.

Program technical requirements:

In order to implement any kind of "timeout" antibiotic renewal program, a system is needed whereby 1) patients receiving targeted antibiotics can be identified 48-72h into the course of therapy, and 2) providers can be notified regarding which of their patients qualify for an antibiotic time out – this can be done by electronic alerting of providers combined with, when possible, notification by clinical pharmacists. A medical center intranet or website where project-specific educational content can be hosted and linked to from antibiotic renewal templates is also recommended.

Preparatory work:

Project team assembly:

Before implementation, a project team should be assembled with each member having clear roles and duties. The team should be led by a medical director, preferably a physician who has credibility and the ability to engender trust among prescribers. Ideally, this person should be trained in infectious diseases, but a hospitalist or other well-respected individual who has an interest in antimicrobial stewardship and is familiar with the concepts of antimicrobial de-escalation can fill this role. The medical director's tasks include presentations to clinical leadership on the "why" and "how" of timeout implementation, giving of lectures to prescribing staff on the importance of antimicrobial stewardship, informally promoting the program in other interactions with hospital staff, and developing timeout-specific guidelines and educational materials that are adapted to ensure appropriateness to local epidemiology and resistance trends.

A lead clinical pharmacist, preferably with infectious diseases training and/or certification, plays a critical role in communicating with all clinical pharmacists and providers the rules of the antibiotic timeout program, particularly with regard to when targeted antimicrobial therapy becomes eligible for timeout intervention and is discontinued if a timeout does not take place. The clinical pharmacist, in collaboration with the medical director, may also take a lead role in identifying patients for timeout intervention on a daily basis. Overall, the clinical pharmacist will generally be responsible for day-to-day oversight of the program.

One or more team members with expertise in medical informatics who can communicate with existing medical center informatics staff is essential in project development as it pertains to constructing

antimicrobial dashboards and antibiotic renewal templates, then integrating these tools into the electronic medical record (see below for a fuller description of these tools). Other informatics-related tasks include integrating antibiotic timeout-related information and links into pre-existing antibiotic order menus in the electronic medical record and incorporating links to educational materials within the templates. Finally, a team member who is facile with obtaining and interpreting antimicrobial utilization data and microbiologic and clinical outcomes is vital in determining the impact of antibiotic timeout implementation on clinical outcomes.

At VA GLA, we thought it was important to also identify clinical champions for the timeout project who were respected individuals in key services throughout the hospital, including hospitalists, intensivists, and surgeons. Prior to implementation, we relied on our clinical champions for advice on constructing our dashboard reports and antibiotic renewal templates and in how the program should be first implemented. After implementation, the clinical champions served in social marketing (i.e. informal peer education) in promoting familiarity with and adherence to the timeout program.

Identification of antibiotics to be targeted for intervention:

Knowledge of local antimicrobial prescription patterns is important in determining the antimicrobials to target for intervention that will result in the best balance of avoidance of inappropriate antimicrobial usage with maintenance of patient safety. Antibiotics should also be chosen for intervention where reduction in usage is an achievable, yet worthwhile goal. At VA GLA, particularly with regard to empiric therapy, vancomycin is by far the most commonly used broad-spectrum agent that targets Gram-positive organisms, and piperacillin-tazobactam is by far the most commonly used antipseudomonal agent; both were the broad-spectrum antibiotics for which antimicrobial stewardship team approval of continuation past day 3 of therapy was most frequently requested, so they were obvious choices for timeout intervention. However, the logic of the timeout intervention supports expanding the vancomycin timeout to other agents with predominantly anti-MRSA activity (e.g., daptomycin, linezolid). Similarly, the piperacillin-tazobactam timeout can be expanded to other agents with antipseudomonal activity (e.g., cefepime, meropenem, imipenem). The choice of antibiotics should be influenced not only by patterns of usage of these agents but also by pre-existing antibiotic restriction policies and provider buy-in.

Stakeholder involvement and communication:

The ultimate goal in implementing an antibiotic timeout program should be to make it a part of the hospital culture and fit into the routine workflow of providers, pharmacists, and the antimicrobial stewardship team. To this end, there must be clear communication between all stakeholders in establishing rules for a firm discontinuation/expiration of targeted antimicrobial therapy if a timeout is not completed within a specified time frame and if there should be any exceptions to these rules. Communication with clinical pharmacists is essential in this regard, as they are typically on the “front lines” in notifying providers when particular medications expire. Buy-in should also be achieved at an institutional level, i.e. the Medical Executive Committee, the Pharmacy and Therapeutics Committee, and clinical leaders of inpatient services across specialties that have an inpatient presence (in particular, the Chiefs of Medicine and Surgery). To further ensure compliance with the program facilities may wish to implement automatic stopping procedures for targeted antibiotics. If so, facility policies may need to be modified to allow for this. Implementation of such stopping orders requires that system be put in place to prevent the inadvertent discontinuation of antibiotics in persons with critical needs for

continued therapy, such as individuals with blood stream infections, meningitis and other deep seated infections.

Determining criteria for appropriateness of continuing, de-escalating, escalating or discontinuing targeted antibiotics during the timeout:

If a medical center does not have pre-existing criteria as to when continuation, de-escalation, escalation, or discontinuation of the antibiotics that are to be targeted by the timeout intervention is appropriate, such criteria should be developed. Two documents were developed by the VA GLA timeout team in this regard; one specific to the management of infections caused by (or likely to be caused by Gram-positive bacteria and another specific to de-escalation of antipseudomonal therapy for common infectious syndromes (currently summarized in Appendix 1). This document will be made available to all sites via a central resource but can also be freely adapted and hosted locally to meet the needs of different facilities.

Overview of antibiotic timeout workflow:

Three sets of stakeholders were impacted by the timeout intervention: the prescribing providers, the antimicrobial stewardship team, and the inpatient clinical pharmacists. A schematic of how the timeout was integrated into the workflow of each stakeholder group is presented as Figure 1.

Specific components of the antibiotic timeout intervention:

Electronic Antimicrobial Dashboard:

Key dashboard elements:

To assist providers in their decision-making during the antibiotic timeout, we developed a report that summarized infection-relevant information into individual patient reports that could not only be used as decision aids during the timeout but also as tools to use during rounding and other patient care activities. An example of an individual patient dashboard report is shown in Figure 2. The dashboard report can roughly be divided into thirds, where the top third contains patient identifiers and recent and/or current antimicrobial therapy, the middle third contains vital signs and relevant laboratory trends, and the bottom third contains recent microbiologic data. Further details on dashboard implementation at VA GLA are available in the legend to Figure 2.

Distribution of dashboard reports to providers:

If desired by the local facility, a system should be in place to allow for providers to view dashboard reports, either online or in printed form. The dashboard reports should not only serve to assist providers in their decision-making by displaying infection-relevant information in a single place but also should assist in the process of identifying which patients are eligible for timeout intervention on any particular day. These reports can be distributed by members of the antimicrobial stewardship team or other personnel. While clinical pharmacists are an appealing way to distribute the reports as they can also answer many relevant clinical questions providers may have, non-clinical personnel can also distribute the reports. When the dashboard reports are distributed to providers, in addition to mentioning that a timeout was due for the antibiotic and patient in question providers should be told how to access educational materials, guidelines, etc. and who to contact if there are questions about the program.

Full program requirements:

At VA GLA, the electronic antibiotic dashboards were reviewed on a daily basis by the project team in order to identify patients eligible for an antibiotic timeout (i.e. vancomycin or piperacillin-tazobactam was due for renewal 48-72 hours into therapy). Dashboard reports were initially printed for timeout-eligible patients and were distributed by a non-clinical member of project team to the providers caring for those patients. In later phases of the project, clinical pharmacists were responsible for printing and distributing the dashboard reports. At VA GLA the dashboard reports were also available for viewing and downloading using CPRS as a portal.

Antibiotic Timeout Templates:

At the time of the Antibiotic Time Out we require that providers answer a series of questions in order to receive approval for continued therapy. We focused on four basic questions:

1. Is a bacterial infection present?
2. Has the site of infection been determined?
3. Has the culprit bacterial pathogen(s) been identified?
4. Is the patient clinically stable?

Full program requirements:

In the VA GLA implementation, we relied on the ability of CPRS to support templated progress notes that support the use of response driven questions, capture of free-text and Yes/No responses and recording of this information in an electronic progress note and as discrete data elements that could be electronically tabulated and analyzed. Throughout the templates, hyperlinks can be clicked to access online resources, including a link to and instructions on how to access the electronic antimicrobial dashboards and educational materials and clinical guidelines pertinent to the antibiotic in question (discussed in more depth below).

If the logic tree indicates that the antibiotic in question should be continued, the provider is instructed to enter an order for antibiotic renewal for the time period designated by the note (typically 48 to 96 hours). When the template is completed, a note that captures all of the answers entered by the provider is generated and the final result as to whether or not the antibiotic in question should be continued based on the logic tree of the template. Once signed, this note is seen by the clinical pharmacists, who process the order for renewal of the antibiotic in question if it is indicated by the logic tree and entered by the provider.

Educational Resources Available via the Timeout:

Education is a critical component of an antibiotic timeout program, and access to educational materials must be made readily available. At VA GLA, the Infectious Diseases Section has maintained an intranet site for several years. This site contains links to antimicrobial formulary guidelines as well as guidelines for the management of common disease states that are locally adapted and agreed upon by consensus of faculty in the Infectious Diseases Section (www.vaglaid.org). A link to this intranet site is available from the main VA GLA intranet homepage.

Several educational documents were developed and placed in an “Antibiotic Timeouts” section of the

"Stewardship" section of the GLA Infectious Diseases (ID) intranet site (http://www.vaglaid.org/antibiotic-timeouts/) that are summarized and updated as Appendices to this document: a) a short guide to antibiotic use for use in conjunction with SSTOP (Appendix 1), b) an operational guide to antibiotic timeouts (Appendix 2), c) general considerations in switching patients from IV to oral antibiotic therapy (Appendix 3), d) what to expect regarding time frame for improvement in skin/soft tissue infections and pneumonia (Appendix 4), and e) a document detailing potential adverse reactions to vancomycin (Appendix 5). Links to these documents can also provided within the context of the antibiotic renewal templates, where appropriate. A link to the Antimicrobial Clinical Dashboards homepage with instructions for access can be provided both in the "Antibiotic Timeouts" intranet section and within the electronic template.

Educational and Social Marketing Campaign:

For an antibiotic timeout program to be successful, providers must know that it exists and why it exists. To this end, at VA GLA, the director of the antimicrobial stewardship program (C.J.G.) gave a Grand Rounds lecture to Department of Medicine faculty, housestaff, and students four months prior to launch that focused on the importance of antimicrobial stewardship and made the case for a timeout intervention. Follow-up talks were also given at Medicine faculty meetings and housestaff meetings in the weeks leading up to the initial vancomycin timeout launch and continued prior to subsequent expansion to piperacillin-tazobactam timeouts and inclusion of the MICU. Immediately prior to the launch of vancomycin and piperacillin-tazobactam timeouts in the SICU, the medical director of the SICU and the housestaff rotating on the service were given a tutorial on how the timeout approval process works. Immediately prior to launch in any new floor/unit, small notes were posted on computer screens in the housestaff team rooms of that floor/unit detailing instructions on the timeout approval process, and flyers were posted on team room walls that encouraged de-escalation of vancomycin (Appendix 6) and piperacillin-tazobactam (Appendix 7) in the proper clinical settings and reinforced guidelines on when conversion from intravenous to oral antibiotic therapy was indicated. Clinical pharmacists were also briefed and updated as necessary as the timeout intervention was introduced and expanded. Pre-existing antibiotic order templates within the electronic medical record were updated with descriptions of the timeout renewal protocol, and links were embedded within these order sets to the electronic antimicrobial dashboards. With the beginning of the new academic year in July 2013, the antimicrobial stewardship program director gave a lecture to new housestaff regarding the importance of antimicrobial stewardship that highlighted the antibiotic timeout intervention. Pocket cards were also distributed to housestaff that detailed antibiotic stewardship policies, including the timeout.

Throughout the pre-implementation process of finalizing the electronic antimicrobial dashboards, the timeout approval templates, and the educational materials, we relied on the input and feedback of four clinical champions of the project: two internal medicine hospitalists, a pulmonary/critical care intensivist, and a surgeon. These clinical champions were also involved in advertising the program to their colleagues, in eliciting further feedback, and in helping to arrange for qualitative evaluations of the antibiotic timeout program.

Conclusions:

The antibiotic timeout, as implemented at VA GLA, is a novel antimicrobial stewardship intervention that fits easily into hospital workflow and allows for more efficient practices by the antimicrobial stewardship team. A key feature of our intervention has been in our application of cognitive support for providers at

the point of care, while at the same time actually increasing provider autonomy and encouraging a culture of self-reliance and "self-stewardship." While there is certainly potential for providers "gaming the system" by providing incorrect information in the renewal templates that would allow for inappropriate approval of continuation of broad-spectrum therapy, it is hoped the fact that the responses to the questions asked in the renewal template are aggregated into an electronic progress note that is signed by the provider and thus becomes part of the permanent electronic medical record serves as a deterrent to this behavior.

Given the success of the timeout concept in the surgical literature, there is immense potential for timeouts to be applied to other healthcare settings, and timeouts that address anti-MRSA and antipseudomonal therapy 48-72 hours into therapy may only be the beginning of its potential applications within the rubric of antimicrobial stewardship.

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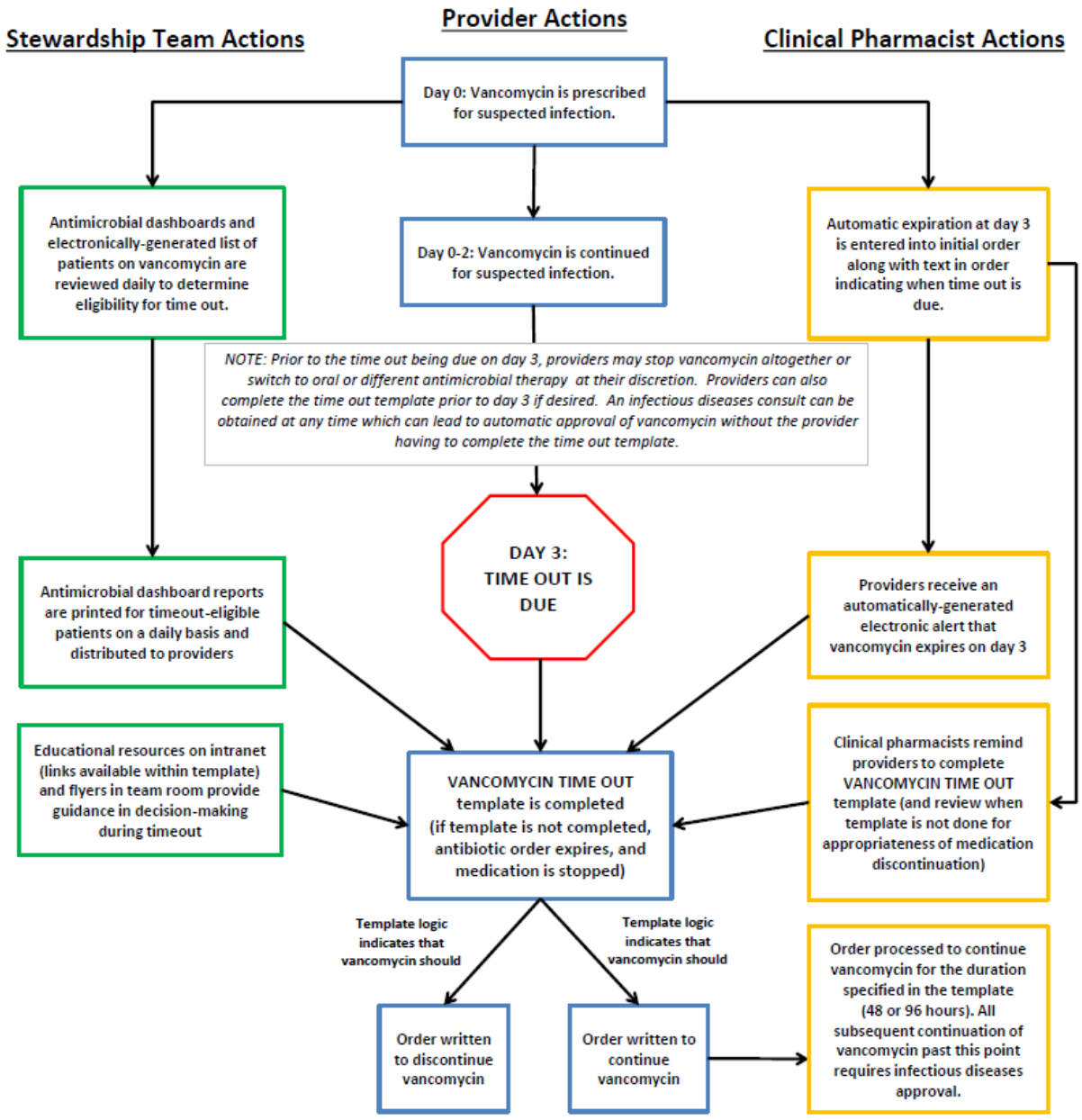
Figures:

Figure 1: Antibiotic timeout workflow schematic

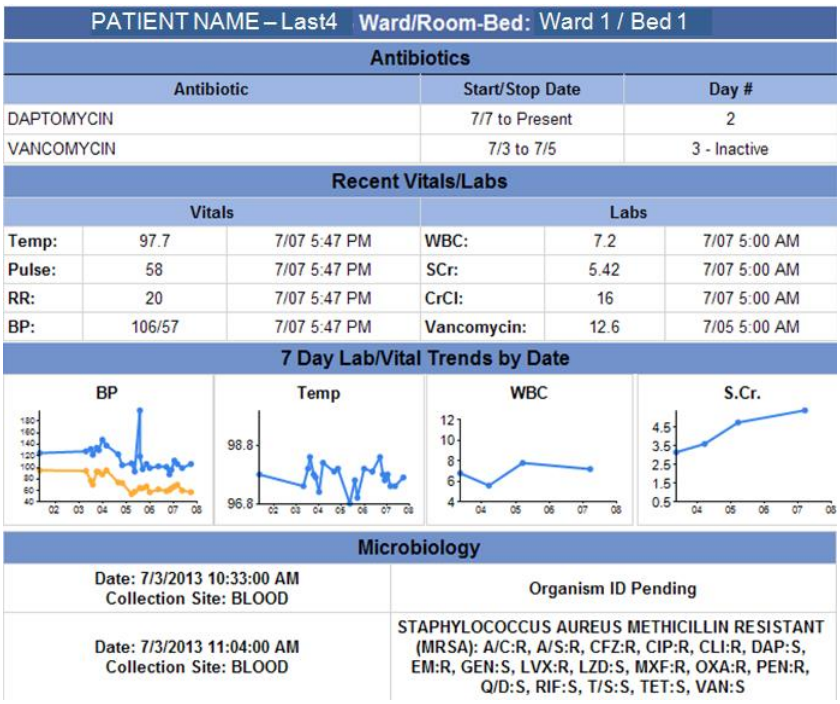
Figure 2: Electronic antibiotic dashboard report example

Figure 1: Antibiotic Timeout Workflow Schematic*



*: Vancomycin is used as an example; workflow associated with piperacillin-tazobactam time outs is identical

Figure 2. Electronic Antibiotic Dashboard Report Example*



*: Dashboard creation and implementation at VA GLA:

Patient information is at the top of the report, including patient name, the last four digits of the social security number (which are typically used in looking up patients in the VA Electronic Health Record), and patient location (ward and bed). Next displayed is antimicrobial information, including any antimicrobial agent started within the prior 30 days, start and end dates of therapy, and the current day of therapy for all active antimicrobials. An antimicrobial agent is defined as active if its order is currently active and that the patient received it within the previous 96 hours. The middle part of the report shows vital signs and laboratory results that are likely to be relevant in judging clinical response to infection, namely white blood cell (WBC) count, serum creatinine and creatinine clearance, and therapeutic drug levels of vancomycin, tobramycin, amikacin, and/or gentamicin, along with the date and time the value was recorded in the electronic medical record. Graphs trending changes in blood pressure, temperature, WBC count, and serum creatinine over the prior 5 days are also displayed to give users a more visual sense of how the patient is responding to treatment. The bottom part of the report displays microbiology results, including all cultures performed within the previous 14 days, with organism identification and antimicrobial susceptibilities, if available.

We relied on the VA Corporate Data Warehouse (CDW) as our data source for dashboard construction. The CDW is a server to which clinical data is uploaded from VA facilities nationwide on a nightly basis. The uploaded clinical data includes patient demographics, admission/discharge/transfer (ADT) data, bar code medication administration (BCMA) data that tracks all inpatient medication use, vital signs, laboratory values, and microbiology culture results and susceptibilities. Microsoft SQL Server 2008 R2 Management Studio is used to query the CDW, and Microsoft SQL Server 2008 R2 Report Builder 3.0 is used to construct the dashboard, which is accessible via a SharePoint website to which users can request access, with permission granted based on user credentials. The dashboard allows users to

select a panel of patients for which reports can be generated, based on facility, whether or not patients are receiving active antimicrobial therapy, ward location, and whether or not patients are eligible for a timeout for vancomycin and/or piperacillin-tazobactam.

Appendices:

Appendix 1: A Short Guide to Antibiotic Use for use in Conjunction with SSTOP (the Self-Stewardship Time Out Project) – VA Boston Edition

Appendix 2: Operational Guide to Antibiotic Timeouts

Appendix 3: Considerations in Switching Patients from Intravenous to Oral Antibiotics

Appendix 4: Is My Patient Getting Better? What to Expect Regarding Time Frame for Improvement in Skin/Soft Tissue Infections and Pneumonia

Appendix 5: Potential Adverse Outcomes Associated with Vancomycin Therapy

Appendix 6: Know When to Say No to Vanco flyer

Appendix 7: Know When to Say No to Pip-Tazo flyer

APPENDIX 1:

A Short Guide to Antibiotic Use for use in Conjunction with SSTOP (the Self-Stewardship Time Out Project) – VA Boston Edition

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This document provides guidance for the selection of empiric antibiotic therapy for common infections, considerations for de-escalation of antibiotic therapy during an antibiotic timeout and the duration of antibiotic therapy for common clinical syndromes.

This guidance, which is based on guidelines issued by the Infectious Diseases Society of America, the Surgical Infection Society and supplemented by expert opinion, emphasizes avoiding fluoroquinolones wherever possible, reducing the use of broad-spectrum, anti-pseudomonal antibiotics and anti-MRSA therapy, and decreasing the use of third and fourth generation cephalosporins. Although this this guidance is directed at patients who warrant inpatient management because of clinical severity in the infected patient, many of the principles are pertinent to outpatients with less severe disease.

For all conditions, providers should reassess daily whether antibiotic therapy should be continued, narrowed, converted to oral therapy or discontinued.

- *Many patients thought to have infection on admission are found to have other explanations for their illness in 1 – 2 days; in such individuals antibiotics can and should be discontinued.*
- *Culture results should be reviewed at least once a day and antibiotic therapy should be adjusted accordingly.*

These guidelines should not be viewed as rules of practice that require 100% compliance. Rather, they should be used to assist in clinical decision-making. Recommendations for de-escalation and the duration of therapy are directed at patients who have had a satisfactory clinical response. If questions or problems arise, then an Infectious Diseases consultant should be contacted.

Outline

Skin-Soft Tissue Infections

Diabetic Foot Infections

Sepsis Syndrome (Use only for patients for whom there is no apparent primary site of infection)

Principles of Adjusting Antimicrobial Therapy During an Antibiotic Timeout

Guidelines for De-Escalation of Anti-MRSA therapy (e.g., vancomycin, daptomycin, linezolid/tedizolid, ceftaroline)

Guidelines for De-Escalation of Broad-spectrum gram-negative therapy (e.g., piperacillin/tazobactam, cefepime, ceftazidime, meropenem, imipenem, doripenem)

Guidance for duration of therapy – listed by clinical syndrome

Pneumonia

Urinary Tract Infections

Skin-Soft Tissue Infections

Diabetic Foot Infections

Sepsis Syndrome (Use only for patients for whom there is no apparent primary site of infection)

Intra-abdominal Infections

Guidelines for empiric antibiotic therapy of common conditions

Pneumonia

See NOTES at end for definition of Healthcare associated pneumonia (HCAP), other risk factors for P. aeruginosa infection and other considerations

Community-onset pneumonia (CAP):

Recommended empiric therapy:

Ampicillin/sulbactam plus doxycycline or azithromycin

Ceftriaxone plus doxycycline or azithromycin

Step down oral therapy in patients with an appropriate clinical response:

Culture-negative cases:

Amoxicillin/clavulanate, amoxicillin or cefpodoxime plus azithromycin or doxycycline

Culture-positive cases:

Manage according to culture results

Levofloxacin or ciprofloxacin are appropriate only if there are no other suitable oral choices.

NOTE: The recovery of *Pseudomonas* or another Gram-negative rod from a sputum culture does not justify broadening antimicrobial therapy in patients who have responded to narrow-spectrum therapy

Total duration of treatment (inpatient plus post discharge): typically 5 days unless delayed response to therapy

Penicillin-allergic patients:

Severe hypersensitivity (e.g., anaphylaxis, hives, Steven Johnson Syndrome): levofloxacin

Rash or non-specific reactions to penicillins: cephalosporins are appropriate.

Healthcare associated pneumonia (HCAP):

Recommended empiric therapy for mild-moderate disease (e.g., patient does **NOT** require ICU-level care):

Ceftriaxone plus doxycycline or azithromycin

Consider a second course of ceftriaxone, or use cefepime or piperacillin/tazobactam and azithromycin for patients recently treated with ceftriaxone

Recommended empiric therapy for severe disease (e.g., patient **DOES** require ICU-level care):

Cefepime (or piperacillin/tazobactam), vancomycin plus doxycycline or azithromycin

Step down oral therapy in patients with an appropriate clinical response:

Culture-negative cases:

Amoxicillin/clavulanate (875/125 mg bid), amoxicillin (500 mg tid) or cefpodoxime plus azithromycin or doxycycline

A negative nasal surveillance specimen for MRSA justifies prompt discontinuation of anti-MRSA therapy

Culture-positive cases:

Manage according to culture results

Levofloxacin or ciprofloxacin are appropriate only if there are no other suitable oral choices.

NOTE: The recovery of *Pseudomonas* or another Gram-negative rod from a sputum culture does not justify broadening antimicrobial therapy in patients who have responded to narrow-spectrum therapy

Total duration of treatment (inpatient plus post discharge): typically 5 days unless delayed response to therapy

Penicillin-allergic patients:

Severe hypersensitivity (e.g., anaphylaxis, hives, Steven Johnson Syndrome): levofloxacin or aztreonam (plus vancomycin for severe disease).

Rash or non-specific reactions to penicillins: cephalosporins are appropriate.

Hospital acquired pneumonia (HAP): identical to healthcare associated pneumonia except that:

Use of doxycycline or azithromycin is not routinely recommended.

Duration of therapy is 7 days unless delayed response to therapy

NOTES:

Healthcare associated pneumonia is relevant in patients with the following risk factors.

Antimicrobial therapy in preceding 90 days

Current hospitalization of 4 days or more

Hospitalization for 2 days or more in the preceding 90 days

Residence in a nursing home or extended care facility

Home infusion therapy (including antibiotics)

Home wound care

Family member with multidrug-resistant pathogen

Immunosuppressive disease and/or therapy

Other risk factors that support initiation of antipseudomonal therapy

Severe structural lung disease (bronchiectasis)

COPD with repeated exacerbations leading to frequent steroid and/or antibiotic use

Cystic fibrosis

[top]

Urinary tract infections (UTI)

Recommended empiric therapy: Use urine culture results to narrow or broaden therapy as appropriate (consider waiting for culture results in cases with mild symptomatology)

Community-onset urinary tract infections

Mild-moderate disease (cystitis): oral 3rd gen. cephalosporin (e.g., cefpodoxime), TMP/SMX or nitrofurantoin

Severe disease (pyelonephritis, urosepsis): ceftriaxone

Hospital acquired or healthcare associated UTI (includes catheter-associated UTI).

Mild-moderate disease (cystitis): Ceftriaxone

Severe disease: piperacillin/tazobactam or cefepime

NOTE: urine cultures from the prior month may be used to further guide initial therapy

Step-down oral therapy in patients with appropriate clinical response: Select using culture results.

Preferred agents (if active): oral 1st gen. cephalosporin, TMP/SMX or nitrofurantoin (cystitis only)

Ciprofloxacin is appropriate only if there are no other suitable oral choices

NOTE: The recovery of resistant organism from the urine does not justify broadening antimicrobial therapy in patients who have responded to narrow-spectrum therapy

Total duration of treatment (inpatient plus post discharge):

Mild-moderate disease (cystitis): 7 days

Severe disease or slow clinical response: 7-10 days; severe complicated infections occasional require 14 days

Penicillin-allergic patients:

Severe hypersensitivity (e.g., anaphylaxis, hives, Steven Johnson Syndrome):

Mild-moderate disease:

TMP/SMX, fosfomycin or nitrofurantoin (cystitis only)

Ciprofloxacin is appropriate only if there are no other suitable oral choices

Severe disease: Aztreonam is preferred

Rash or non-specific reactions to penicillins: cephalosporins are appropriate.

NOTES:

Hospital acquired infections are defined as infections with onset on hospital day 3 or later

Healthcare associated urinary tract infections are defined as infections occurring in context of

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of 4 days or more
- Hospitalization for 2 days or more in the preceding 90 days
- Residence in a nursing home or extended care facility
- Home infusion therapy (including antibiotics)
- Home wound care
- Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy
- Prior UTI within 90 days with *Pseudomonas* or otherwise resistant Gram-negative rod

Asymptomatic bacteriuria should be treated only in the context of pregnancy or prior to a urologic procedure where mucosal bleeding is anticipated (not routine placement of an indwelling catheter)

[top]

Skin-soft tissue infections

Non-purulent cellulitis

Recommended empiric therapy:

Cefazolin

Step-down oral therapy in patients with an appropriate clinical response:

Culture positive: determined by culture results.

NOTE: The recovery of resistant organism from a superficial culture does not justify broadening antimicrobial therapy in patients who have responded to narrow-spectrum therapy

Culture negative: an oral first-generation cephalosporin (e.g., cephalexin, cefadroxil)

Total duration of treatment (inpatient plus post discharge): 5 – 7 days (7 - 10 days for slow response)

Penicillin-allergic patients:

Severe hypersensitivity (e.g., anaphylaxis, hives, Steven Johnson Syndrome): vancomycin, clindamycin for oral therapy

Rash or non-specific reactions to penicillins: cephalosporins are appropriate.

Purulent infections with or without abscess formation

Recommended empiric therapy: vancomycin; consider cefazolin in facilities with a low rate of MRSA infections

Promptly substitute cefazolin for vancomycin if MRSA not identified in appropriate cultures

Step-down oral therapy in patients with an appropriate clinical response:

Culture positive: select according to results.

Levofloxacin or ciprofloxacin are appropriate only if there are no other suitable oral choices.

NOTE: The recovery of resistant organism from a superficial culture does not justify broadening antimicrobial therapy in patients who have responded to narrow-spectrum therapy

Culture negative:

TMP/SMX or doxycycline

Consider an oral 1st generation cephalosporin in facilities with a low rate of MRSA

Total duration of treatment (inpatient plus post discharge): 5 – 7 days (7 - 10 days for slow response)

Necrotizing fasciitis

Recommended empiric therapy:

Piperacillin/tazobactam (or cefepime) and vancomycin; add clindamycin to decrease toxin production

Promptly de-escalate if MRSA or resistant gram-negatives not identified in appropriate cultures

Step-down oral therapy in patients with an appropriate clinical response:

Culture positive: select according to results.

Levofloxacin or ciprofloxacin are appropriate only if there are no other suitable oral choices.

NOTE: With full sources control, the recovery of resistant organism may not require broadening antimicrobial therapy in patients who have responded to more narrow-spectrum therapy

Culture negative:

Amoxicillin/clavulanate plus either TMP/SMX or doxycycline

Consider an oral 1st generation cephalosporin in facilities with a low rate of MRSA

Total duration of treatment (inpatient plus post discharge): Therapy can be discontinued within 3 days after completing debridement in patients who are clinically stable

Penicillin-allergic patients:

Severe hypersensitivity (e.g., anaphylaxis, hives, Steven Johnson Syndrome): combined use of aztreonam, clindamycin and vancomycin

Rash or non-specific reactions to penicillins: cephalosporins are appropriate

NOTES:

1. Skin and soft tissue cultures that are not obtained aseptically, through deep debridement, or in surgery may represent external wound colonization rather than true infection.
2. Worsening lesion size may occur in the first 24 hours and overall improvement in both physical and laboratory markers of infection may take 48-72 hours so early changes from guideline-based empiric

therapy are not recommended in the absence of clinical instability (Clin Infect Dis 2016;63:1034; Clin Infect Dis 2017;64:214).

3. Resolution of redness and swelling may take beyond seven days but is not an indication for extending antibiotic duration in the absence of other signs of infection (Scand J Infect Dis 1997;29:377; Cutis 2005;75:177; Clin Infect Dis 2016;63:1034).

4. Additional consideration should be given to the use of anti-MRSA and/or broad-spectrum gram-negative therapy in the presence of severe immunosuppression, deep puncture wound, especially while wearing shoes/sneakers, chronic wound infections, infections involving deeper structures, surgical site infections, perineal infections, periorbital infections, bite- or water- related infections. Both human bite-related infections and perineal infections warrant addition of anti-anaerobic therapy.

[top

Diabetic foot infection

Mild infection:

Definition: infection involving only the skin and the subcutaneous tissue WITHOUT involvement of deeper tissues and WITHOUT signs of systemic inflammatory response syndrome (SIRS)

Recommended therapies:

Non-purulent infections

Amoxicillin-clavulanate or an oral 1st generation cephalosporin

Purulent infections with or without abscess formation

Doxycycline, TMP-SMX, or clindamycin

Step-down oral therapy in patients with an appropriate clinical response:

Culture positive: determined by culture results.

NOTE: The recovery of resistant organism from a superficial culture does not justify broadening antimicrobial therapy in patients who have responded to narrow-spectrum therapy

Culture negative: oral 1st generation cephalosporin

Total duration of treatment (inpatient plus post discharge): 7-10 days

Penicillin-allergic patients:

Severe hypersensitivity (e.g., anaphylaxis, hives, Steven Johnson Syndrome): consider doxycycline, depending on susceptibility results clindamycin

Rash or non-specific reactions to penicillins: cephalosporins are appropriate

Moderate infection:

Definition: infection involving the skin and subcutaneous tissue with extensive erythema, involving deeper structures (e.g. deep abscess, osteomyelitis) or presence of one or more SIRS criteria

Recommended therapies:

Vancomycin plus either ampicillin/sulbactam or ceftriaxone plus metronidazole

NOTE: omission of vancomycin may be appropriate in facilities with a low rate of MRSA

Promptly substitute cefazolin for vancomycin if MRSA not identified in appropriate cultures

Step-down oral therapy in patients with an appropriate clinical response:

Culture positive: determined by culture results.

Levofloxacin or ciprofloxacin are appropriate only if there are no other suitable oral choices.

NOTE: The recovery of resistant organism from a superficial culture does not justify broadening antimicrobial therapy in patients who have responded to narrow-spectrum therapy

Culture negative:

TMP/SMX or doxycycline

An oral 1st generation cephalosporin may be appropriate in facilities with a low rate of MRSA

Total duration of treatment (inpatient plus post discharge): 7-10 days, unless osteomyelitis is present, in which case therapy is generally for at least 4-6 weeks.

Duration of therapy may need to be extended if adequate source control and vascularization is not achieved

Many diabetic foot infections complicated by osteomyelitis can be treated with oral antibiotics.

Penicillin-allergic patients:

Severe hypersensitivity (e.g., anaphylaxis, hives, Steven Johnson Syndrome):

Vancomycin, aztreonam and metronidazole or clindamycin

Rash or non-specific reactions to penicillins: cephalosporins are appropriate

Severe infection (e.g., necrotizing fasciitis or other immediate life- or limb-threatening infection)

Recommended empiric therapy:

Piperacillin/tazobactam (or cefepime) and vancomycin; add clindamycin to decrease toxin production

Promptly de-escalate if MRSA or resistant gram-negatives not identified in appropriate cultures

Step-down oral therapy in patients with an appropriate clinical response:

Culture positive: select according to results.

Levofloxacin or ciprofloxacin are appropriate only if there are no other suitable oral choices.

NOTE: With full sources control, the recovery of resistant organism may not require broadening antimicrobial therapy in patients who have responded to more narrow-spectrum therapy

Culture negative:

Amoxicillin/clavulanate plus either TMP/SMX or doxycycline

Consider an oral 1st generation cephalosporin in facilities with a low rate of MRSA

Total duration of treatment (inpatient plus post discharge):

Necrotizing fasciitis: Therapy can be discontinued within 3 days after completing debridement in patients who are clinically stable

Other: 7-10 days unless osteomyelitis is present

Duration of therapy may need to be extended if adequate source control and vascularization is not achieved

Penicillin-allergic patients:

Severe hypersensitivity (e.g., anaphylaxis, hives, Steven Johnson Syndrome): combined use of aztreonam, clindamycin and vancomycin

Rash or non-specific reactions to penicillins: cephalosporins are appropriate

NOTES:

5. Skin and soft tissue cultures that are not obtained aseptically, through deep debridement, or in surgery may represent external wound colonization rather than true infection.
6. Worsening lesion size may occur in the first 24 hours and overall improvement in both physical and laboratory markers of infection may take 48-72 hours so early changes from guideline-based empiric therapy are not recommended in the absence of clinical instability (Clin Infect Dis 2016;63:1034; Clin Infect Dis 2017;64:214).
7. Resolution of redness and swelling may take beyond seven days but is not an indication for extending antibiotic duration in the absence of other signs of infection (Scand J Infect Dis 1997;29:377; Cutis 2005;75:177; Clin Infect Dis 2016;63:1034).
8. Additional consideration should be given to the use of anti-MRSA and/or broad-spectrum gram-negative therapy in the presence of severe immunosuppression, deep puncture wound, especially while wearing shoes/sneakers, chronic wound infections, bite- or water- related infections, infections involving deeper structures, surgical site infections or periorbital/perineal infections.

[top

Sepsis syndrome:

Use this guidance only for patients for whom there is no apparent primary site of infection. Patients in whom sepsis is due to a specific site of infection (e.g., pneumonia, UTI) should receive antibiotics specified for that syndrome.

Recommended empiric therapy:

Community-onset infection

Vancomycin plus ceftriaxone

May omit vancomycin in facilities with a low rate of MRSA infections

Healthcare Associated or Hospital Acquired infection

Vancomycin plus either piperacillin/tazobactam or cefepime

Use culture results to promptly narrow therapy if possible

Reassess whether infection is the cause of illness If cultures are negative and no primary site of infection is identified

Step down oral therapy in patients with an appropriate clinical response:

Determined by the site of infection which is identified and culture results.

Total duration of treatment (inpatient plus post discharge):

Determined by the site of infection which is identified and culture results.

Penicillin-allergic patients:

Severe hypersensitivity (e.g., anaphylaxis, hives, Steven Johnson Syndrome): levofloxacin

Rash or non-specific reactions to penicillins: cephalosporins are appropriate.

Risk factors for Healthcare Associated Infections (e.g., that support initiation of antipseudomonal therapy

Antimicrobial therapy in preceding 90 days

Current hospitalization of 4 days or more

Hospitalization for 2 days or more in the preceding 90 days

Residence in a nursing home or extended care facility

Home infusion therapy (including antibiotics)

Chronic dialysis within 30 days

Home wound care

Family member with multidrug-resistant pathogen

Immunosuppressive disease and/or therapy

Neutropenia

[top]

Principles of Adjusting Antimicrobial Therapy During an Antibiotic Timeout

(discontinuation, de-escalation, conversion to oral therapy and intensification of therapy)

Antimicrobial therapy is often initiated based on suspicion of the presence of infection without knowledge of the identity of the responsible micro-organism (pathogen).

An Antibiotic Timeout offers the opportunity to modify therapy based upon the clinical course of the patient and preliminary and/or final microbiology results

This information may lead to one of the following assessments:

Infection requiring antibiotic therapy is no longer clinically suspected. For example, the patient may be found to have an exacerbation of CHF rather than pneumonia or venous stasis rather than cellulitis. *This should lead to the discontinuation of antibiotic therapy*

The infecting micro-organism may be susceptible to more an antibiotic that has a narrower spectrum or activity (which less risk of facilitating the emergence of further antibiotic resistance) and/or less toxic antibiotic. *This should lead to antibiotic de-escalation.*

The patient may have clinically improved to such an extent that *oral antimicrobial therapy can be substituted for parenteral therapy*. Diagnoses that EXCLUDE a switch to oral antimicrobial therapy include (but are not limited to) *Staphylococcus aureus* bacteremia, endocarditis and CNS infections (e.g. meningitis). The following criteria should also be satisfied.

- The patient's gastrointestinal (GI) tract is functioning (i.e. tolerating medications via oral or enteral route for 24 hours and tolerating food or enteral feeds for 24 hours).
- The patient is hemodynamically stable for 24 hours (i.e. heart rate < 100 beats per minute, systolic blood pressure > 99 mm Hg, and respiratory rate < 20 breaths per minute)
- The patient shows clinical improvement (i.e. afebrile (temperature < 100°F or < 37.7°C) for at least 24 hours and white blood cell (WBC) count improving or normalized).

The infecting microorganism may be resistant to the initially selected therapy and *require intensification of therapy with an antibiotic with additional antimicrobial activity*. Infectious diseases consultation should also be considered.

[top]

Guidelines for De-Escalation of Anti-MRSA therapy (e.g., vancomycin, daptomycin, linezolid/tedizolid, ceftaroline)

These criteria are intended to provide guidance; clinical judgement is still required. Individual patients may warrant continuation of therapy and other patients may warrant de-escalation.

When to consider de-escalation:

Patients should be considered for de-escalation of anti-MRSA therapy (e.g., vancomycin) in EITHER of the following circumstances. *NOTE: this is NOT a comprehensive list of all situations in which anti-MRSA therapy can be de-escalated.*

Patients with positive cultures:

Identification of a pathogen other than MRSA, or a β-lactam resistant coagulase-negative Staphylococcus or Enterococcus

NOTE: β coagulase-negative Staphylococcus and Enterococcus are common contaminants and usually do not require therapy.

Patients with negative cultures or in whom cultures were not obtained (all of the following criteria should be true)

Absence of a suspected or confirmed infection with a moderate to high-risk of being due to MRSA such as:

- Vascular catheter/device associated bacteremia
- Endocarditis
- Purulent or necrotizing skin and soft tissue infections (SSTI)
- Prosthetic joint and other orthopedic surgery-related infections
- Osteomyelitis or septic arthritis
- Epidural or paraspinous abscesses

Absence of pneumococcal meningitis

Presence of pneumonia with negative MRSA nares surveillance test

The chance of MRSA pneumonia is less than 10% in persons with negative nasal surveillance specimen

How to de-escalate

If cultures are positive: narrow-spectrum therapy should be selected to cover the responsible organism(s).

If cultures are negative:

If an infection by a gram-positive pathogen still considered likely, **cefazolin** should generally replace vancomycin.

If infection by a gram-positive pathogen is not demonstrated and no longer considered likely, anti-MRSA therapy should be discontinued rather than replaced.

[top]

Guidelines for De-Escalation of Broad-spectrum gram-negative therapy (e.g., piperacillin/tazobactam, cefepime, ceftazidime, meropenem, imipenem, doripenem)

These criteria are intended to provide guidance; clinical judgement is still required. Individual patients may warrant continuation of therapy and other patients may warrant de-escalation.

When to consider de-escalation:

Patients should be considered for de-escalation of broad-spectrum gram-negative therapy (e.g., piperacillin/tazobactam) in EITHER of the following circumstances. *NOTE: this is NOT a comprehensive list of all situations in which* broad-spectrum gram-negative *therapy can be de-escalated.*

Patients with positive cultures:

Identification of one or more pathogens responsible for the suspected infection that are uniformly susceptible to less broad-spectrum therapy (e.g., ceftriaxone)

Patients with negative cultures or in whom cultures were not obtained

Patient is clinically stable, is not neutropenic (ANC < 500) **AND** is being treated for one of the following conditions

Healthcare-associated pneumonia, hospital-associated pneumonia or ventilator-associated pneumonia in the setting of:

A high-quality lower respiratory tract specimen was obtained and did NOT demonstrate a pathogen

OR

A high-quality lower respiratory tract specimen was NOT obtained AND the patient does not have multiple risk factors for infection with Pseudomonas or multidrug-resistant Gram-negative rods, e.g.,

Antimicrobial therapy in preceding 90 days

Onset of infection on hospital day 3 or later

Structural lung disease (e.g. bronchiectasis)

COPD with repeated exacerbations leading to frequent steroid and/or antibiotic use

Hospitalization for 2 days or more in the preceding 90 days

Residence in a nursing home or extended care facility

Home infusion therapy (including antibiotics)

Chronic dialysis within 30 days

Home wound care

Family member with multidrug-resistant pathogen

Immunosuppressive disease (including severe neutropenia)

UTI, non-purulent or purulent skin-soft tissue infection, necrotizing fasciitis, diabetic foot infection (any severity) sepsis, intra-abdominal infection

NOTE: Therapy for urinary tract pathogens should generally be discontinued if reliable urine cultures are negative.

How to de-escalate

<u>If cultures are positive</u>: narrow-spectrum therapy should be selected to cover the responsible organism(s).

NOTES:

Cefazolin is reliable in the treatment of susceptible urinary tract infections and some other uncomplicated gram-negative infections, but should generally be not used to treat complicated or severe gram-negative infections.

Culture results from wound swabs often colonization rather than true infection. Thus, recovery of *Pseudomonas* or another highly resistant Gram-negative rod from a wound swab does not necessarily require starting or maintaining antipseudomonal or other broad-spectrum anti-Gram-negative therapy in clinically stable patients.

<u>If cultures are negative:</u>

If an infection by a gram-negative pathogen still considered likely, **ceftriaxone** should generally replace broad-spectrum gram-negative therapy (e.g., piperacillin/tazobactam); metronidazole should be added to ceftriaxone for non-biliary intrabdominal infection.

If infection by a gram-negative pathogen is not demonstrated and no longer considered likely, gram-negative therapy should be discontinued rather than replaced.

In persons with a **severe hypersensitivity to beta-lactams** (e.g., anaphylaxis, hives, Steven Johnson Syndrome), one of the following can be used in patients who have been receiving aztreonam (NOTE: if the patient has been tolerating a cephalosporin or a carbapenem, de-escalation to ceftriaxone is appropriate).

Ciprofloxacin ± metronidazole

TMP/SMX ± metronidazole

[top]

Guidance for duration of therapy – listed by clinical syndrome

The total duration is the sum of parenteral and oral therapy given in the inpatient and outpatient settings.

Pneumonia:

Community-acquired pneumonia: 5 days

Healthcare-associated pneumonia: 5 days

Hospital associated pneumonia: 7 days

Ventilator associated pneumonia: 7 days

Urinary Tract Infections

Mild-moderate disease (cystitis): 7 days

Severe disease or slow clinical response: 7-10 days; severe complicated infections occasional require 14 days

Skin and Soft Tissue Infection (Cellulitis and Complicated Soft Tissue Infection):

Non-purulent cellulitis: 5 – 7 days (7 - 10 days for slow response)

Purulent infections with or without abscess formation: 5 – 7 days (7 - 10 days for slow response)

Necrotizing fasciitis: within 3 **days** after completing debridement

Diabetic foot infection:

Mild infection (e.g., no osteomyelitis): 7-10 days

Moderate infection (without osteomyelitis): 7-10 days

Severe infection (e.g., necrotizing fasciitis or other immediate life- or limb-threatening infection)

Necrotizing fasciitis: Therapy can be discontinued within 3 days after completing debridement in patients who are clinically stable

Other: 7-10 days unless osteomyelitis is present

Duration of therapy may need to be extended if adequate source control and vascularization is not achieved

NOTE: When a radical resection leaves no remaining infected tissue, antibiotic therapy can be kept short (i.e. 2–5 days following surgery). When there is persistent infected or necrotic bone, more prolonged therapy (i.e. 4-6 weeks or more) is typically necessary. Oral therapy is appropriate when soft tissue inflammation is controlled.

Sepsis syndrome: Duration should be based on eventual clinical syndrome that emerges.

Intra-abdominal infection

Antimicrobial therapy can be of short duration (3-5d) if source control has been achieved (e.g., through IR or surgical drainage). Uncomplicated diverticulitis that does not require surgery can typically be treated with 7-10d of antibiotics.

The following conditions may only require 24h or less of antimicrobial therapy:

- Acute stomach and proximal jejunal perforations where source control is achieved within 24h, in the absence of acid-reducing therapy or malignancy
- Bowel injuries attributable to penetrating, blunt, or iatrogenic trauma that are repaired within 12h and any other intraoperative contamination of the operative field by enteric contents
- Acute appendicitis without evidence of perforation, abscess, or local peritonitis

Extended therapy may be necessary for patients with poor source control. Rather than extending antibiotic therapy, further efforts should be made to achieve source control.

[top]

APPENDIX 2

Operational Guide to Antibiotic Timeouts

VA GLA Infectious Diseases Section, July 2013 – last reviewed December 2018

The antibiotic timeout is intended to promote critical thinking about whether or not continuation of broad-spectrum antimicrobial therapy is indicated 48-72h into its course. By reviewing clinical dashboard data and completing a templated progress note to determine the appropriateness of broad-spectrum therapy, you will be able to gain automatic approval of continuation of therapy for up to an additional 4 days without having to contact infectious diseases via the antibiotic approval pager. However, infectious diseases approval will be required for all subsequent continuations beyond this initial period of automatic renewal.

The antibiotic timeout is currently active on all floors and services for vancomycin and piperacillin-tazobactam renewal at 48-72h following its start.

How to Access Clinical Dashboards:

The infectious diseases team will print out and distribute dashboard printouts on a daily basis for patients that are eligible for an antibiotic timeout. You may also access the clinical dashboard data on your own and view them for all of your patients (NOTE: You must be logged on to your computer with your own Windows VHA login).

For first time users:

Click here to register for approval to view the clinical dashboards. For UCLA residents, please list Christopher Graber as your supervisor and only request access for Greater Los Angeles HCS, with the reason for PII/PHI access “antibiotic timeout”).

For users that are registered:

Click here to access the clinical dashboards.

How to access vancomycin and piperacillin-tazobactam renewal templates this needs to be updated for each site:

For Greater Los Angeles, to generate the antibiotic timeout templated progress note for vancomycin or piperacillin-tazobactam renewal, go to the “Notes” tab and select the title, “TIME OUT – VANCOMYCIN RENEWAL NOTE” or “TIME OUT – PIPERACILLIN\TAZOBACTAM RENEWAL NOTE” as appropriate.

If the templated progress note indicates that vancomycin continuation is approved, go to the "Medications" or "Orders" tab and renew vancomycin or piperacillin-tazobactam for the duration indicated by the template.

Questions? Contact Christopher Graber at christopher.graber@va.gov.

APPENDIX 3

Considerations in Switching Patients from Intravenous to Oral Antibiotics

Infectious Diseases Section, VA Greater Los Angeles Healthcare System

Conversion from intravenous to oral antibiotic therapy should be considered in patients meeting ALL of the following criteria:

- The patient has a diagnosis and, when a pathogen has been identified, antimicrobial susceptibility compatible with oral antibiotic therapy. Diagnoses that EXCLUDE a switch to oral antimicrobial therapy include (but are not limited to) *Staphylococcus aureus* bacteremia, neutropenic fever, endocarditis, CNS infections (e.g. meningitis), and septic shock, and any infection in which source control has not been adequately achieved.
- The patient's gastrointestinal (GI) tract is functioning (i.e. tolerating medications via oral or enteral route for 24 hours and tolerating food or enteral feeds for 24 hours). Exclusions to this criterion include active nothing by mouth (NPO) order, severe nausea, vomiting, actively receipt of anti-emetics, or severe diarrhea, mucositis, malabsorption, or ileus, receipt of vasopressor therapy, receipt of total parenteral nutrition within the last 72 hours, and active GI bleed.
- The patient is hemodynamically stable for 24 hours (i.e. heart rate < 100 beats per minute, systolic blood pressure > 99 mm Hg, and respiratory rate < 20 breaths per minute)
- The patient shows clinical improvement (i.e. afebrile (temperature < 100°F or < 37.7°C) for at least 24 hours and white blood cell (WBC) count downtrending or normalized).

Intravenous antibiotics that also have excellent bioavailability when given orally are particularly good candidates for IV-to-oral conversion if the above criteria are met. These antibiotics include azithromycin, clindamycin, doxycycline, fluconazole, ciprofloxacin, levofloxacin, metronidazole, and trimethoprim-sulfamethoxazole.

APPENDIX 4

Is My Patient Getting Better? What to Expect Regarding Time Frame for Improvement in Skin/Soft Tissue Infections and Pneumonia

Infectious Diseases Section, VA Greater Los Angeles Healthcare System

March 2013 – last reviewed December 2018

Skin/Soft Tissue Infection:

General principles:

Due to the inherent variability in its presentation, improvement of skin/soft tissue infections (SSTIs) with antimicrobial therapy can be difficult to gauge.

Even with appropriately-directed antimicrobial therapy, some presentations of SSTI may appear worse in the initial 24-48 hours of antimicrobial treatment.

Therapy directed against Gram-negative pathogens is typically not necessary in most SSTI but should be considered if:

- A deep surgical site infection or moderate to severe diabetic foot infection is present, OR
- There is concern for polymicrobial necrotizing fasciitis (which can be associated with surgical procedures involving the bowel or penetrating abdominal trauma, infections originating in the perineum, or from sites of injection in injection drug users).

Worsening of skin/soft tissue infections where the above two diagnostic entities are not present should prompt consideration of surgical consultation rather than broadening of therapy to include Gram-negative pathogens, *per se.*

[TOP]

Clinical course of SSTI: What the literature suggests:

One study of intravenous antimicrobial treatment for cellulitis at home versus in the hospital determined a mean time of 1.5 days to achieve no advancement of cellulitis. Approximately 90% of patients achieved no advancement of cellulitis by treatment day 3.

Two randomized trials of ceftaroline vs. vancomycin plus aztreonam for the treatment of complicated SSTI were conducted in which patients were included only if the infection required hospitalization and involved deeper soft tissue or required significant surgical intervention (apart from bedside I&D) OR consisted of cellulitis or lower extremity abscess in patients with diabetes mellitus or peripheral vascular disease. Diabetic foot infections with underlying osteomyelitis, human or animal bite wounds, necrotizing fasciitis, gangrene, and prosthesis-associated infections were excluded. By end of treatment (typically 14 days), approximately 90% of all patients enrolled achieved clinical cure, defined as resolution of all signs and symptoms of SSTI to the extent that further antimicrobial therapy was not necessary. **Early clinical response was defined as cessation of spread of the lesion from baseline and absence of fever at day 3; this was seen in approximately 70% of patients.** Only 50-60% of analyzed patients had a 20% decrease in lesion size by day 3.

Another randomized trial comparing the new oxazolidinone tedizolid to linezolid in the treatment of acute SSTI enrolled patients who had cellulitis, major cutaneous abscess, or wound infection surrounded by erythema with a minimum total lesion surface area of 65 cm^2 accompanied by at least 1 local and regional (lymphadenopathy) or 1 systemic sign of infection, and a Gram-positive pathogen was suspected or documented. **At 48-72h approximately 90% had early clinical treatment response, and approximately 75% of analyzed patients had a 20% decrease in lesion size.** Overall, these are higher early response rates than that observed in the ceftaroline studies, potentially due to lower acuity of underlying disease (fever on presentation was less common and median lesion areas were smaller in the tedizolid study).

In summary, it seems reasonable to expect resolution of fever and, at minimum, cessation of spread of lesion at 72h in the large majority of cases of SSTI that require hospitalization and are appropriately treated. However, lack of early response does not necessarily imply later clinical failure.

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Pneumonia:

General principles:

- Due to competing clinical morbidities in our patient population (e.g. congestive heart failure, COPD), discerning clinical improvement of pneumonia may be more difficult than in other populations with less comorbid conditions.
- While the appearance of new infiltrates on chest radiograph in ventilated patients is a sensitive (78-100%) marker for ventilator-associated pneumonia, it is not particularly specific (33-75%), particularly when there is little else to support the diagnosis.
- Improvement and/or resolution of infiltrates due to pneumonia on chest radiograph often lags other markers of clinical improvement with appropriate antimicrobial therapy.
- Encouragement of early mobilization and early switch to oral antimicrobial therapy has been associated with decreased length of stay without decreasing subsequent readmission or mortality.

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Clinical course of community-acquired pneumonia: What the literature suggests:

Two recent randomized trials of ceftaroline vs. ceftriaxone for the treatment of community-acquired pneumonia were conducted in which patients with acute onset of illness (≤ 7 days) that required initial dosing with an intravenous agent and hospitalization were enrolled. **By day 4 of therapy, roughly 60-70% of patients for whom data was available experienced clinical stability (i.e. no fever, stable vital signs, baseline mental status, and improvement in either cough, dyspnea, pleuritic chest pain, and sputum production).** Clinical cure was defined as total resolution of all signs and symptoms of pneumonia or improvement to such an extent that further antimicrobial therapy was not necessary (i.e. absence of fever for at least 24h and a substantial improvement in signs and symptoms of pneumonia). **By end of therapy at 5-7 days, over 80% of patients experienced clinical cure.**

Patients admitted to the general medical ward for community-acquired pneumonia may be able to be converted to oral antimicrobial therapy and discharged fairly quickly. A recent analysis of implementation of a 3-step critical pathway that encouraged early mobilization and use of objective criteria for switching to oral antimicrobial therapy and for deciding on hospital discharge or usual care

for community-acquired pneumonia enrolled 401 immunocompetent patients admitted to general medicine wards at a single medical center in Spain. The median length of stay was 3.9 days in the group receiving the 3-step intervention, compared to 6.0 days in the usual care group. The median duration of intravenous antimicrobial therapy was 2.0 days in the 3-step group and 4.0 days in the usual care group. No significant differences were found with regard to subsequent readmission, 30-day mortality, or patient satisfaction with care.

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APPENDIX 5

Potential Adverse Outcomes Associated with Vancomycin Therapy

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The following is adapted from guidelines sponsored by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists.

Introduction:

Vancomycin is a glycopeptide antibiotic that has been in clinical use for nearly 50 years as a penicillin alternative to treat penicillinase-producing strains of *Staphylococcus aureus*. It is one of the most widely used antibiotics in the United States for the treatment of serious gram-positive infections involving methicillin-resistant S. aureus (MRSA). Early use of vancomycin was associated with a number of adverse effects, including infusion-related toxicities, nephrotoxicity, and possible ototoxicity. Upon further investigation, it appears that the impurities in early formulations of vancomycin caused many of these adverse events.

Over the years, vancomycin has been one of the most studied antibiotics. Extensive pharmacokinetic studies in a variety of patient populations and the availability of commercial drug assays have allowed clinicians to target serum vancomycin concentrations precisely in a relatively narrow range. This approach has been advocated to lessen the potential for nephrotoxicity and ototoxicity and to achieve therapeutic concentrations. However, it should be noted that the practice of routine monitoring and adjusting of serum vancomycin drug concentrations has been the subject of intense debate for many years. The controversy has resulted from conflicting evidence regarding the use of serum vancomycin concentrations to predict and prevent drug-induced toxicity and as a measure of effectiveness in

treating infections. Further, data derived from more recent studies appear to suggest that vancomycin has little potential for nephrotoxicity or ototoxicity when used at conventional dosages (e.g., 1 g every 12 hours [15 mg/kg every 12 hours]), unless it is used concomitantly with known nephrotoxic drugs or at very high dosages.

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Potential for decreased efficacy of vancomycin with suboptimal dose and trough concentrations:

Concern exists regarding vancomycin efficacy based on dosing and trough concentrations. While vancomycin is considered a bactericidal antibiotic, the rate of bacterial kill is slow when compared with that of β-lactams, and vancomycin's activity is affected by the bacterial inoculum. Large bacterial burdens in the stationary growth phase or in an anaerobic environment pose a significant challenge to the speed and extent of vancomycin's bactericidal activity.

In recent years, VISA or glycopeptide-intermediate susceptible S. aureus (GISA) and vancomycin-resistant *S. aureus* (VRSA) have appeared and raised questions about the overall utility of this antibiotic. Although infection with these organisms is infrequent, there is fear that the organisms could become more prevalent if the high rate of use and exposure pressure of vancomycin continues. The discovery of inducible hVISA (i.e., strains with MIC values in the susceptible range of 0.5–2 mg/L in patients whose therapy with standard dosages of vancomycin has failed) raises further questions regarding current dosing guidelines and the overall use of this antibiotic. Concerns are related to treatment failures and the inability to easily detect hVISA isolates in clinical settings.

In 2006, the Clinical and Laboratory Standards Institute (CLSI) lowered the susceptibility and resistance breakpoints for the MIC of vancomycin from ≤4 to ≤2 mg/L for "susceptible," from 8–16 to 4–8 mg/L for "intermediate," and from ≥32 to ≥16 mg/L for "resistant." The decision to move the breakpoints was primarily based on clinical data indicating that patients were less likely to be successfully treated with vancomycin if the *S. aureus* MIC was ≥4 mg/L. Despite the change in susceptibility and resistance breakpoints, two reports have suggested that patients with *S. aureus* isolates having vancomycin MICs of 1–2 mg/L are less likely to be successfully treated with vancomycin compared with patients with S. aureus isolates that demonstrate greater susceptibility. However, this information alone does not address whether the use of higher concentrations of vancomycin would improve overall effectiveness. Low serum vancomycin concentrations may also create problems, as there appears to be a direct correlation between low serum vancomycin levels and the emergence of hVISA, VISA, or both, at least with certain genotypes of MRSA. In addition, studies have suggested that trough serum vancomycin concentrations of <10 mg/L may predict therapeutic failure and the potential for the emergence of VISA or VRSA.

Studies of MRSA and hVISA bacteremia have revealed significantly higher rates of morbidity in patients infected with hVISA. These patients were more likely to have high bacterial load infections, low initial trough serum vancomycin concentrations, and treatment failure. It was recently reported that approximately 74% of hVISA strains and 15% of wild-type S. aureus strains were tolerant (minimum bactericidal concentration of ≥32 mg/L) to the effects of vancomycin, which contributes to a low probability of success in patients harboring these organisms.

The ASHSP/IDSA/SIDP guidelines conclude that, based on evidence suggesting that *S. aureus* exposure to trough serum vancomycin concentrations of <10 mg/L can produce strains with VISA-like characteristics, it is recommended that trough serum vancomycin concentrations always be maintained above 10 mg/L to avoid development of resistance (Level of evidence = III, grade of recommendation = B) and that, based on the potential to improve penetration, increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes for complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital- acquired pneumonia caused by *S. aureus*, total trough serum vancomycin concentrations of 15–20 mg/L are recommended. Trough serum vancomycin concentrations in that range should achieve an AUC/MIC of ≥400 in most patients if the MIC is ≤1 mg/L. (Level of evidence = III, grade of recommendation = B)

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Fever, chills, phlebitis, and the “red man” syndrome:

The most common vancomycin adverse effects are unrelated to serum drug concentration and include fever, chills, and phlebitis. “Red man” syndrome may be associated with histamine release and manifests as tingling and flushing of the face, neck, and upper torso. It is most likely to occur when larger dosages are infused too rapidly (>500 mg over ≤30 minutes). Vancomycin should be administered intravenously over an infusion period of at least 1 hour to minimize infusion-related adverse effects. For higher dosages (e.g., 2 g), the infusion time should be extended to 1.5–2 hours.

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Nephrotoxicity:

The exact mechanism and incidence of vancomycin nephrotoxicity have been investigated in animals and humans. The filtration and energy-dependent transport mechanisms found in the proximal tubular epithelium render the kidneys susceptible to toxicant-induced injury. Vancomycin exposure in renal proximal tubule epithelial cells results in increased cell proliferation. The stimulation of oxygen consumption and the increase in ATP concentrations support the role of vancomycin as a stimulant of oxidative phosphorylation. In rats, antioxidants protect kidneys against vancomycin-induced injury, in

theory, by inhibiting free oxygen radical production. Human data suggest toxicity from vancomycin (or aminoglycosides) is not confined to the proximal tubule but may also involve the medullary region (loop of Henle and collecting duct) of the nephron. Vancomycin destruction of glomeruli and necrosis of the proximal tubule are thought to be due to oxidative stress.

Human trials have suggested that trough serum vancomycin concentrations of >10 mg/L are associated with an increased risk of nephrotoxicity. No correlation has been observed between peak vancomycin concentrations and nephrotoxicity. Studies that investigate vancomycin-associated nephrotoxicity are intriguing but often limited by small sample size, retrospective design, and questionable methodology. Additional data are needed, including the timing of the relationship between high vancomycin levels and nephrotoxicity (i.e., which one precedes the other). In addition, while statistically relevant, the clinical significance of minor and transient changes in creatinine clearance can be debated. However, a patient should be identified as having experienced vancomycin-induced nephrotoxicity if multiple (at least two or three consecutive) high serum creatinine concentrations (increase of 0.5 mg/dL or ≥50% increase from baseline, whichever is greater) are documented after several days of vancomycin therapy in the absence of an alternative explanation.

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Ototoxicity:

Vancomycin-induced hearing loss is controversial. Vancomycin has not been found to be ototoxic in animal models. Early literature attributed ototoxic events to impurities or to concurrent ototoxic agents. Early studies indicated that other ototoxic agents, such as the aminoglycosides kanamycin and streptomycin, may have additive or synergistic toxicity when used in combination with vancomycin. The frequency of ototoxicity in humans has been reported to range from 1% to 9% and to be associated with serum vancomycin concentrations above 40 mg/L. This most likely represents an inflated occurrence rate due to impurities associated with the older formulation or poor documentation of cause and effect as they relate to serum concentrations. The true risk of ototoxicity from vancomycin monotherapy is low without concurrent therapy with ototoxic agents.

Severe ototoxicity induced by vancomycin is rare and characterized as damage to the auditory nerve that initially affects high-frequency sensory hairs in the cochlea, then the middle- and low-frequency hairs, and eventually can lead to total hearing loss. High-tone deafness occurs before low-tone deafness at all frequencies and is permanent. Inability to hear high-frequency sounds and tinnitus are ominous signs that should result in discontinuation of vancomycin. Also rare is reversible ototoxicity such as tinnitus, which can occur with or without high-tone deafness.

Monitoring serum vancomycin levels to prevent ototoxicity is not recommended because this toxicity is rarely associated with monotherapy and does not correlate with serum vancomycin concentrations. Monitoring may be more important when other ototoxic agents, such as aminoglycosides, are administered.

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Neutropenia:

Neutropenia is an infrequent complication of vancomycin therapy and appears to be unrelated to serum concentration.

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APPENDIX 6

Know when to say…

No to Vanco!

<u>Consider stopping vancomycin when…</u>

- Relevant cultures grow organisms susceptible to narrower therapy
- Patient is low-risk for MRSA infection:
  - Pneumonia with negative nasal surveillance test for MRSA
  - Purulent skin and soft tissue or joint infection not present
  - No recent surgery or hemodialysis
  - No recent homelessness, incarceration or nursing home residence
- Patient has no surveillance or clinical culture positive for MRSA within the past 12 months **AND** clinical cultures are negative for MRSA 48-72 hours after collection

APPENDIX 7

Know when to say…

No to Pip-Tazo (and Cefepime)!

<u>Consider stopping broad spectrum Gram-negative therapy when…</u>

- Relevant cultures grow organisms susceptible to narrower therapy
- Patient has few to no risk factors for acquisition of infection with *Pseudomonas* or other multidrug-resistant Gram-negative rods (e.g., community-acquired infection without antibiotics in the prior 90 days or evidence of colonization by a resistant organism).
- Patient has skin-soft tissue infection (including diabetic foot infection) other than necrotizing fasciitis thought to be due to gram-negative infection
- Patient has asymptomatic bacteriuria (no antibiotics should be given unless patient is pregnant or is undergoing invasive urologic procedure [on routine catheter placement] associated with mucosal bleeding
- Patient has community-acquired intra-abdominal infection that is mild-to-moderate or source control has been achieved