BayCare Antimicrobial Stewardship Guide for Physicians

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- **Antimicrobial Stewardship-** Optimal selection, dosage and duration of antimicrobials that result in the best clinical outcome for the treatment and prevention of infections, with minimal toxicity to the patient and minimal impact on subsequent resistance.
    - Cost reduction is a secondary goal, but follows with any effective antimicrobial stewardship program.
- **Joint Commission Antimicrobial Stewardship Standards**
    - Leaders establish antimicrobial stewardship as an organizational priority
    - The hospital educates staff and licensed independent practitioners involved in antimicrobial ordering, dispensing, administration, and monitoring about antimicrobial resistance and antimicrobial stewardship practices. Education occurs upon hire or granting of initial privileges and periodically thereafter, based on organizational need.

- The hospital educates patients, and their families as needed regarding the appropriate use of antimicrobial medications, including antimicrobials.
- The hospital has an antimicrobial stewardship multidisciplinary team that includes the following members, when available in the setting:
  - Infectious disease physician
  - Infection preventionist
  - Pharmacist(s)
  - Practitioner
- The hospital's antimicrobial stewardship program includes the following core elements:
  - Leadership commitment: Dedicating necessary human, financial, and information technology resources.
  - Accountability: Appointing a single leader responsible for program outcomes
  - Drug expertise: Appointing a single pharmacist leader responsible for working to improve antimicrobial use
  - Action: Implementing recommended actions, such as systemic evaluation of ongoing treatment need, after a set initial treatment period
  - Tracking: Monitoring the antimicrobial stewardship program, which may include information on antimicrobial prescribing and resistance patterns
  - Reporting: Regularly reporting information on the antimicrobial stewardship program, which may include information on antimicrobial use and resistance, to doctors, nurses, and relevant staff
  - Education: Educating practitioners, staff, and patients on the antimicrobial program, which may include information on antimicrobial use and resistance, to doctors, nurses, and relevant staff
- The hospital's antimicrobial stewardship program uses organization-approved multidisciplinary protocols.
- The hospital collects, analyzes, and reports data on its antimicrobial stewardship program.
- The hospital takes action on improvement opportunities identified in its antimicrobial stewardship program.

- **BayCare Antimicrobial Stewardship Program Infrastructure**
  - ID Steering Committee- Consists of Physician Leadership, ID Physicians, Infection Prevention, Pharmacy, and Microbiology Lab representatives. Ultimately decides upon all BayCare Antimicrobial Stewardship Initiatives.
  - BayCare Antimicrobial Stewardship Subcommittee- Reviews system wide antimicrobial stewardship metrics such as antimicrobial days of therapy, resistance trends, *C. difficile* rates, and disease specific antimicrobial usage evaluations. Acts as a think tank for BayCare Antimicrobial Stewardship Initiatives. Reports to ID Steering Committee.
  - Local Pharmacy/Infection Control Antimicrobial Stewardship Work Groups- Review site specific antimicrobial utilization data, trouble cases, and hospital acquired *Clostridium difficile* for opportunities for improvement. Reach out to physicians regarding antimicrobial prescribing patterns.
  - Site specific Clinical Pharmacy teams- Respond to antimicrobial stewardship related alerts using Theradoc, an electronic data capture system. Contact physicians to recommend optimal usage. Also, provide education regarding new Antimicrobial Stewardship initiatives.

- **BayCare Wide Antimicrobial Stewardship Initiatives**
  - Clinical pharmacists performs automatic renal dosing and IV to PO conversions throughout BayCare, which includes many antimicrobials.
  - **Pharmacokinetic consult service**- Clinical pharmacists can be consulted to dose vancomycin and aminoglycosides, and follow these patients daily.
  - **Surgical antibiotic prophylaxis**
    - Perioperative Power Plans are available within Cerner for many surgical procedures. These include antibiotic subphases designed to steer providers to the appropriate antibiotic choice.
    - With the exception of vancomycin and fluoroquinolones, all preoperative antibiotics must be given within one hour of incision.

- Vancomycin and fluoroquinolones must be given within two hours prior to incision.
- In order to allow perfusion to the incision site, IV antibiotic should be hung at least 15 minutes prior to incisions. Antibiotics with longer infusion times will need to be hung earlier to allow time for complete infusion.
- Antibiotics should be completely infused or nearly completely infused (>75%) prior to incision to ensure adequate tissue concentrations. For orthopedic surgery, antibiotics should be completely infused prior to tourniquet application.
- Single dose therapy (preoperatively) is recommended for the majority of surgical procedures per the 2013 IDSA/SHEA/ASHP/SIS guidelines.
  - As of 2016, the WHO is recommending single dose preoperative prophylaxis for all procedures, including cardiac, orthopaedic, and vascular.
- For more information regarding our surgical prophylaxis protocol, please refer to the BayCare Antibiotic Stewardship Webpage
  - http://intranet.teambaycare.org/CD/Pages/Antibiotic-Stewardship-Program.aspx

- **Automatic Discontinuation of Metronidazole in Patients Receiving Concurrent Appropriate Anaerobe Coverage for Non-*Clostridium* difficile indications**
  - Protocol allows for Pharmacy to automatically discontinue metronidazole in **non-*Clostridium difficile*** anaerobic infections if used concomitantly with β-lactam/β-lactamase inhibitors or carbapenems.
  - Beta-lactam/beta lactamase inhibitors (ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin/tazobactam) and the carbapenems have very good anaerobe coverage including *Bacteroides fragilis*.
  - No currently available guidelines published by the Infectious Disease Society of America (IDSA) or CDC recommend the use of double anaerobic coverage.
  - Excluded indications where concomitant use would be allowed: Clostridium difficile, bacterial vaginosis, trichimoniasis, amebiasis, giardiasis, *H. pylori* eradication.
- **Flagyl dose interchange**
  - Flagyl doses will be converted as follows:
    - *Clostridium difficile*: All orders will be changed to 500 mg IV/PO q8h.
    - Non-*Clostridium difficile*: All orders will be changed to 500 mg IV/PO q12h. Therapeutic levels and efficacy have been proven to adequate with this dosing regimen.
- **MRSA Nasal PCR in pneumonia**
  - MRSA Nasal PCR is a tool with **strong negative predictive value** for pulmonary MRSA. Patients with a negative MRSA nares are 94 to 100% likely to not have MRSA pneumonia. It does not have predictive value at other non-pulmonary sites.
  - Strongly consider discontinuing empiric MRSA coverage (i.e. vancomycin or linezolid) for pneumonia if MRSA nasal PCR is negative.
    - Do not discontinue empiric MRSA coverage if empyema or pulmonary abscess are suspected, as data for these infections are lacking.
  - Results are available in approximately 70 minutes.
  - Test may be performed even after antibiotics are initiated, as the PCR does not require live organism to be present.
  - Consider ordering any time anti-MRSA antibiotics are initiated for pneumonia.
  - MRSA nares PCR is prechecked on existing HCAP power plans.
  - Poor positive predictive value- Positive results do NOT confirm MRSA pneumonia. Will need to assess cultures and patient's clinical status.
- **MRSA Skin and Soft Tissue Infection PCR Rapid Testing**
  - MRSA wound PCR can be ordered for patients with **purulent SSTI** that will require antibiotics.
    - Not recommended for mild purulent SSTIs that only require incision and drainage.
    - Review the results of the STAT MRSA wound PCR.
      - Negative MRSA PCR → recommended beta-lactam antibiotic, i.e. cefazolin (Ancef®)

- Positive MRSA PCR → recommend anti-MRSA antibiotic, i.e. vancomycin

- **Minimum Inhibitor Concentration (MIC) Clinical Laboratory Standards Institute (CLSI) discrepancy**
  - Current BayCare Microbiology Laboratory susceptibility breakpoints in some cases do not match CLSI recommendations. This is because it takes some time to validate these changes.

	CLSI	BayCare	Action
Pseudomonas- Piperacillin/tazobactam	16	64	MICs of 32-64 are intermediate, not susceptible. Use another antibiotic based on susceptibilities
Pseudomonas- Meropenem	2	4	MICs of 4 are intermediate, not susceptible. Use another antibiotic based on susceptibilities
Acinetobacter- Meropenem	2	4	MICs of 4 are intermediate, not susceptible. Use another antibiotic based on susceptibilities

- **Verigene Rapid Diagnostic Blood Test**
  - Verigene is a multiplex nucleic acid test which probes for DNA targets from various blood pathogens and common resistant genes.
  - Detects common blood pathogens and contaminants.
  - Species identification 2.5 hours after gram stain. Not all pathogens are identified by Verigene.
  - Can identify resistance genes for MecA (MRSA), Van A and Van B (VRE), CTX-M (ESBL) and carbapenemase producers.
  - High sensitivity and specificity (>95%)
  - Performed in addition to traditional culture, which is still needed to determine full susceptibilities.
  - Antibiotic recommendations are included with the Verigene result in Cerner, based on BayCare antibiogram data and the literature.
  - Pharmacy will also respond to results, and will call physicians to make recommendations if needed.
- **Antibiotic Allergy Assessment**
  - Beta-lactams are the antibiotic of choice for many infections. Subjects with penicillin “allergy” history are often exposed to substandard therapy.
  - When encountering a reported antibiotic allergy please document the following in the medical record:
    - Name of the drug; type of reaction; when the reaction occurred; timing of reaction relative to receiving the drug.
  - Serious allergies include
    - Anaphylaxis, shortness of breath/bronchospasm, hives (urticaria), angioedema
  - Newer data suggests cross sensitivity between cephalosporins and penicillins is 1 to 2%. Anaphylaxis resulting from cross sensitivity is very rare (1:1000 to 1:1,000,000). J Allergy Clin Immunol 2015 Mar;135(3):745-52.e5.
  - Patients with a documented minor allergy/adverse reaction to penicillin may still safely receive a cephalosporin or carbapenem.
  - For patients with no penicillin reaction listed and unable to provide further history, consider a challenge with a second beta lactam class. One cautious way to do this is a graded challenge (give 1% of the dose and observe, followed by 10% of the dose and observe, followed by the remainder of the dose).
  - For patients with more severe penicillin allergies, use your clinical judgment, and weigh additional factors such as how long ago the reaction (anaphylaxis, IgE mediated). 80% of IgE mediated allergies will subside after 10 years. A graded challenge with rescue meds on hand may still be an option for select patients. Cross sensitivity and risk of subsequent anaphylaxis with cephalosporins is still low, even in this population.
  - Desensitization should be considered when a patient requires treatment with a specific antibiotic that have a known history of IgE mediated allergy. Examples include penicillin therapy for syphilis

in pregnancy, or ampicillin for susceptible Enterococcal endocarditis. Transfer to an intensive care area is required, as well as a consult to Pharmacy to prepare and schedule the desensitization.

- **Asymptomatic Bacteriuria**
  - A recent usage evaluation revealed that 86% BayCare patients with asymptomatic bacteriuria were treated with antibiotics unnecessarily.
  - Presence of an abnormal UA, or bacteria is not enough to warrant treatment in patients without urinary symptoms or systemic signs of infection.
  - IDSA approved exceptions where treatment is appropriate: pregnancy, upcoming urological procedure.
- **High Risk Antibiotics for *Clostridium difficile* Infection**
  - All systemic antibiotics can disrupt gut flora precipitating CDI.
  - However, other factors being equal, antibiotics with the lowest Clostridium difficile risk are preferred. For example, for uncomplicated UTI in a patient with normal urine function, nitrofurantoin has less risk than cephalexin, which in turn has less of risk than ciprofloxacin.
  - *Highest Risk*: fluoroquinolones, clindamycin, cephalosporins (2^{nd}, 3^{rd}, 4^{th} generation)
  - *High Risk*: carbapenems, beta-lactam/beta-lactamase inhibitors, sulfamethoxazole/trimethoprim
  - *Moderate Risk*: cephalosporins (1^{st} generation), macrolides, linezolid
  - *Low or Unstudied*: aminoglycosides, tetracyclines, vancomycin, metronidazole, all other systemic antibiotics
- **Procalcitonin Testing Policy**
  - Procalcitonin (PCT) levels predictably rises with the onset of bacterial infection, and fall as the infection responds to antibiotic therapy.
  - The role of PCT in the diagnosis of bacterial infection is limited due to confounding factors which may also cause an elevated level (renal failure, surgery, trauma, some cancers). The Surviving Sepsis guidelines and IDSA HAP/VAP guidelines recommend against the use of procalcitonin in the diagnosis of infections.
  - Use of PCT for antibiotic deescalation is most validated for pneumonia and sepsis. Use in other infections is limited, and guidelines on how to interpret levels are unclear.
  - For appropriate indications, PCT is a useful tool for antibiotic streamlining and early discontinuation.
  - Baseline procalcitonin levels are recommended prior to antibiotic initiation for all patients with suspected sepsis or lower respiratory tract infection.
    - Prechecked on HCAP power plans
  - Follow up level is recommended 12 to 24 h after initial level, especially if initial level is low. This helps determine the peak level.
  - Obtain repeat level every 2-3 days if antibiotics are initiated.
  - PCT ≤ 0.25 ng/L in Lower respiratory tract infections (mild to moderate acuity) indicates bacterial infection likely.
  - PCT ≤ 0.5 ng/L in severe sepsis, septic shock or high acuity lower respiratory infections in ICU indicates ongoing bacterial infection unlikely.
  - If PCT is below threshold, or has decreased 80 to 90% from initial peak, consider discontinuation of systemic antibiotics. This assumes the patient is clinically stable.
  - CONSIDER TX FAILURE if PCT remains elevated. (PCT will decrease 50% every 1 to 2 days in appropriately treated patients.) If PCT does not decrease appropriately after 48 hours, the patient may need expanded antibiotic coverage, further diagnostic evaluation, or improved source control.
  - In all cases, ESRD or severe renal insufficiency may elevated baseline PCT levels, and decrease the time needed for resolution of elevated levels.

- **Restricted Antimicrobials**
  - **Aztreonam**
    - Should be reserved for patients with severe (IgE mediated) beta-lactam allergies
    - Pseudomonal coverage is not as reliable as other beta-lactam agents. Pseudomonal dose is 2 g q8h.

- **Ceftaroline**
  - MRSA skin and soft tissues with allergy/intolerance/failure/MIC >1 to vancomycin
  - Salvage therapy for pneumonia, endocarditis, osteomyelitis, deep seated infection
- **Ceftolozane/tazobactam**
  - For the treatment of extensively drug-resistant, meropenem resistant *Pseudomonas aeruginosa*
  - Restricted to Infectious Disease and Pulmonology
- **Daptomycin**
  - Complicated skin and skin structure infection due multidrug resistant Gram positive organism in patients with vancomycin resistance, intolerance, failure, or allergy- 4 mg/kg
  - Endocarditits due to MRSA in patients failing, resistance to, or intolerant to vancomycin- 8 to 10 mg/kg
  - Endocarditis due to VRE- 10 to 12 mg/kg
  - Bacteremia due to MRSA in patients with vancomycin intolerance, resistance, or allergy- 6 mg/kg; 10 mgkg if previous failure to vancomycin
  - Bacteremia due to VRE- 6 mg/kg
  - MRSA Bone and Joint infections in patients with vancomycin resistance, intolerance, failure, or allergy- 6 to 8 mg/kg
  - VRE Bone and Joint infections 6 to 8 mg/kg
  - For susceptible Enterococcal isolates with MICs of 3 to 4, consider addition of a beta lactam, such as ampicillin or ceftriaxone.
  - CPKs to be ordered at least once weekly. If dose ≥ 6 mg/kg, or CrCL ≤ 30 ml/min, order twice weekly.
  - All statins will be held while patient daptomycin orders are active
- **Ertapenem**
  - For treatment of ESBL infections. Preferred over meropenem for non-Pseudomonal infections if susceptible due to more narrow spectrum.
  - Polymicrobial infections (i.e. diabetic foot infections) as a single agent once daily option.
- **Fluoroquinolones**
  - Formulary fluoroquinolones are ciprofloxacin and levofloxacin
  - Fluoroquinolones are no longer recommended as first line therapies for most indications including UTI, intraabdominal infections, surgical prophylaxis, healthcare-associated and hospital-acquired pneumonia.
  - The FDA released a black box warning in 2016 advising against the use of fluoroquinolones in uncomplicated infections such as UTIs, AECOPD, and sinusitis.
  - Fluoroquinolones also have a black box warning about severe side effects including tendinitis and tendon rupture, peripheral neuropathy, and central nervous system side effects. Additional side effects include hepatoxicity, phototoxicity, QT prolongation, and Clostridium difficile infection.
  - Fluoroquinolones are considered the highest risk category for *Clostridium difficile* infection, and have been associated with the NAP1 hypervirulent strain.
  - BayCare wide E. coli ciprofloxacin susceptibility is < 70%. Pseudomonal susceptibility is < 80%.
  - Fluoroquinoles should not be used as first line therapy for most indications. They should only be used if there are allergies or adverse effects preventing use of preferred agents.
    - Pharmacy is currently calling and challenging fluoroquinolone orders for UTI when clear alternatives may be used.
    - More indications will follow.
- **Fosfomycin**
  - For the treatment of multi-drug resistant urinary tract infections.
  - Useful as an oral alternative to carbapenems in the treatment of ESBL *E. coli.* BayCare susceptibility is >96%.
  - Contraindicated in pyelonephritis, perinephric abscess. Use of as a single agent for UTI with concurrent bacteremia should also be avoided.
- **Linezolid**

- An option in the treatment of suspected or confirmed MRSA pneumonia. Suspected or confirmed infection with Vancomycin-Resistant Enterococcus spp.
- Suspected or confirmed infection with MRSA or MRSE with a documented history of vancomycin allergy, intolerance, treatment failure, MIC ≥2 (for MRSA)
- Step down oral therapy for patients being discharged following a course of therapy with vancomycin, daptomycin, or ceftaroline and for whom treatment with alternate oral agents is not possible due to either lack of pathogen susceptibility or patient intolerability.
- Documented infections with susceptible acid fast organisms where first line treatment options are not possible due to failure, intolerance, allergies, or critical drug interactions. (i.e. XDR M. tuberculosis, rapid growing Mycobacterium, Nocardia).
- Linezolid is contra-indicated in patients with concurrent use of certain psychiatric agents with a high risk of causing serotonin syndrome or hypertensive crisis (SSRIs, SNRIs, bupropion, tricyclic antidepressants). If linezolid must be started in these patients, hold the interacting agent and reinitiate 24 hours after linezolid course is complete.
- Linezolid is contra-indicated in patients who received MAOIs in the previous 2 weeks.
- Relative contraindications include thrombocytopenia, use of serotonergic drugs not specifically mentioned above, use of aympathomimetics, and hypertensive diseases states.
- CBC is recommended at baseline and weekly.
- Treatment courses > 14 days are discouraged due to increased risk of bone marrow suppression and neuropathy
- Linezolid is 100% bioavailable. Convert to oral therapy if tolerated.

○ **Meropenem**
- Serious infections due to multidrug-resistant gram-negative bacilli (e.g. Acinetobacter, Enterobacter, Pseudomonas*)
- As monotherapy for empiric treatment of patients with febrile neutropenia
- As monotherpay for complicated polymicrobial skin and soft tissue infection, where one or more organisms are resistant to other beta-lactam antibiotics.
- As monotherapy for patients with complicated intra-abdominal infection when other beta-lactam antibiotics are not appropriate
  - Documented allergy to penicillin-like antibiotics
  - At least one organism isolated is resistant to other beta-lactam antibiotics
- Necrotizing pancreatitis
- As monotherapy for patients with hospital acquired pneumonia, when other beta-lactam antibiotics are not appropriate, such as recent history of MDRO pathogens (ESBL, MDR Pseudomonas)

○ **Micafungin**
- Empiric treatment of candidemia or invasive candidiasis. May narrow to fluconazole based on susceptibilities and species ID. Most candida species are susceptible to fluconazole. *Candida krusei* is intrinsically resistant. While resistance is higher for *Candida glabrata*, BayCare wide susceptibility is 80%. May use fluconazole for susceptible Candida glabrata.
- Treatment of documented fungal infection caused by resistant *Candida* spp. (*Candida glabrata* or *Candida krusei*).
- Treatment of *Candida* fungemia or oropharyngeal/esophageal candidiasis in patients refractory/failing or intolerant to other antifungal therapies.
- Alternative therapy for the treatment of invasive aspergillosis.

○ **Telavancin**
- MRSA skin and skin structure infections in vancomycin failure or intolerance as an alternative to daptomycin (Cubicin) and linezolid (Zyvox)
- Hospital acquired pneumonia caused by MRSA in vancomycin failure or intolerance as an alternative to linezolid (Zyvox)
- Note, telavancin may retain activity against MRSA isolates with elevated MICs ≥ 2mcg/mL

- Renal function assessment is to be done every 48 hours while on therapy. Pharmacy may order labs if needed.
- Recommended that females of childbearing age receive a serum pregnancy test and instructions on effective contraception prior to telavancin therapy.
- For patients receiving warfarin, obtain INR prior to telavancin dose to minimize the potential laboratory interaction.

- **Tigecycline**
  - Reserve for multidrug resistant infections for which there are no other alternative. Tigecycline has been associated with increased mortality compared to alternative therapies.

- **Additional BayCare Antimicrobial Stewardship Resources**
  - BayCare Antimicrobial Stewardship Page-
    - **http://intranet.teambaycare.org/CD/Pages/Antibiotic-Stewardship-Program.aspx**
    - May be accessed from any BayCare computer