Macro Micro Misconceptions

Bacteriuria in Patients with Neurogenic Bladder and/or Indwelling Catheters

Patients with neurogenic bladder and/or indwelling catheters are overtreated for UTI, often developing early resistance to antibiotics when they do actually need them. Patients with indwelling chronic catheters often have positive cultures in the absence of UTI due to colonization, which begins a few days after the catheter is placed and increases with duration.

Recommendations:

- Instruct the patient to avoid having urine studies in the absence of active symptoms/signs of cystitis/pyelonephritis, and to avoid antibiotics for UTI unless there is a evidence of infection and a positive UA.
- If sensation is intact, UTI symptoms may include suprapubic discomfort or pain, bladder spasm, fever, and costovertebral angle tenderness. Confusion/delirium may be a useful sign in the older patient, especially if sensation is nonintact. Change in odor or color alone are not reliable.
- When symptomatic, UA with a CONCURRENT culture is always VERY helpful, looking specifically for elevated WBC, +/- hematuria, and large leukocyte esterase.
- In symptomatic patients, elevated WBC, +/- hematuria, and large leukocyte esterase should be treated as a UTI.
- If WBC is less than 50, do not treat but observe closely. Consider changing Foley catheter. Repeat the UA and culture in a few days if symptomatic.
- If 0 WBC, look for other cause of symptoms.
- If urine culture is worrisome for resistance to PO agents, please feel free to call the Antimicrobial Stewardship Program at 310-267-7567 or consult ID. We are most happy to assist with interpreting cultures.

Additional considerations:

- Antibiotic prophylaxis is actively discouraged, as it is not preventive, and consistently leads to worsening resistance.
- Practice frequent handwashing, especially before handling the catheter.
- Keep the bag off the floor, keep the catheter unkinked, and watch for the patient resting on top of it.
- AVOID routine UA and/or urine cultures to "screen" for UTI in asymptomatic patients.

- Bacteriuria does not equal infection, since bacteria predictably colonize catheters over time.
- Screening and treating asymptomatic bacteriuria is only helpful or necessary before GU tract instrumentation that may involve mucosal bleeding.
- Do not irrigate catheters
- Once a catheter is in place, do not use antiseptics to clean around the meatus.

VRE in the Stool (VRE Colonization)

Enterococcus is normal bowel flora and does not cause enteric infection regardless of its vancomycin susceptibility.

VRE in stool is therefore colonization, and treatment with antibiotics is neither necessary nor prudent, due to the risk that the VRE will then become resistant to other antibiotics as well. Linezolid in particular is more prone to development of resistance than vancomycin; resistance to linezolid may arise *de novo* without antibiotic pressure. The incidence of linezolid resistance in VRE is rising with the overuse of this antibiotic. The overuse of oral vancomycin (for *C. difficile*) is in fact how VRE first became established as a nosocomially-transmitted organism. In addition, antibiotic exposure may actually increase transmission by causing diarrhea and therefore increasing environmental contamination with VRE (which is very hardy in the environment). There is also the risk that eradication of VRE will permit more aggressive nosocomial pathogens to take up residence in the bowel.

Unlike certain cases of MRSA colonization, attempts to decolonize patients with VRE are not supported by the literature as either a benefit to the patient or as an infection control measure in any but those at highest risk of severe VRE infections (ie, selected transplantation patients).

Future options for VRE control are under investigation, however, infection control measures remain, very unfortunately, the best option for management.

The role of *Candida* isolated from bronchoscopic samples in nonneutropenic patients

Candida is frequently isolated from cultures of the respiratory tract, such as bronchoscopic samples (BAL), especially in patients who are on broad-spectrum antibacterials. Studies have shown that isolation of *Candida* in immunocompetent (e.g. not neutropenic or transplant) patients has no clinical significance. True lower respiratory tract infection due to *Candida* is extremely infrequent in these patients. Isolation of *Candida*, even in high concentrations, in respiratory samples of in immunocompetent patients should be interpreted as airway colonization. Antifungal therapy should not be initiated in the absence of identification of *Candida* from sterile specimens or by histologic evidence in tissue from at-risk patients.

Reference:
Rello, J. et al. The role of Candida sp isolated from bronchoscopic samples in nonneutropenic patients. *Chest* **114**, 146–149 (1998).

"Double coverage"

The use of "double coverage" (two antibiotics used to provide coverage for the same organism) is based upon the following assumptions: the combination provides a broad spectrum of coverage for empiric treatment, before you know the identification and susceptibility of the offending pathogen; the combination may provide additive or synergistic effects against the pathogen; or the combination of antibiotics may decrease or prevent the emergence of resistant bacteria. Contemporary data do not support the use of "double coverage" for the latter two indications.

Inappropriate initial therapy has been shown to cause increased morbidity and mortality, specifically related to Gram-negative infections (usually *Pseudomonas* and *Acinetobacter* spp.). Thus, double coverage serves the purpose of providing broad spectrum initial empiric coverage until susceptibility data are known. However, once susceptibility data are known, double coverage does not need to be continued. **No evidence exists to support the superiority of combination therapy over monotherapy for Gram negative infections once susceptibilities are known**. Thus, once culture identification and susceptibilities have been reported, de-escalation to a single agent is strongly recommended.

Broadening of initial empiric coverage

- Should be considered in patients with life-threatening infections (ventilator-associated pneumonia, sepsis).
- Second agent should offer additional coverage and generally should be an aminoglycoside at UCLA.
- Coverage MUST be narrowed based on culture results; negative cultures can be used to rule out infections with most organisms.

Prevention of emergence of resistance

- Emergence of resistance on therapy is uncommon, occurring in 5–10% of infections treated.
- Emergence of resistance to beta-lactams while on therapy with these agents occurs in ~20% of patients infected with organisms with inducible beta-lactamases (Serratia, Enterobacter, Citrobacter, Acinetobacter); beta-lactams are best avoided in these patients if other options are available.
- Emergence of resistance is more common in pneumonia and osteomyelitis due to decreased antibiotic penetration at these sites; attention should be given to appropriate dosing in these patients.

- The addition of additional agents may lead to increased toxicity from adverse drug reactions without preventing emergence of resistance.

Data regarding combination therapy

- An early study by Hilf suggested that combination therapy was superior to monotherapy in patients with Pseudomonas bacteremia BUT 84% of monotherapy patients received inadequate monotherapy with an aminoglycoside. Five more recent studies have not shown a difference in mortality when patients received appropriate monotherapy for *Pseudomonas* bacteremia.
- Recent prospective studies have not shown a benefit to combination therapy over monotherapy in the treatment of serious Gram-negative infections in both non-neutropenic AND neutropenic patients
- Two recent meta-analysis showed no difference in outcomes of patients with sepsis or febrile neutropenia treated with beta-lactams alone vs beta-lactam/aminoglycoside combinations although patients in the latter group had a higher incidence of nephrotoxicity.

Recommendations for use of combination therapy

- Data suggest that monotherapy is sufficient for the treatment of most Gram-negative infections.
- The use of 2 agents to treat proven or suspected Gram-negative infections should be limited to the following situations:
    - **Empiric treatment** of serious infections manifested by sepsis, including hypotension, pressor dependence, or mechanical ventilation (to broaden spectrum) until cultures return
    - **Documented infection** with a resistant Gram-negative organism (particularly *Pseudomonas, Acinetobacter, Citrobacter, Enterobacter,* and *Serratia* when antibiotic penetration to the site of infection is poor (pneumonia, osteomyelitis). Consideration should be given to stopping one of the agents after 5-7 days of therapy when the bacterial burden has decreased. Infectious Diseases consutlation is highly recommended in such cases.
- The second agent should be an aminoglycoside in most cases. Fluoroquinolone resistance is common among Gram-negative organisms at UCLA.
- Double beta-lactam combinations (e.g. zosyn + meropenem) should be avoided.

References:

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Antimicrob Agents Chemother 1994;38(6):1309.
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Int J Antimicrob Agents 1999;11:7.

Pharmacother 1995;15(3):279.

Anaerobes

Anaerobic pathogens are normal flora of the oral cavity and the gastrointestinal tract. While oral anaerobic flora are mostly Gram-positive organisms such as *Peptococcus* and *Peptostreptococcus spp.,* the principal anaerobic intestinal flora are Gram-negative bacilli such as *Bacteroides fragilis*, *Prevotella melaninogenica*, and *Fusobacterium spp.* Gram-positive oral anaerobes are widely covered by most of the orally-available agents, including penicillin. However, antibiotic activity against the most common intestinal anaerobic bacteria, *Bacteroides spp.*, is variable.

Anaerobic coverage is indicated in a variety of infectious processes, including but not limited to aspiration pneumonia, intra-abdominal infection, gynecologic infection, and diabetic foot ulcer infection. Antimicrobial agents with appreciable anaerobic activity include the following: Amoxicillin/clavulanate, Ampicillin/sulbactam, Cefotetan, Cefoxitin, Clindamycin, Ertapenem, Imipenem, Meropenem, Metronidazole, Moxifloxacin, Piperacillin/tazobactam, Tigecycline. Double anaerobic coverage is the use of any combination of the above agents, which is prevalent at UCLA. A common combination is piperacillin/tazobactam + metronidazole. Redundant anaerobic coverage is a common problem intervened upon by the Antimicrobial Stewardship Program.

Double anaerobic coverage is not necessary and puts the patient at risk for additional drug toxicities. No data or guidelines support double anaerobic coverage in clinical practice, with two clinical exceptions:

Exceptions:

1. Metronidazole can be added to another agent with anaerobic activity when being used to treat *Clostridium difficile* infection.
2. Clindamycin can be added to another agent with anaerobic activity when being used for the treatment of necrotizing fasciitis or toxic shock.