An Overview about Carbapenem-Sparing Strategies

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Abstract
Antimicrobial stewardship involves optimizing antibiotic use while using cost-effective interventions to minimize antibiotic resistance and control Clostridium difficile infection. For decades before the widespread introduction of antimicrobial stewardship programs (ASPs), infectious disease (ID) clinicians have been the antibiotic stewards in hospitals. Recently, the Centers for Disease Control and Prevention (CDC) has mandated and codified ASPs for all US hospitals. The CDC has based its ASP recommendations on 7 key elements. Firstly, the hospital must designate a single ID clinician who will direct the hospital's ASP efforts. To be effective, the ID clinician leader must possess the requisite interpersonal, diplomatic, and leadership skills that are the basis for the enthusiastic support of the medical staff. The ID clinician leader should have special expertise in various aspects of antimicrobial therapy, that is, pharmacokinetics, resistance, pharmacoeconomics, and C difficile. To head an effective hospital-wide ASP, the ID ASP team leader needs full and ongoing financial support for the ASP from the hospital administration. Support includes a staff of ID-trained clinical pharmacists, a vital component of ASPs. The ID team leader and clinical pharmacists need committed information technology (IT) support, that is, prospective audits, data collection to track and monitor antibiotic resistance and C difficile, as well as ASP cost savings to the institution. Furthermore, carbapenem-sparing strategies have generated substantial debate and are advocated with judicious use of novel antibiotics,antibiotic stewardship programs, proper measures of infection control, staff educational programs and care bundels.
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Introduction

Antimicrobial stewardship involves optimizing antibiotic use while using cost-effective interventions to minimize antibiotic resistance and control Clostridium difficile infection. For decades before the widespread introduction of antimicrobial stewardship programs (ASPs), infectious disease (ID) clinicians have been the antibiotic stewards in hospitals. Recently, the Centers for Disease Control and Prevention (CDC) has mandated and codified ASPs for all US hospitals **(1)**.

Principles of antimicrobial stewardship programs:

The CDC has based its ASP recommendations on 7 key elements. Firstly, the hospital must designate a single ID clinician who will direct the hospital's ASP efforts. To be effective, the ID clinician leader must possess the requisite interpersonal, diplomatic, and leadership skills that are the basis for the enthusiastic support of the medical staff. The ID clinician leader should have special expertise in various aspects of antimicrobial therapy, that is, pharmacokinetics, resistance, pharmacoeconomics, and C difficile. To head an effective hospital-wide ASP, the ID ASP team leader needs full and ongoing financial support for the ASP from the hospital administration. Support includes a staff of ID-trained clinical pharmacists, a vital component of ASPs. The ID team leader and clinical pharmacists need committed information technology (IT) support, that is, prospective audits, data collection to track and monitor antibiotic resistance and C difficile, as well as ASP cost savings to the institution **(1)**.

Aside from the basics of ASPs cited earlier, a successful ASP depends on medical staff's understanding and support. Ongoing antibiotic education tailored to each clinical service's needs is essential for the acceptance of ASP interventions. The medical staff needs to understand the principles of antibiotic therapy in ASP initiatives to accept and support ASP recommendations for the benefit of patients and the hospital. Most physicians need relevant antibiotic education to understand optimal antimicrobial therapy, that is, pharmacokinetic/pharmacodynamic-based dosing, intravenous (IV) versus oral administration, dosing adjustments in renal/hepatic insufficiency, factors in tissue penetration, shortest duration of therapy for cure, antibiotic resistance potential, antibiotic C difficile potential **(1)**.

ASPs' success also depends on a coordinated multidisciplinary approach, which includes the critical support of the microbiology laboratory and infection control and hospital epidemiology. Antibiotic therapy has potential untoward consequences, for example, antibiotic resistance and C difficile; but it is equally important to recognize that control of multidrug-resistant organisms and C difficile are not entirely related to antibiotic factors **(2)**.

Carbapenem-sparing strategies

Antimicrobial resistance is one of the most serious public health menaces worldwide. Among the biggest threats, multidrug-resistant (MDR) or extensively drug-negative (XDR) Gram-negative bacteria such as carbapenem-resistant Enterobacteriaceae (CRE), extended-spectrum b-lactamase producing (ESBL) Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter baumannii have been labeled as the most serious or urgent. With regard to MDR and XDR-Gram-negative bacteria, the use of carbapenems, alone or in combination with other agents, is one the most controversial issue: on the one hand their efficacy is well established in many scenarios (for instance, infections by ESBL-Enterobacteriaceae), on the other hand, their misuse and overuse (both as empiric or targeted therapy) has resulted in the emergence of CRE which represent a paramount therapeutic challenge. Furthermore, carbapenem-sparing strategies have generated substantial debate and are advocated with judicious use of novel antibiotics,antibiotic stewardship programs, proper measures of infection control, staff educational programs and care bundels **(3)**.

Carbapenem sparing strategies (regarding antibiotics):

1. **Piperacillin–tazobactam (PTZ):**

It is clear that piperacillin–tazobactam (PTZ) among non-carbapenem β lactams represents the most interesting alternative to carbapenems in the treatment of infections causes by ESBL-PE, as well as for de-escalating carbapenems. Despite the fact that a high percent of ESBL isolates demonstrate in vitro susceptibility to PTZ (current break point according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) ≤8 mg/L, and to Clinical & Laboratory Standards Institute (CLSI) <16 mg/L), the significance of PTZ for treating ESBL-PE has remained cloudy. Tazobactam by itself is a potent β-lactamase inhibitor. However, Gram-negative bacteria have the ability to produce concomitantly multiple ESBLs and AmpC β -lactamases, as well as possess other resistance mechanisms such as porin mutations and efflux activation, diminishing the activity of PTZ. On the other hand, tazobactam is influenced by the "inoculum effect" **(3)**.

2. **Ceftolozane–tazobactam:**

Ceftolozane–tazobactam is a novel combination of a cephalosporin with a _-lactamase inhibitor that exhibits excellent in vitro activity against a broad spectrum of Enterobacterales and Pseudomonas aeruginosa, including ESBL strains, and has been recently approved for the treatment of complicated intra-abdominal infections (cIAI) and cUTI. The in vitro activity of ceftolozane–tazobactam against ESBL-PE from U.S. hospitals revealed an overall susceptibility of 83.9% (CLSI/EUCAST breakpoints) to ceftolozane–tazobactam. Ceftolozane–tazobactam inhibited 95.5% of the E. coli isolates, but only 83% of K. pneumoniae producing ESBL. Regarding ESBL-encoding genes, ceftolozane–tazobactam inhibited 92.9% of the isolates harboring blaCTX-M and exhibited limited activity against isolates carrying blaSHV (61.1% susceptible), **(4)**.

3. **Ceftazidime–Avibactam**

Avibactam, a novel non-b-lactam, b-lactamase inhibitor, restores the activity of ceftazidime against the majority of β-lactamases (ESBLs and carbapenemases, including Klebsiella pneumoniae carbapenemase (KPCs) and OXA-48), resulting in activity of ceftazidime–avibactam combination against a wide range of MDR Gram-negative bacteria. In vitro activity of ceftazidime–avibactam against Enterobacterales from 18 European countries as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance program from 2012 to 2015 revealed ceftazidime–avibactam was the most active agent, compared with all other tested comparator agents, against non-susceptible ceftazidime isolates (97.7% susceptible) **(3)**.

4. **Cephamycins**

Cephamycins include cefoxitin, cefotetan, cefmetazole, moxalactam and flomoxef. They belong to a subclass of second-generation cephalosporins that confers resistance to degradation by ESBL enzymes. However, cephamycins are not active against AmpC cephalosporinases and porin mutations. **(5)**.

5. **Cefepime**

Cefepime, a "fourth-generation" cephalosporin, possesses in vitro activity against most Gram-negative pathogens, including Enterobacterales, due in part to its relatively low

susceptibility to degradation by chromosomal and plasmid-mediated extended-spectrum AmpC lactamases and ESBLs compared to that of other cephalosporins. CLSI breakpoints for cefepime MIC against the Enterobacterales family are 2 mg/L (susceptible), 4–8 mg/L (susceptible dose dependent; SDD) and 16 mg/L (resistant) [58]. In contrast, EUCAST breakpoints for cefepime MIC are 1 mg/L (susceptible) and 4 mg/L (resistant). However, MICs of cefepime for Gram-negative organisms that produce ESBLs are often increased compared to non-producers **(3)**.

On the other hand, concerns of diminished efficacy of cefepime for the treatment of ESBL infections with high bacterial inoculum (i.e., pneumonia, osteoarthritis and endocarditis, so called "inoculum effect" in which there is a marked increase in MIC with increased inoculum), has been illustrated in animal studies. In order to highlight this phenomenon, inkjet printing technology testing the inoculum effect on cefepime was performed in a recent study with ESBL Escherichia coli and Klebsiella spp. In 13 cefepime-resistant and SDD strains, as well as 11 cefepime-susceptible isolates, a 2-fold increase in inoculum resulted in a 1.6 log 2-fold increase in MIC. In contrast, in cefepime-susceptible, non-ESBL producing clinical strains, only a minor inoculum effect at very high inocula ($>10^7$ cfu/mL^{-1}) was depicted **(3)**.

6. **Temocillin**

Temocillin is a b-a-methoxy-derivative of ticarcillin that is only available in UK, Belgium, France and Luxembourg. The chemical modification of ticarcillin to temocillin increased its stability to β-lactamases. Temocillin possesses very attractive characteristics: narrow spectrum mainly restricted to Enterobacterales, high resistance to hydrolysis by numerous β -lactamases including ESBL and hyperproduced AmpC and minimal risk of Clostridium diffcile infection. Against a collection of 157 ESBL-producing E. coli and 95 ESBL-producing K. pneumoniae strains harvested in 2015 from three French centers, in vitro susceptibility to temocillin was observed in 71.3% of the ESBL-producing E. coli and in 77.9% of the ESBL-producing K. pneumoniae tested, according to the Antibiogram Committee of the French Society for Microbiology guidelines. These rates increased to 98.7% and 98.9% according to the urinary tract infection breakpoint (i.e., 32 mg/L) of the British Society for Antimicrobial Chemotherapy. Similarly, susceptibility rate was 94.6% according to the 8mg/L clinical breakpoint against ESBL-producing isolates from community-acquired UTI **(6)**.

7. **Quinolone:**

Plasmid-mediated quinolones resistance (PMQR) determinants frequently appear associated with extended-spectrum ESBL genes. A study from Canada including outpatients revealed quinolone resistance of 18.2% in urinary ESBL-positive E. coli, whereas in a study from Spain the prevalence of PMQR genes were found in 28.6%, limiting the activity of quinolones for the treatment of ESBL infections **(3)**.

8. **Aminoglycosides**

Aminoglycosides have been shown to be active against Gram-negative bacteria, including ESBL pathogens. In vitro susceptibility rates may vary significantly, depending on the dissemination of aminoglycoside modifying enzymes, which are frequently co-transferred along with other resistance genes on mobile genetic elements. The presence of genes encoding aminoglycoside-modifying enzymes with genes located on integrons or transposons also coding for ESBLs have been reported. Amikacin has been shown to be the most active aminoglycoside

against ESBL-PE. The advantageous pharmacokinetic parameter of the aminoglycosides consisting of high urine concentrations, therefore, have been utilized in urinary tract infections as monotherapy **(7)**.

9. **Tigecycline–Eravacycline–Omadacycline**

Tigecycline, a glycylcycline, is a bacteriostatic derivative of minocycline. It was approved by the FDA and the European Medicines Agency (EMA) in 2005 and 2006, respectively, for the treatment of cIAIs and complicated skin and skin structure infections, and the FDA in 2009 added community-acquired pneumonia to the list. However, nowadays tigecycline is frequently administered off-label for treating MDR infections. Tigecycline antimicrobial spectrum includes ESBL-PE, MDR and extensively-drug resistant (XDR) Acinetobacter baumannii and K. pneumoniae **(3)**.

10. **Fosfomycin**

Fosfomycin inhibits phosphoenolpyruvate transferase, the first enzyme involved in the synthesis of peptidoglycan. It possesses advantageous pharmacokinetics mainly in the urinary tract system as well as in cerebrospinal fluid, lungs, bone and soft tissue. Fosfomycin is active against a broad spectrum of Gram-positive and Gram-negative bacteria, including ESBL isolates and possesses a low potential for cross resistance with other classes of antibiotics. The relevant available formulation for intravenous administration is fosfomycin disodium. The current recommended intravenous dosage ranges from 16–24 g daily **(8)**.

Prevention of hospital and ventilator acquired pneumonia:

Prevention (VAP bundle)

One of the five goals of the 'Saving 100,000 Lives' campaign launched by the Institute for Healthcare Improvement (IHI) is to prevent VAP and deaths associated with it by implementing a set of interventions for better patient care known as the (VAP bundle). Bundling multiple measures together is hypothesized to provide synergistic protection against VAP **(9)**.

These interventions should be implemented together with standard precautions (hand hygiene and use of gloves when handling respiratory secretions) as well as adequate disinfection and maintenance of equipment and devices

Elements of VAP bundle

The IHI guidelines for the prevention of VAP recommended the following lines **(9)**.

1. Elevation of the head of the bed to 30^0–45^0
2. Daily 'sedation vacation' and daily assessment of readiness to extubate
3. Peptic ulcer disease prophylaxis
4. Deep venous thrombosis prophylaxis
5. Daily oral care with chlorhexidine
6. Subglottic secretion drainage
7. Initiation of safe enteral nutrition within 24-48 hours of ICU admission.

Regular oral care, assessment of the need for proton-pump inhibitor and histamine-2-receptor blocker therapy, and early identification and treatment of dysphagia especially in the elderly and in patients with recent stroke or surgical procedures are key features to preventing oropharyngeal colonization of pathogenic organisms, aspiration, and ensuing HAP or VAP. A

systematic review and meta-analysis including 2 studies of critically ill, non-ventilated patients reported significant risk reduction in HAP through the use of chlorhexidine oral cleansing, electric toothbrushing, and oral hygiene instruction **(10)**.

Data supporting oral care in VAP prevention are more robust, with several institutions worldwide reporting reduced VAP incidence in association with ICU "bundles" including an oral care component. One institution implemented a protocol involving twice-daily chlorhexidine oral cleansing in addition to elevating the head of the bed to more than 30 degrees, once daily respiratory therapy-driven weaning attempts, and conversion from a nasogastric to an orogastric tube as feasible for all ventilated trauma patients. One year after this protocol was implemented, the incidence of VAP had declined, and patients without VAP accrued fewer total ventilator days, ICU days, and hospital days, although their mortality rate was no lower than in patients with VAP **(11)**.

Other strategies to reduce aspiration risk include maintaining tracheal cuff pressure, eliminating nonessential tracheal suction, and avoiding gastric overdistention **(12)**.

Managing the microbiome

Probiotics and antibiotics in HAP and VAP prevention are still under evaluation. In theory, probiotics could reduce VAP by improving intestinal barrier function, increasing host cell antimicrobial peptides, and regulating the composition of intestinal flora to reduce overgrowth and colonization by pathogenic organisms **(13)**.

Infection control

In addition to addressing individual patient risk factors for HAP and VAP, clinicians should address potential for nosocomial transmission of pathogens typically responsible for pneumonia. Timely vaccinations for both patients and providers reliably reduce transmission of influenza, *Haemophilus influenzae*, and *Streptococcus pneumoniae* pneumonia. While these pathogens are not commonly associated with the hospital setting, transmission from patients hospitalized with community-acquired pneumonia or from ill healthcare providers to others on the same unit has been reported and may precipitate HAP and VAP. Hospital-wide respiratory hygiene measures such as hand hygiene and the use of masks or tissues for patients with a cough can reduce the spread of respiratory pathogens. Observational studies suggest some benefit to routine stethoscope and procedural equipment cleaning, though single-patient stethoscopes and universal gown-glove contact isolation are primarily supported by theoretical benefit **(10)**.

Clean and disinfects the environment appropriately:

According to evidence from CRE outbreaks, the environment can be a source of transmission. To reduce the risk of transmission, facilities should do daily cleanings that include areas near the patient (e.g., bed rails, patient tray) to reduce the burden of organisms. Furthermore, CRE have been discovered in patient room sink drains, raising the chance that equipment and patient supplies could become contaminated if placed in the zone where sink splash could occur **(14)**.

Staff education:

To change the VAP rate in any given ICU, a change in human behavior is needed. Like all behavioral changes, education and reinforcement is required. Education is therefore the first step in a VAP best practice program, followed by reduction of oropharyngeal colonization and

reduction of aspiration. Education of the staff about VAP is absolutely necessary for a successful program. The implementations of all these strategies are required to maximally lower the VAP rate over the long term **(15)**.

ASP interventions often contain an educational component; however, current guidelines suggest that educational interventions should not be used alone but to support other stewardship interventions. Such interventions are most commonly directed towards prescribers (often general practice physicians) with few studies offering education towards other healthcare providers such as pharmacists, nurses, or even members of the stewardship team. Educational interventions are offered most frequently, but not exclusively, with concomitant stewardship interventions such as prospective audit and feedback. Such strategies appear to positively impact prescribing behaviours, but it is not possible to isolate the effect of education from other interventions. Common educational methods include one-time seminars and online e-learning modules, but unique strategies such as social media platforms, educational video games and problem-based learning modules have also been employed. Education directed towards patients often occurs in conjunction with education of local prescribers and wider community-based efforts to impact prescribing. Such studies evaluating patient education often include passive educational leaflets and focus most often on appropriate treatment of upper respiratory tract infections. Educational interventions appear to be an integral component of other interventions of ASPs; however, there is a paucity of evidence to support use as a stand-alone intervention outside of regional public health interventions. Future studies should focus on efficacy of educational interventions including providing education to non-prescribers and disease states beyond upper respiratory tract infections to demonstrate a broader role for education in ASP activities **(16)**.

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