

Conceptual framework for assessing strengths and weaknesses of antimicrobial stewardship programs

1. **Rationale for stewardship programs:** to mitigate the unintended consequences of antimicrobial use:
 - a. Direct harms to antimicrobial recipients:
 - i. *Clostridium difficile* diarrhea and colitis
 - ii. Rash, renal insufficiency and other adverse drug events
 - iii. Complications of antimicrobial delivery devices, e.g., peripheral or central intravenous catheters
 - iv. Treatment failure from inappropriate drug selection or insufficient treatment duration
 - v. Patient colonization and subsequent infection by multi-drug resistant organisms (MDROs)
 - vi. “Enabling agents” that can facilitate misguided pursuit of errant diagnoses
 - b. Indirect patient harms:
 - i. Promotion of MDRO and *C difficile* colonization and spread via unwashed hands of healthcare workers and, in some cases, through environmental transmission
 - ii. Excess costs: though a limited proportion of hospitalization costs, antimicrobials constitute a large fraction of variable costs, i.e., those whose expenditure is discretionary
 - c. Regulatory burden and public perception:
 - i. Management of surgical antimicrobial prophylaxis and treatment of pneumonia are prominent among CMS-mandated hospital core measures.
 - ii. *C difficile* and MRSA surveillance and reporting now mandatory in Illinois; MDRO surveillance via NHSN is or soon will be
 - iii. Antimicrobial use surveillance and reporting via NHSN coming soon
 - iv. Important component of infection control assessment in Joint Commission surveys

- v. The need for hospitals to address and improve antimicrobial use is codified in California state statute; under consideration by CMS
- vi. Perception of MDROs, MRSA and *C difficile* as making hospitals hazardous places is widespread and growing

2. **Operational goals** of antimicrobial stewardship: the 5 Ds. While the bedside clinician must generally establish the diagnosis, defining the optimal drug selection, dose, duration and de-escalation strategies for common infection syndromes should be the task of the stewardship team.

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- a. Right diagnosis: general degradation of clinical skills and widespread incentives for antimicrobial use have led to widespread over-diagnosis and errant treatment of many clinical syndromes, e.g., pneumonia, cellulitis, UTI, osteomyelitis
- b. Right drug selection: the ideal antibiotic regimen is:
 - i. Effective against infecting pathogens as shown by high-quality clinical evidence.
 - ii. When used empirically (as is the case in the great majority of patients), effective against commonest pathogens and susceptibility patterns among the local patient population
 - iii. Minimally associated with adverse drug events
 - iv. Minimally associated with the emergence of *C difficile* or MDROs. In general, these are the regimens with the narrowest antimicrobial spectrum.
 - v. Minimally expensive
 - vi. Minimally cross-sensitive to patients with drug allergies
- c. Right dose: adjusted for sex, body size, renal and, to a lesser extent, hepatic function
- d. Right duration:
 - i. The incidence and magnitude of all the unintended clinical consequences listed above are proportionate to duration of antimicrobial use
 - ii. Though the optimal duration of therapy has been defined through well conducted clinical trials for few infections (e.g., ventilator-associated pneumonia, cystitis), an operational ideal can be defined as treatment until the resolution of systemic and improvement in local manifestations of infection. Some infections by pathogens less susceptible to eradication

and prone to local or distant relapse (e.g., *Staphylococcus aureus*) may be exceptions to this principle.

e. Right de-escalation:

- i. Antimicrobial resistance necessitates broad-spectrum (and therefore high-risk) empiric antimicrobial regimens. Thus, narrower-spectrum (and often less expensive) regimens should be substituted when:
 1. Culture results define infecting pathogen(s)
 2. Culture results, though non-specific, are sufficiently sensitive to rule out MDRO classes (e.g., endotracheal aspirates in ventilator pneumonia)
- ii. Less intensive therapy, especially oral regimens, can often be substituted after definite clinical improvement for many infections requiring hospitalization (e.g., pneumonia, cellulitis, pyelonephritis)

3. Measures of stewardship impact:

- a. Most important but difficult to measure are the clinical outcomes of patients treated with antimicrobials:
 - i. Treatment success and survival rates among patients with severe infection, ideally adjusted for severity of illness and comorbidities
 - ii. Rates of *C difficile*, hospital-acquired MDRO infection (also impacted by staffing resources and infection control practices) and adverse drug events
 - iii. Surgical site infections among recipients of perioperative prophylaxis (also impacted by operative volume and skill)
- b. Process measures pertaining to operational goals are more readily available:
 - i. Misdiagnosis rates, e.g., patients treated for pneumonia later diagnosed with non-infectious cardiopulmonary causes of the clinical presentation, treatment for asymptomatic bacteriuria
 - ii. Initial antimicrobial regimens that, compared to recommended alternatives, are:
 1. Excessively complex, expensive or broad-spectrum
 2. Inadequately broad-spectrum (e.g., piperacillin-tazobactam for cellulitis with abscess)
 - iii. Use of multi-drug regimens with redundant or superfluous antimicrobial spectra
 - iv. Use of drugs to which the patient is allergic or intolerant

- v. Under- or overdosing drugs relative to manufacturers' recommendations for patient size and renal function
- vi. Treatment for excessive duration
- vii. Failure to de-escalate:
 1. Spectrum of activity according to culture results
 2. Route of delivery according to clinical response
- c. The relationship between the quality and quantity of antimicrobial use is complex; the optimal incidence density of antimicrobial use within a given patient population has not been established (indeed, valid antimicrobial use measures for inter-institutional benchmarking are not yet available). Nonetheless, measurement of aggregate and targeted class- and drug-specific antimicrobial use is an important index of stewardship effectiveness because:
 - i. Surveys of hospital antimicrobial use consistently document rates of excessive and/or inappropriate use of these drugs from 25% to 50%
 - ii. Reductions of targeted and/or aggregate antimicrobial use have been strongly correlated with reductions in incidence of *C difficile* and, to a lesser extent, hospital-acquired MDRO infection
 - iii. Reducing antimicrobial use reduces costs.

4. Essential attributes of stewardship programs and interventions:

- a. Each intervention must be revenue-neutral or revenue-producing. If investment is required to implement a stewardship intervention, a compelling case must be made that implementing the intervention will recoup that investment.
- b. A compelling rationale for stewardship that is familiar to and understood by all involved is essential. Apart from traditional concepts of patient safety, e.g., responding to renal dysfunction or drug allergy, the need for the other four Ds is not sufficiently well understood to induce many clinicians to comply with interventions that may be experienced as intrusive and threatening to their autonomy. Thus, planning and implementation of each intervention must incorporate "social marketing" messages as well as operational pathways:
 - i. Stewardship programs should adopt general "marketing" strategies that highlight the adverse impacts of unintended consequences of antimicrobial use on the institution and its patients, and that promote the general efficacy of the operational goals (i.e., "the 5 Ds") listed above in addressing these problems.
 - ii. Specific stewardship interventions should be shown to address one or more of the unintended consequences
- c. Also, interventions should:

- i. Plausibly (when initially proposed) and demonstrably improve attainment of one or more of the operational goals listed above
 - ii. Be within the competence and resources of the institution and its stewardship team
 - iii. Fit comfortably within the competence and workflow of affected clinicians
 - iv. Demonstrably (hopefully) improve attainment of one or more of the operational goals as shown via periodic assessment
- d. Establishing institutional, patient-care unit-specific and, where feasible, clinician-specific goals for outcome and/or process measures and regularly reporting progress towards those goals may reinforce compliance with and understanding of interventions.
- e. Finally, stewardship programs and interventions must be authoritative:
 - i. Stewardship activities must be pursued under the auspices of the hospital's QA apparatus, ideally with its own committee or P&T subcommittee
 - ii. Well-respected clinicians with expertise in antimicrobial use and infectious diseases are essential to provide:
 - 1. A public face to the stewardship program
 - 2. Credibility to informational interventions such as institutional guidelines
 - 3. Back-up to front-line pharmacists and other personnel interacting with prescribing clinicians pursuing stewardship interventions
 - 4. Responses to clinician questions and complaints
 - iii. Hospital leadership must support stewardship activities by:
 - 1. Hiring stewardship staff
 - 2. Publicly supporting stewardship goals and interventions
 - iv. Medical staff leadership, department chairs and other opinion leaders must also be informed and encouraged to provide feedback to and support for these activities.