Role of PK-PD In Antibiotic Stewardship Program

Dr Asish Kumar Saha, PharmD

Introduction-Antibiotic Stewardship

Defined: The right antibiotic for the right patient, at the right time, with the right dose, and the right route, causing the least harm to the patient and future patients

Introduction-Antibiotic Stewardship

Primary Goal: to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use

- Consequences
  - Toxicity
  - Selection of pathogenic organisms
  - Emergence of resistant pathogens

Secondary goal: to reduce health care costs without adversely affecting the quality of care

Dellit TH, e. (2018). *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to... - PubMed - NCBI*. [online] Ncbi.nlm.nih.gov. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17173212 [Accessed 23 Sep. 2018].

Methods for Implementing ASP

Forming antimicrobial subcommittee within Pharmacy and Therapeutics committee

- Representatives from surgery, pediatrics, internal medicine, transplantation, critical care, infectious disease, pharmacy and nursing

Martin, C., Ofotokun, I., Rapp, R., Empey, K., Armitstead, J., Pomeroy, C., Hoven, A. and Evans, M. (2018). *Results of an antimicrobial control program at a university hospital*. [online] American Journal of Health-System Pharmacy. Available at: http://www.ajhp.org/content/62/7/732.long?sso-checked=true [Accessed 23 Sep. 2018].

Methods for Implementing ASP

Subcommittee Responsibilities

- Develop and implement initiatives to ensure appropriate antimicrobial use
- Review the existing formulary and recommend cost effective agents that may reduce the selection of resistant nosocomial pathogens

Martin, C., Ofotokun, I., Rapp, R., Empey, K., Armitstead, J., Pomeroy, C., Hoven, A. and Evans, M. (2018). *Results of an antimicrobial control program at a university hospital*. [online] American Journal of Health-System Pharmacy. Available at: http://www.ajhp.org/content/62/7/732.long?sso-checked=true [Accessed 23 Sep. 2018].

Dellit TH, e. (2018). *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to... - PubMed - NCBI*. [online] Ncbi.nlm.nih.gov. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17173212 [Accessed 23 Sep. 2018].

IDSA Guidelines: Elements of a successful stewardship program

- Comprehensive program
  - Active monitoring of resistance
  - Fostering of appropriate use
    - Often used as a surrogate marker for impact on resistance
  - Collaboration of effective infection control to minimize secondary spread of resistance

Dellit TH, e. (2018). *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to... - PubMed - NCBI*. [online] Ncbi.nlm.nih.gov. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17173212 [Accessed 23 Sep. 2018].

IDSA Guidelines: Collaborative effort

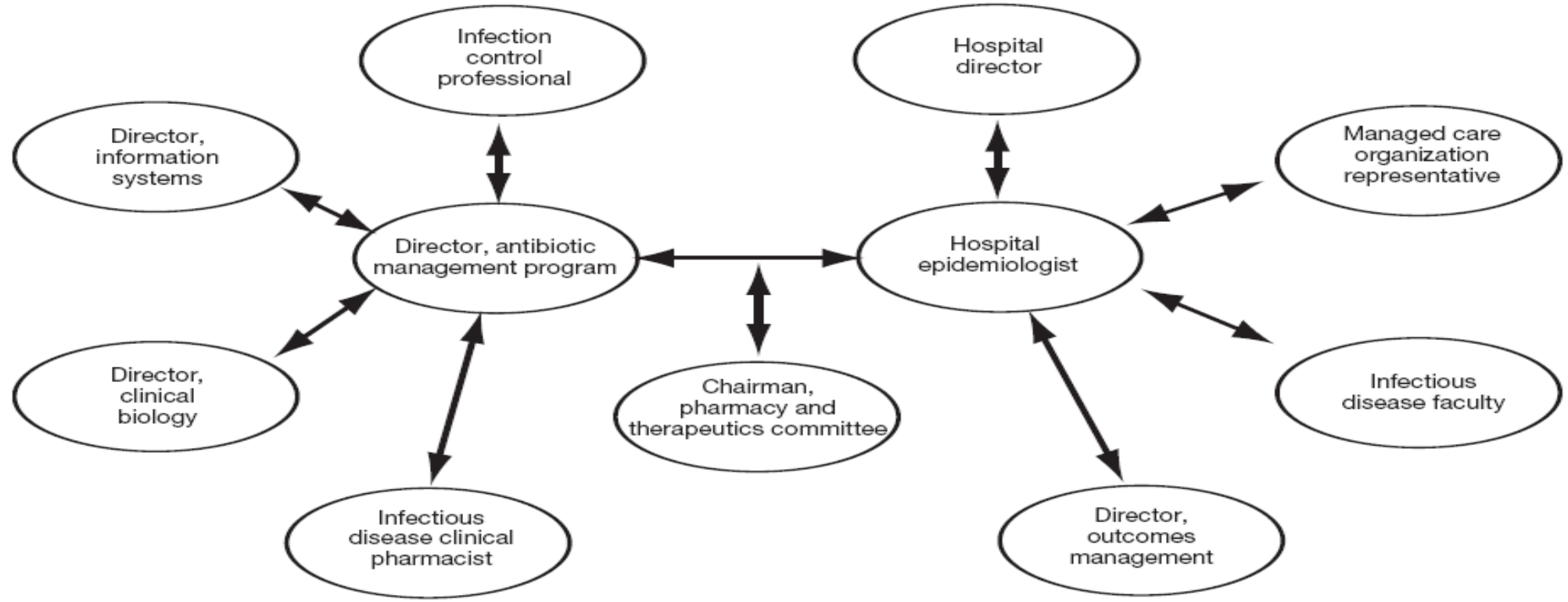


Figure 2. Multidisciplinary members of the antimicrobial stewardship team. (Adapted from reference 6.)

Rybak M. Pharmacotherapy; 27:131S

IDSA Guidelines: Key Recommendations

- Two proactive core strategies:
  - Prospective audit with intervention and feedback to prescriber
  - Formulary restriction and preauthorization

Dellit TH, e. (2018). *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to... - PubMed - NCBI*. [online] Ncbi.nlm.nih.gov. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17173212 [Accessed 23 Sep. 2018].

Prospective Audit

- ID pharmacist and physician work together
- Select drugs and units
- Review cases and make recommendations within certain time frame after drug is ordered
  - Appropriate drug
  - Dose
  - Route

Dellit TH, e. (2018). *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to... - PubMed - NCBI*. [online] Ncbi.nlm.nih.gov. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17173212 [Accessed 23 Sep. 2018].

Formulary Restriction and Preauthorization

- Stewardship team works closely with Pharmacy and Therapeutics Committee to designate restricted drugs and evidence-based indications
- Pager for authorization
- Success depends on who is authorizing
- Challenges:
  - May shift resistance to alternative agent
  - Must monitor trends

IDSA Guidelines: Additional Recommendations (Level A)

- Education
  - Essential, but insufficient alone
- Development of guidelines and clinical pathways
  - Can improve utilization
  - Can decrease amount of critical thinking

IDSA Guidelines: Additional Recommendations (Level A)

- Streamlining or de-escalation of therapy
- Dose optimization
- Parenteral to oral conversion

IDSA Guidelines: Additional Recommendations (Level A)

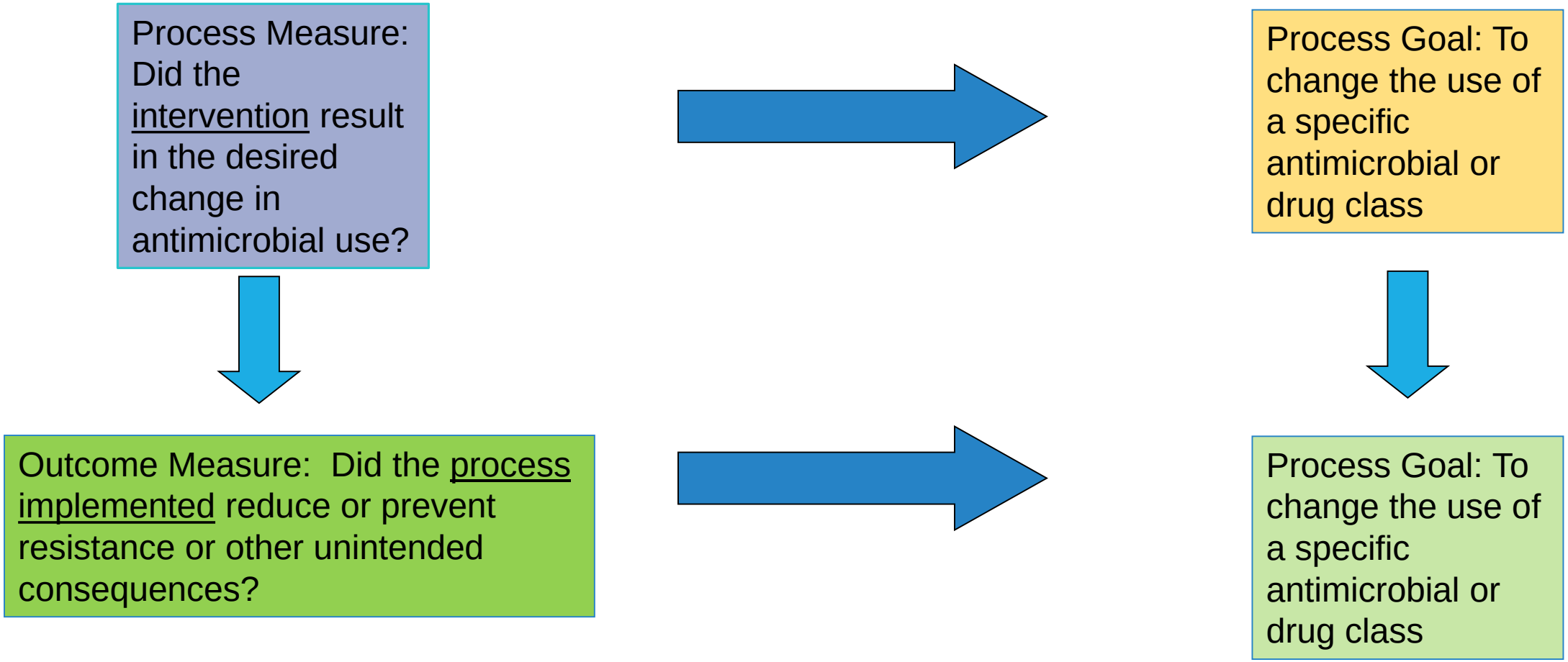
- Optimization of health care information technology
- Integral role of clinical microbiology lab for rapid return of cultures and sensitivities and trend surveillance

IDSA Guidelines: Additional Recommendations (Levels B & C)

- Antimicrobial order forms
  - may be an effective component of stewardship
- Computer-based surveillance
  - increased efficiency in targeting interventions, tracking resistance patterns, and identifying nosocomial infections

IDSA Guidelines: Additional Recommendations (Levels B & C)

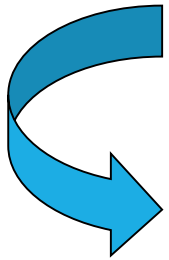
- Antimicrobial cycling: insufficient data; not recommended
- Combination therapy: role in certain clinical contexts but routine use not recommended
- Monitor process and outcome measures to determine impact of stewardship program


Process Measure: Did the intervention result in the desired change in antimicrobial use?
Process Goal: To change the use of a specific antimicrobial or drug class
Outcome Measure: Did the process implemented reduce or prevent resistance or other unintended consequences?
Process Goal: To change the use of a specific antimicrobial or drug class

Determining the Impact of Stewardship

Front End Components

- Prior Authorization
- Health care information technology/clinical decision support
- Guidelines/order sets



Antibiotic Order

Back End Components

- Feedback audit
- Streamlining/de-escalation
- Dose optimization
- IV to PO conversion

PK & PD In ASP

Dose Optimization

- In order to individualize antimicrobial therapy clinicians must understand and incorporate the underpinnings of a key component of antimicrobial stewardship -- **dose optimization** -- into their everyday clinical decision making.
- Dose optimization combines pharmacokinetic (PK) and pharmacodynamic (PD) principles to increase the likelihood of achieving the pharmacodynamic target, and to reduce drug resistance and costs associated with treating MDRO.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Dose Optimization

- PK parameters that reflect the serum level time course (drug concentration over time) of an antibiotic to determine dosing regimens.
- However, PD parameters that quantify the serum level time course of the antibiotic are equally important and should be used in combination with PK parameters to quantify the killing activity of an antimicrobial agent.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Pharmacodynamic and Pharmacokinetic Parameters: Time, Potency, and Killing Activity

PK (time)	PD (potency)	PK/PD (activity)
Cmax	MIC	Cmax/MIC ratio
Cmin		T>MIC
AUC		AUC 24/MIC ratio

AUC = area under the serum concentration curve, measurement of drug absorbed and Persistence

AUC24/MIC ratio = AUC over 24 hours divided by the MIC, predicts efficacy of concentration-dependent antibiotics

Cmax = peak plasma level, highest concentration of drug in the blood

Cmax/MIC ratio = Peak/MIC ratio, predicts efficacy of concentration-dependent antibiotics

Cmin = trough level

MIC = minimum inhibitory concentration, lowest concentration of an antibiotic that completely inhibits the growth of bacteria in vitro

T>MIC = time above MIC, percentage of time over 24 hours that drug concentration exceeds the MIC

Applying the PD and PK Principles

Three PD properties of antibiotics are used to describe their patterns of microbiologic and bactericidal activity:

1. Concentration dependence
2. Time dependence
3. Persistence of effect or post antibiotic suppression of bacterial growth

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

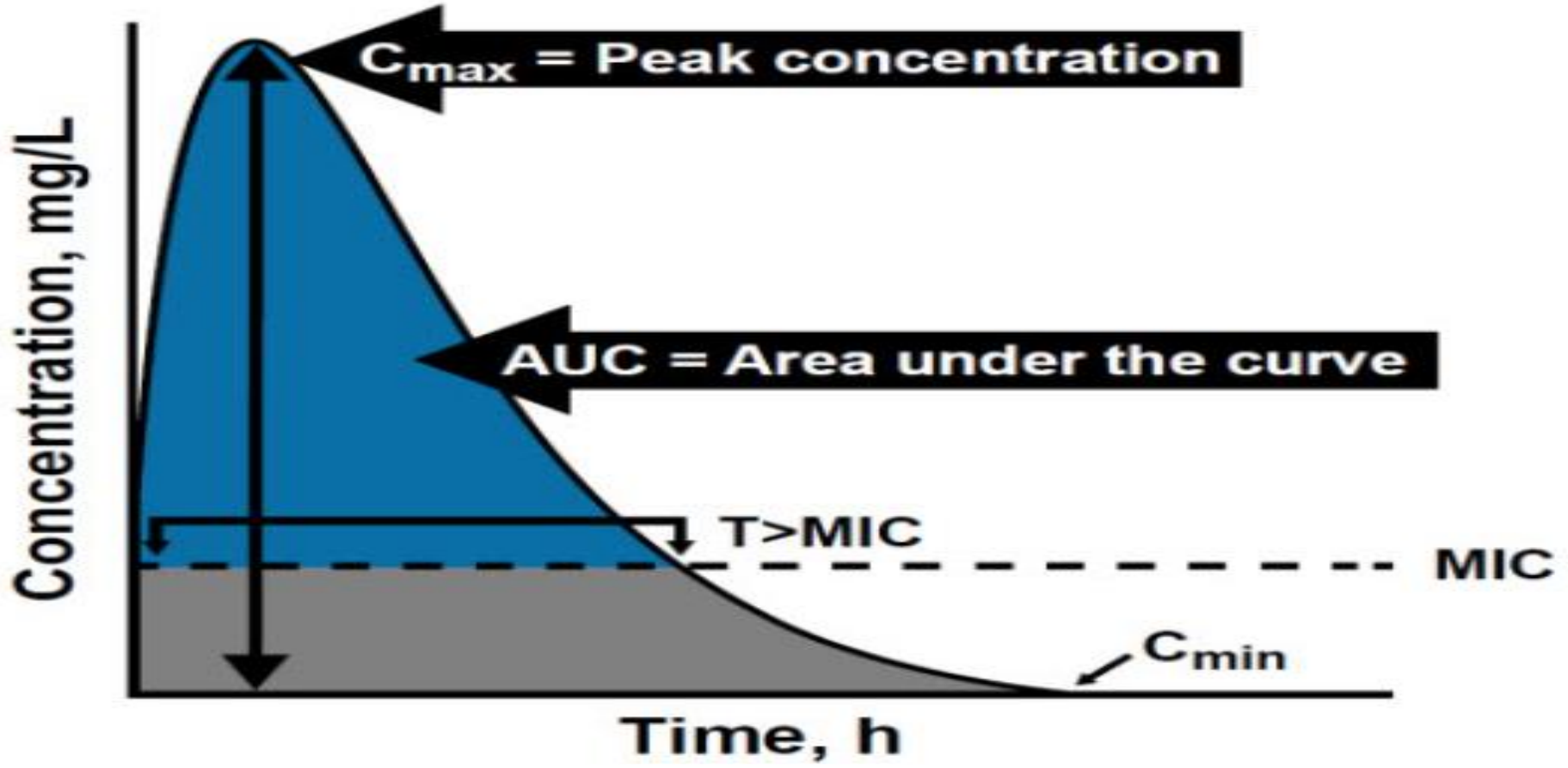
Applying the PD and PK Principles

- These strategies relate to the goal of treatment and includes
  - maximizing drug concentration
  - maximizing duration of drug exposure
  - maximizing the amount of drug (differ according to drug class)

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Patterns of Antimicrobial Activity

Antibiotics	PD Properties	PK/PD Parameter	Goal of Therapy
Aminoglycosides Daptomycin Fluoroquinolones Ketolides	Concentration-dependent killing, prolonged persistence	AUC24/MIC C max/MIC	Maximize drug concentration
Carbapenems Cephalosporin s Erythromycin Linezolid Penicillin s	Time-dependent killing, minimal persistence	T>MIC	Maximize duration of drug exposure
Azithromycin Clindamycin Oxazolidinon es Tetracyclines Vancomycin	Time-dependent killing, moderate-to-prolonged persistence	AUC24/MIC	Maximize amount of drug



Pharmacokinetic and pharmacodynamics parameters of antibiotics on a concentration vs time curve.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Concentration-dependent Antibiotics

- Concentration-dependent antibiotics, such as the aminoglycosides (eg, gentamicin, tobramycin, amikacin), demonstrate increased killing rates as concentration rises.
- The dosing strategy (high-dose) used for aminoglycosides optimizes the concentration-dependent killing activity of these agents.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Concentration-dependent Antibiotics

- The higher-dosage regimen (eg, 7 mg/kg for gentamicin and tobramycin or 15 mg/kg for amikacin) in patients with normal renal function maximizes the Cmax/MIC ratio.
- Optimization of PD reduces toxicity due to less overall drug exposure and improves clinical outcomes.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Concentration-dependent Antibiotics

- Aminoglycosides exhibit a significant post antibiotic effect against gram-negative aerobes; the effect lasts for 2 to 8 hours after drug concentrations reach undetectable levels.
- The duration of this effect primarily depends on the height of the preceding aminoglycoside peak.
- Standard-dosing regimens tend to result in relatively low C /MIC ratios (less than 5); much higher ratios (greater than 10) are achieved when the same once-daily dose is given as a 30- to 60-minute infusion, leading to higher cure rates and lower toxicity.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Time-dependent Antibiotics

- Time-dependent antibiotics, such as the beta-lactams (eg, penicillins, cephalosporins, carbapenems, monobactams), have a slow, continuous kill characteristic.
- The bacteriostatic and bactericidal activities of beta-lactams are associated with the T>MIC.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Time-dependent Antibiotics

- Conventional beta-lactam dosing fails to achieve target T>MICs for drugs in this class that are linked to favorable outcomes in specific patient populations.
- For example, penicillins and cephalosporins have no post antibiotic effect, and carbapenems have a limited post antibiotic effect.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Alternative Dosing Strategies

- Antibiotics that require intravenous (IV) administration are typically administered by intermittent infusion (eg, 1 dose every 4 hours). In some cases however, alternative dosing regimens (eg, continuous IV infusion and extended IV infusion) are indicated.

- For example, critically ill patients with severe infections requiring antibiotic courses of 4 days or more achieve better outcomes with a continuous IV infusion.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Therapeutic Dose Monitoring In ASP

- Therapeutic dose monitoring (TDM) is the taking of samples to estimate antibiotic concentration in a patient's blood, while the patient is receiving a particular dose of the antibiotic.
- If the concentrations are too low, maximal killing of bacteria will not be achieved and the patient's dose or dosing frequency will need to be increased.
- If the concentrations are too high, the patient may experience side-effects from the antibiotic, and the dose or dosing frequency will need to be decreased.

Bettercare.co.za. (2018). *9. Antimicrobial stewardship*. [online] Available at: https://bettercare.co.za/learn/infection-prevention-and-control/text/09.html#case-study-1 [Accessed 23 Sep. 2018].

Therapeutic Dose Monitoring In ASP

- TDM is important for antibiotic stewardship because if the patient is under-dosed, there is a greater chance that antibiotic resistance will develop.
- TDM is usually required for aminoglycosides (gentamicin, amikacin) and glycopeptides (vancomycin).

Bettercare.co.za. (2018). *9. Antimicrobial stewardship*. [online] Available at: https://bettercare.co.za/learn/infection-prevention-and-control/text/09.html#case-study-1 [Accessed 23 Sep. 2018].

Vancomycin

- It is a classical example of time-dependent antibiotic.
- Optimal dosing of vancomycin for the complex eradication of methicillin-resistant *Staphylococcus aureus* (MRSA)
- AUC/MIC ratio of greater than 400 is recommended for vancomycin to optimize MRSA eradication

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Vancomycin

- Since it is very difficult to calculate this ratio, the vancomycin trough level is used as a surrogate marker.
- Monte Carlo simulation studies have shown that a trough level of 15 mg/L to 20 mg/L and a vancomycin MRSA MIC of 1 mg/L or less achieve an AUC/MIC ratio of greater than 400.

Duration of Therapy

- Duration of therapy are another key component of successful antimicrobial stewardship
- Reducing unnecessary antibiotic use can reduce the incidence and selection of resistant pathogens
- For example, in a retrospective cohort study, Stevens and colleagues identified 241 cases of *Clostridium difficile* infection (CDI) among 7792 unique patients with 10,154 hospitalizations
- They demonstrated a relationship between cumulative antibiotic exposure and risk for CDI.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Duration of Therapy

- Dose-dependent increases in risk were associated with increasing cumulative antibiotic dose, number of antibiotics, and number of days of antibiotic exposure.
- They concluded that antimicrobial stewardship programs that focus on reducing the total dose and duration of antibiotic exposure, and substituting high-risk antibiotics with low-risk antibiotics can reduce the incidence of hospital-acquired CDI and related adverse effects.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Common Clinical Syndromes: Durations of Antimicrobial Treatment

Community-Acquired Pneumonia
Adults: 5 days, longer duration for *S aureus* pneumonia, empyema, lung abscess, extrapulmonary complications, and infection due to *Pseudomonas aeruginosa*
Children: 10 days, shorter courses may be as effective for milder disease, outpatient management; longer courses (greater than10 days) may be required for complicated infections with empyema or lung abscess

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Common Clinical Syndromes: Durations of Antimicrobial Treatment

Ventilator-Associated Pneumonia
7 days, 15 days for nonfermenting Gram-negative organisms
Urinary Tract Infections
Acute uncomplicated cystitis[a] • Nitrofurantoin 100 mg, twice daily, 5 days • TMP-SMX 160/800 mg (1 double-strength tablet) twice daily, 3 days (if resistance < 20% or if the infecting strain is known to be susceptible) • Fosfomycin: 3 g, single dose *Pyelonephritis*: several randomized controlled trials have demonstrated that 7 days of treatment with ciprofloxacin was as successful as 14 days of treatment with trimethoprim/sulfamethoxazole; 2 randomized controlled trials demonstrated that 5 days of high-dose levofloxacin (750 mg/d) was as effective as 10 days of Ciprofloxacin

[a] Owing to increased resistance and the adverse ecologic effects, fluoroquinolones should not be used for acute cystitis.

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Common Clinical Syndromes: Durations of Antimicrobial Treatment

Uncomplicated Skin and Soft-Tissue Infection [b]
5-10 days (5 days is generally adequate)

[b] For simple abscesses, drainage (without antibiotics) is the primary treatment.

Complicated Intra-abdominal Infections
4-7 days with adequate source control, longer duration may necessary when adequate source control is not possible or is delayed

Medscape.org. (2018). *Medscape Log In*. [online] Available at: https://www.medscape.org/viewarticle/767071 [Accessed 23 Sep. 2018].

Case study 1

A 15-year-old schoolgirl is taken by her mother to see her local general practitioner (doctor). She is complaining of a sore throat, fever and body aches. She is not particularly unwell but is worried because she has an exam later that week. Her mother asks the doctor to prescribe a course of antibiotics, because she thinks this will get her daughter better faster.

Bettercare.co.za. (2018). *9. Antimicrobial stewardship*. [online] Available at: https://bettercare.co.za/learn/infection-prevention-and-control/text/09.html#case-study-1 [Accessed 23 Sep. 2018].

Case study 1

1. What is the best management for viral infections such as viral pharyngitis?

Most viral infections present with fever plus other symptoms like tiredness, body aches and poor appetite. Since there is no effective treatment available for most viral infections, management includes supportive care with medicines to address the complaints of the patient. Antibiotics have no role in the management of viral infections.

Bettercare.co.za. (2018). *9. Antimicrobial stewardship*. [online] Available at: https://bettercare.co.za/learn/infection-prevention-and-control/text/09.html#case-study-1 [Accessed 23 Sep. 2018].

Case study 1

2. How should prescribers handle patients who insist on having antibiotics prescribed for a viral infection?

Pressure from patients and their family members is one of the reasons for antibiotic overuse. Many patients expect a prescription of antibiotics every time they go to the doctor for various complaints like fever, sore throat or diarrhoea, even if these infections will not be helped by antibiotics.

Prescribers should take time to explain the diagnosis and reassure them that their condition does not require antibiotics. They could also educate patients about the potential harmful effects of giving unnecessary antibiotics.

Bettercare.co.za. (2018). *9. Antimicrobial stewardship*. [online] Available at: https://bettercare.co.za/learn/infection-prevention-and-control/text/09.html#case-study-1 [Accessed 23 Sep. 2018].

Case study 1

3. What problems can arise when a patient is given antibiotics unnecessarily?

The patient may experience side-effects (adverse drug reactions) from antibiotics such as rash, diarrhoea (as in *Clostridium difficile* infection) and fungal infections (e.g. vaginal thrush). Antibiotics also cause changes in the flora of the gut, selective pressure and development of antibiotic resistance.

Bettercare.co.za. (2018). *9. Antimicrobial stewardship*. [online] Available at: https://bettercare.co.za/learn/infection-prevention-and-control/text/09.html#case-study-1 [Accessed 23 Sep. 2018].

Case study 2

A 28-year-old healthy pregnant lady is scheduled to have her baby delivered by Caesarean section. She is given a dose of cefazolin as pre-operative prophylaxis four hours before the operation starts. The baby is delivered successfully without any complications. After delivery, the obstetrician continues the patient on cefazolin 1 gram every eight hours for three more days.

Bettercare.co.za. (2018). *9. Antimicrobial stewardship*. [online] Available at: https://bettercare.co.za/learn/infection-prevention-and-control/text/09.html#case-study-1 [Accessed 23 Sep. 2018].

Case study 2

1. What are the main concerns regarding antibiotic stewardship in this case?

The timing of the pre-operative antibiotic should be less than one hour before the first skin incision is made (operation starts). In uncomplicated, clean (non-infected) cases, a single dose of pre-operative antibiotics is sufficient.

Bettercare.co.za. (2018). *9. Antimicrobial stewardship*. [online] Available at: https://bettercare.co.za/learn/infection-prevention-and-control/text/09.html#case-study-1 [Accessed 23 Sep. 2018].

Case study 2

2. Why are patients sometimes given extra postoperative doses of antibiotics?

Many doctors feel that additional doses of antibiotics will somehow ‘protect’ the patient from surgical site infection. This is especially true in training hospitals where doctors may be young and inexperienced. Many research studies have shown no benefit from giving extra doses of antibiotics postoperatively for routine surgical procedures. The extra antibiotic doses unnecessarily expose patients to side-effects and increase the chance of developing antibiotic resistance.

Bettercare.co.za. (2018). *9. Antimicrobial stewardship*. [online] Available at: https://bettercare.co.za/learn/infection-prevention-and-control/text/09.html#case-study-1 [Accessed 23 Sep. 2018].

Conclusion

- Pharmacodynamic dose optimization leads to improved use of current antimicrobial agents and results in improved outcomes, decreased potential for antimicrobial resistance, and reduced costs.
- Limiting antimicrobial exposure based on scientific evidence reduces consumption, cost, and more importantly, collateral damage such as *C difficile* infections.


Thank You