Antibiotics in General Surgical Practice

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INTRODUCTION

Surgery has evolved to a great extent under the protective umbrella of antibiotics. In 1967, when US General surgeon, H. Stewart announced that, “we had essentially defeated infectious diseases and could close the book on them”^[1]. But we have not conquered this fight yet as almost 50% of mortality and morbidity is due to communicable diseases in spite of full range of antibiotics available against them. Antibiotic prescription practices worldwide have depicted that prescription in surgical practices are more inappropriate in comparison to other specialities of modern medicine, which is a great concern to medical fraternity and general public. Already in his Nobel Prize speech in 1945, Alexander Fleming warned that bacteria could become resistant to these remarkable drugs. Antimicrobial resistance (AMR) was the focus of World Health Day in 2011 when a 6-point AMR policy package was issued^[2]. AMR surveillance is also included in international health regulations^[3]. It has been estimated that at least fifty percent of patients receive antibiotics needlessly. Reasons include inappropriate prescription of antibiotic prophylaxis, continuation of empiric therapy despite negative cultures in a stable patient, and a lack of awareness of susceptibility

patterns of common pathogens. Over prescribing not only increases the costs of health care, but may result in superinfection due to antibiotic-resistant bacteria, as well as opportunistic fungi, and may increase the likelihood of an adverse drug reaction. On the other hand, not prescribing (when there is an urgent need at the bedside) may also lead to serious consequences. But the Main problem is over-prescribing. Bacteria evolve when subjected to selection pressure and multiantibiotic resistance in organisms as ubiquitous as *Escherichia coli* and *Staphylococcus aureus* has been observed^[4]

Following are some guiding principles and recommendations for prescribing antibiotics in general surgical practice with ultimate aim of decreasing antimicrobial resistance:

1. Antibiotic combinations to be avoided:

- The antagonistic combination of penicillin with bacteriostatic agents (e.g., tetracycline, chloramphenicol) should be avoided.^[5]
- Combinations of macrolides and lincosamides create an antagonism in *S. aureus*^[5].
- Antagonism between beta-lactams occur when one of them is an inducer of a chromosomal beta-lactamase (*E. Coli*, *Ps. aeruginosa*, *Morg*)^[5].
- Two or more agents with anti-anaerobic activity like piperacillin-tazobactam, ampicillin-sulbactam,

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ertapenem, meropenem, or imipenem-cilastatin in combination with metronidazole doesn't confer any advantage.

- Concurrent use of multiple beta-lactams and/or carbapenems is again a mis-combination.
- Concurrent use of a respiratory fluoroquinolone (e.g., moxifloxacin or levofloxacin) with a macrolide.
- Routine addition of an aminoglycoside to other agents having broad-spectrum gram-negative coverage, such as imipenem/cilastatin, piperacillin/tazobactam or third/ fourth generation cephalosporins, provides no additional benefit in intrabdominal infections.
- Mixing ticarcillin or carbenicillin with aminoglycosides results in the inactivation of the aminoglycosides.

2. Surgical prophylaxis: ^[6-26].

- Whenever possible, providers should employ hospital-specific antibiograms and diverse antibiotic agents to decrease resistance among pathogens ^[6].
- Cefazolin is drug of choice for most of the general surgical procedures.
- Broad-spectrum antimicrobial agents don't result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity.
- Overuse of 3rd Generation cephalosporins has been associated with increased incidence of MRSA and their long-term prophylaxis do not decrease incidence of surgical site infections.
- Routine use of vancomycin prophylaxis is not recommended for any procedure. Not only Vancomycin is less effective than cefazolin for preventing SSIs caused by methicillin-susceptible *S. aureus* (MSSA) but also that the use of vancomycin alone in MRSA-negative patients is associated with a higher risk of Methicillin sensitive *Staph. Aureus* SSI ^[7-13].
- Vancomycin may be included in the regimen of choice when a cluster of MRSA cases (e.g., mediastinitis after

cardiac procedures) or methicillin resistant coagulase-negative staphylococci SSIs have been detected at an institution.

- Vancomycin prophylaxis should be considered for patients with known MRSA colonization or at high risk for MRSA colonization in the absence of surveillance data (e.g., patients with recent hospitalization, nursing-home residents, hemodialysis patients) and allergy to b-lactam antimicrobials.
- The inclusion of vancomycin may be appropriate for a patient with a life-threatening allergy to b-lactam antimicrobials (type 1-IgE mediated reactions including anaphylaxis, urticaria, bronchospasm) or exfoliative dermatitis (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Cephalosporins and carbapenems can safely be used in patients with an allergic reaction to penicillins that is not an IgE-mediated reaction.
- Typical preoperative decolonization for protocols *staph aureus* include the use of 2% nasal mupirocin, BID for 5 days and bathing with chlorhexidine gluconate days 1, 3, and 5 preoperatively ^[13,14].
- Elective laparoscopic cholecystectomy, parotidectomy, chest tube insertion and other clean procedures don't warrant use of prophylaxis. ^[15,16,18].
- For most patients who have had their wounds opened and adequately drained, antibiotic therapy is unnecessary. Use antibiotics only when there are significant systemic signs of infection (temperature higher than 38.5C or heart rate greater than 100 beats/min) and erythema extends more than 5 cm from the incision. ^[15,16].
- Prophylactic antibiotic dosing should be adjusted based on the patient's weight. Use higher dosages of prophylactic antibiotics for morbidly obese patients ^[17].
- Administer prophylactic antibiotics within 1 h before incision (2 h for vancomycin and fluoroquinolones)

- Prophylactic antibiotics should be re-dosed during surgery to maintain adequate tissue levels based on the agent's half-life or for every 1500 mL of estimated blood loss ^[13,14]. (for cefazolin if operation is >3 h).
 - In elective colorectal surgeries a combination of antibiotic be delivered both orally as part of a preoperative bowel preparation the day before surgery as well as IV in the immediate preoperative period ^[19,20].
 - Antibiotics should be discontinued at time of incision closure (exceptions include implant-based breast reconstruction, joint arthroplasty, and cardiac procedures and liver transplantation). ^[21,22].
 - The use of antibiotic (triclosan) coated suture is recommended for wound closure in clean and clean-contaminated abdominal cases when available ^[2-25].
 - Most superficial SSIs can be managed in the outpatient setting, whereas deep and organ space SSIs require readmission ^[26].
 - The most important consideration in surgical antibiotic prophylaxis is that there is array of web of factors which affect the occurrence of SSI and antibiotics should not be answer or replacement to any of those factors.
- 3. Intraabdominal infections (IAI):** ^[27].
- Routine use of antimicrobial therapy is not appropriate for all patients with intra-abdominal infections e.g. uncomplicated diverticulitis (defined on CT imaging) as antibiotics do accelerate recovery or prevent complications/recurrence.
 - In Severe acute pancreatitis including those with sterile pancreatic necrosis, prophylactic antibiotics are not recommended.
 - In uncomplicated IAIs, when the focus of infection is treated effectively, the administration of antibiotics is unnecessary beyond prophylaxis or beyond 24hrs
 - Acute unperforated appendicitis removed surgically
 - Cholecystitis removed surgically
 - Bowel necrosis due to a vascular accident
 - Bowel necrosis due to strangulating bowel obstruction, in whom there is no evidence of perforation or infected peritoneal fluid
 - Gastroduodenal perforations operated within 24 hours in the absence of antacid therapy or malignant disease
 - Traumatic or iatrogenic bowel injury repaired within 12 hours
 - Initiate empiric antimicrobial therapy within one hour, if possible, once a diagnosis of IAI is made in patients presenting with sepsis or septic shock.
 - While selecting empirical antimicrobial therapy, factors to be considered include probable contaminating pathogen/s, individual risk assessment and possibility of resistant pathogens.
 - Higher risk patients are those, with severe sepsis/septic shock, elevated APACHE II score (>10), multiple medical comorbidities, problematic or delayed source control.
 - Patients with intrabdominal infection and having any of the following criteria should be considered having Healthcare or hospital-associated infection
 - Hospitalized currently or previously within 90 days for >48 h.
 - Residing in a long-term care facility.
 - Receiving hemodialysis, IV infusion therapy
 - Complex wound care within the previous 30 days.
 - Received >48 hr of broad-spectrum antimicrobials within the previous 90 days.
 - Lower risk patients with community-acquired IAI: Narrower-spectrum therapy (E. coli, Bacteroides) is recommended and there is no need for anti-enterococcal or antifungal therapy.

- Single agents: Ticarcillin/clavulanate, Ertapenem, Moxifloxacin (Serious β -lactam allergy).
- Combination regimens: Cefuroxime/ ceftriaxone/ cefotaxime plus metronidazole. Ciprofloxacin/ levofloxacin plus metronidazole (Serious β -lactam allergy).
- Moxifloxacin or ciprofloxacin plus metronidazole are alternatives to above regimen
- Low risk regimens are recommended for patients with perforated appendicitis, unless they meet criteria as higher-risk patients or at risk of HAI.
- Higher risk patients with community-acquired IAI: Broader-spectrum therapy is recommended with selective use of anti-enterococcal and antifungal therapy.
- Piperacillin/tazobactam, Imipenem/cilastatin, Meropenem, Doripenem.
- Ceftazidime/cefepime plus metronidazole (add ampicillin or vancomycin if anti-enterococcal coverage needed).
- Aztreonam plus metronidazole plus vancomycin (Serious β -lactam allergy).
- Antifungal coverage if severely ill with a gastroduodenal source of infection.
- Patients with healthcare/hospital-associated IAI: Broader-spectrum therapy is recommended with additional agents for resistant pathogens.
- Add MRSA coverage only if known to be infected or colonized with MRSA.
- Additional Gram-negative coverage according to expected resistant pathogens (aminoglycoside, a polymyxin, or a tetracycline).
- Add Antifungal (an echinocandin) for patients at risk for Candida (recurrent GI perforations, esophageal perforation, persistent GI leak, prolonged antacids or antibiotic therapy, repeated courses of broad-spectrum antibiotics, surgically-treated pancreatitis, yeast colonization at multiple sites or immunosuppression).
- Fluconazole is preferred for the treatment of susceptible Candida albicans infections, while echinocandins (e.g., anidulafungin, caspofungin, micafungin) are recommended for fluconazole-resistant Candida species and critically ill patients.^[28]
- Enterococcus faecium infections should be suspected among high-risk patients for these infections, including liver transplant recipient, biliary infections, or colonized patients.^[29]
- Empiric anti-enterococcal therapy include (e.g., ampicillin, piperacillin- tazobactam, and vancomycin).^[29]
- Consider limiting antimicrobial to 57 days in patients with established IAI in whom a definitive source control procedure is not performed.
- Consider limiting antimicrobials to seven days in patients with secondary bacteremia because of IAI, who have undergone adequate source control and are no longer having bacteremia.
- Duration of antimicrobial therapy in secondary peritonitis/ GI perforation:

	Stomach	Small bowel	Colon	Appendix
Uncomplicated	Operated on within 24 h	Operated on within 12 h	Operated on within 12 h	Non-necrotic/- gangrenous appendix
Duration	24-48 h	24-48 h	24-48 h	24 h
Complicated	Late operation/no operation/gangrenous or necrotic changes			
Duration	4 days unless adequate source control is not achieved			

- Ceftolozane/Tazobactam: Newly approved drug by the FDA for treatment of complicated intra-abdominal and complicated urinary tract infections with enhanced anti-pseudomonas activity without anti-anaerobic activity.^[30]
- Eravacycline: A fluorocycline with activity against many resistant Gram-negative pathogens, comparable to ertapenem.^[30]
- Do not use tigecycline for empiric therapy under most circumstances. Consider its use in adult patients with resistant pathogens, as a component of a combination regimen, if other agents are not suitable
- Use metronidazole as the preferred anti-anaerobic agent in combination regimens, not clindamycin, for empiric therapy in adults and children.
- Use clindamycin in children < 1 month of age and when metronidazole cannot be used.
- Fluoroquinolones can be used in lower-risk adults, but with caution in areas where there is a high incidence of fluoroquinolone-resistant *E. coli*.
- Use oral antibiotics only to complete a short course of treatment and not to prolong antimicrobial use beyond current recommendations.
- Antibiotics which can be used orally in patients with bacteremia or fungemia include moxifloxacin, ciprofloxacin, metronidazole, trimethoprim sulfamethoxazole, linezolid, variconazole, and fluconazole, as all these drugs have good oral absorption.^[31]
- Clinical dilemma: Do we really need to change the regimen after culture sensitivity reports are available, if patient is improving? This is an important clinical situation. Evidence suggests that in such situations the empiric therapy should be continued in low risk patients.
- Consider modification of antimicrobial therapy in higher-risk patients if culture results identify organisms resistant to the initial empiric regimen.
- Do not routinely change antimicrobial therapy when patients have early treatment failure and undergo repeat source control within 48 hours of the initial source control intervention.
- Pancreatitis with abdominal sepsis: Piperacillin/tobactam or Cefipime plus Metronidazole or Ciprofloxacin plus metronidazole are optimal antimicrobial therapy. The recommended duration of antimicrobial therapy is 14 days, more than this dangerous.
- Indication mismatch: Antibiotics recommended for drug-resistant pathogens should not be used for community onset infections, where there is no concern for a resistant infection e.g., piperacillin/tazobactam.
- Follow ladder of prescription:
- After culture sensitivity reports are available, where sensitivity is retained to first line antibiotics and still 2nd and 3rd line antibiotics are used e.g. Vancomycin (and other drugs used to treat MRSA) can often be stopped if appropriate cultures do not grow MRSA. Moreover, these drugs should almost always be switched to a beta-lactam when appropriate cultures grow methicillin-susceptible *S. aureus*. Vancomycin is less effective against methicillin sensitive *Staph aureus*, so its empirical use needs rigorous efforts to justify the indication
- First line use of Linezolid/clindamycin for staph is not recommended
- Changing antibiotics too early is not recommended as most of the times non-improvement in intrabdominal infections is usually due to failure to achieve source control not due to problem of antibiotics.

CONCLUSION

Available Antibiotics are a limited treasure. New antibiotic discovery has become limiting, as focus has shifted towards chronic diseases. We are already losing antibiotic function

at a faster rate due to ever-evolving resistant strains. Humans are speeding up this process by antibiotic utilization leading to increasing selective pressures and risk of developing superbug strains. Antibiotics are not the answer to lacunae in our working system, to our lack of knowledge and multitude of other factors. Appropriate use is the need of hour to save our present and future generations.

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