



Received on 15 April, 2016; received in revised form, 23 May, 2016; accepted, 14 July, 2016; published 01 September, 2016

ANTIBIOTIC DE-ESCALATION IN THE INTENSIVE THERAPY UNIT- A REVIEW

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Keywords:

ITU – (Intensive Therapy Unit), MDR – (Multi Drug Resistant), Antibiotics, MRSA ("methicillin-resistant *Staphylococcus aureus*) PCT: (Procalcitonin).

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ABSTRACT: An antibiotic may be defined as a substance or compound that kills or inhibits the growth of, bacteria. Antibiotics belong to the broader group of antimicrobial compounds, used to treat infections caused by microorganisms, including fungi and protozoa, viruses. Antibiotic de-escalation is a mechanism whereby the provision of effective initial antibiotic treatment is achieved while avoiding unnecessary antibiotic use that would promote the development of resistance. The embodiment of de-escalation is that based on microbiology results around the day 3 therapy point; the empiric antibiotic(s) that were started are stopped or reduced in number and/or narrowed in spectrum.

INTRODUCTION: Patients admitted to Intensive therapy units (ITU) are critically ill patients and most often associated with infection or gets associated with infection due to their prolonged stay (Chronic conditions) in hospital and due to the various invasive treatment options like catheter, tracheotomy tube, ventilation etc that they are treated with, and due to the prevailing hospital flora.

Optimal antibiotic use is crucial in the critical care setting, especially in the era of rising antibiotic resistance and lack of new antimicrobial development. Study results indicate that 30% to 60% of antibiotics prescribed in ICUs are unnecessary, inappropriate or suboptimal.

Over prescribing and misprescribing antibiotics are undoubtedly contributing to the growing challenges posed by antibiotic resistant bacteria and epidemiological studies have clearly demonstrated direct relationships between antibiotic consumption and the emergence and dissemination of resistant strains in hospitals and ICUs.

The increasing resistance rate among nosocomial pathogens is particularly disconcerting. Powerful antibiotics first became commercially available in the 1940s and have saved untold millions of lives. But after years of widespread use, evolution of disease-causing microbes has resulted in many antimicrobials losing their effectiveness. As microbes evolve, they adapt to their environment. If something stops them from growing and spreading such as an antimicrobial they evolve new mechanisms to resist the antimicrobials by changing their genetic structure. Changing the genetic structure ensures that the offspring of the resistant microbes are also resistant.

QUICK RESPONSE CODE	DOI: 10.13040/IJPSR.0975-8232.7(9).3596-01
	Article can be accessed online on: www.ijpsr.com
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7(9).3596-01	

The inappropriate and widespread use of antibiotics in ICU is a potential cause of emergence of antibiotic resistance which in turn has turned out to be a variable that influences patient's outcome, patient's overall healthcare cost.

Spread of antibiotic resistance is also resulting in failure of current antibiotic treatment as the available antibiotics are turning absolute. To help prevent the antibiotic resistance, various effective strategies are being developed and focusing on limiting the overuse or unnecessary use of antibiotics and also complying with infection control practices. The practice of de-escalation of antibiotic can serve as an effective tool to cut down the unnecessary use of antibiotics and thus preventing antibiotic resistance.

Antibiotic resistance is a specific type of drug resistance when a microorganism has the ability of withstanding the effects of antibiotics.

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

1. Drug inactivation or modification: e.g. enzymatic deactivation of *Penicillin G* in some Penicillin-resistant bacteria through the production of β -lactamases.
2. Alteration of target site: e.g. alteration of PBP—the binding target site of penicillins—in MRSA and other penicillin-resistant bacteria.
3. Alteration of metabolic pathway: e.g. some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides.
4. Reduced drug accumulation: by decreasing drug permeability and/or increasing active efflux (pumping out) of the drugs across the cell surface.

Resistant pattern of the few common bacterial isolates in ITUs:

Among Gram-positive organisms, the most important resistant pathogens are methicillin-(oxacillin) resistant *Staphylococcus aureus*, β -lactam-resistant and multi drug-resistant pneumococci, and vancomycin-resistant enterococci. Important causes of Gram-negative resistance include extended-spectrum β -lactamases (ESBLs) in *Klebsiella pneumoniae*, *Escherichia coli* and *Proteus mirabilis*, high-level third-generation cephalosporin (Amp C) β -lactamase resistance among *Enterobacter* species and *Citrobacter freundii*, and multi drug-resistance genes observed in *Pseudomonas aeruginosa*, *Acinetobacter* and *Stenotrophomonas maltophilia*.

Patients hospitalized in Intensive therapy Units (ITUs) are 5 to 10 times more likely to acquire nosocomial infections than other hospitalized patients. This will result in consumption of nearly 10 times the antimicrobial agents used in general wards. Based on these reports ITUs are considered epicenters of antibiotic resistance and the principal sources of multi-resistant bacteria outbreaks. This increase in bacterial resistance will result in increased morbidity and mortality, and inflation of health care costs. Therefore optimizing the treatment of infectious diseases in the ICUs is crucial and requires the following:

- 1) To be aware of the antimicrobial resistance pattern in the ITU, in order to guide the clinician in the choice of an optimal empiric antibiotic regimen. In fact, updated unit-specific antibiograms should be provided to the clinicians at least once a year to ensure that the data are current and useful.
- 2) To be insured of the validity of the results of in vitro antibiotic susceptibility testing. There are various in vitro antibiotic susceptibility tests that will assist the clinician in the choice of an appropriate antibiotic for the treatment of infected patients.

Unfortunately, improving in-ITU antibiotic use is particularly difficult for three main reasons: infection severity often precludes withdrawing or

postponing antibiotics, the complex decision-making process frequently involves doctors with limited expertise, and it is difficult to ensure disease-long continuity of care by the same medical team 24 hours a day, 7 days a week.

Identification of intensive therapy unit patients with bacterial infections:

The inaccuracy of conventional approaches to diagnose hospital-acquired infections (HAIs) and the impossibility of those strategies to avoid antibiotic over prescription led some investigators to hypothesize that using biological markers - for example, C-reactive protein, soluble-triggering receptor expressed on myeloid cells-1, or procalcitonin (PCT) - might better identify true bacterial infections and facilitate therapeutic decisions. However, although PCT is a good marker of community-acquired infections (CAIs), it does not seem to be for HAIs. Indeed, blood PCT concentrations can rise in various non-septic conditions: major trauma, surgery, acute respiratory distress syndrome, and multiorgan failure, post-transplantation rejection, cardiogenic shock, severe burns, heat stroke, and so on.

Thus, high PCT concentrations the day sepsis is suspected are non-contributory because increases that are attributable to a prior non-infectious condition or active infection cannot be distinguished. Moreover, PCT can remain low in some microbiologically proven bacterial infections,

either because the infection remains contained in a tissue compartment that can synthesize PCT locally without systemic release, thereby explaining the low serum level despite true infection, or because of a 24- to 48-hour lag time infection onset to peak PCT release. Thus, intensivists are rightly reluctant to rely exclusively on biological markers when severe infection is suspected.

Implementing a structured antibiotic de-escalation program:

Optimizing in antimicrobial therapy is difficult. No single measure alone can succeed, emphasizing the need to devise a structured antibiotic stewardship program. Unfortunately, the exact set of key interventions essential to this multifaceted and multidisciplinary 'care bundle remains unknown, as do the factors contributing to its success. The interventions should be packaged so that compliance is readily assessable and achievable, which usually means that each bundle includes no more than five to eight interventions. Successful implementation requires an interdisciplinary team, educational interventions, system innovations, process indicator evaluation, and feedback to health-care workers.

Computerized decision-support programs linked to electronic patient records can facilitate the dissemination of information to physicians for immediate use in therapeutic decision making and improving quality of care.

TABLE 1: A PERSONAL CARE BUNDLE FOR OPTIMIZING ANTIMICROBIAL TREATMENT FOR INTENSIVE CARE UNIT PATIENTS

Steps	Antibiotic items	Rationale
Step 1	Obtain specimens for Gram staining and cultures before introducing new antibiotics.	Every effort should be made to obtain reliable specimens from the specific infection site For direct microscope examination and cultures in order to enable de-escalation.
Step 2	Start antibiotics less than 2 hours	Time to appropriate antimicrobial administration is a major outcome determinant for intensive care unit patients with severe bacterial infections.
Step 3	Start therapy using broad-spectrum antibiotics unless no risk factors for resistant pathogens are present.	Owing to the emergence of multiresistant GNB (for example, <i>Pseudomonas aeruginosa</i> and ESBL-producing GNB), empirical broad-spectrum antibiotics are justified for most patients.
Step 4	Stop therapy on day 3 if infection becomes unlikely.	Antibiotics can be discontinued very early when diagnosis becomes highly unlikely based on negative cultures and clinical course.
Step 5	Use pharmacokinetic pharmacodynamic data to optimize treatment.	Clinical and bacteriological outcomes can be improved by optimizing the therapeutic regimen according to pharmacokinetic-pharmacodynamic properties of the selected agents.
Step 6	Streamline antibiotic therapy by using narrower-spectrum antibiotics once the etiological agent is identified	For many patients, including those with late-onset infections, therapy can be narrowed once blood culture results become available, either because an anticipated bacterium (for example, <i>P. aeruginosa</i> , <i>Acinetobacter</i> spp., or methicillin-resistant <i>Staphylococcus aureus</i>) was not recovered or because the isolated pathogen is sensitive to a narrower-spectrum antibiotic than that used initially.
Step 7	Switch to monotherapy on days 3	Using a two-antibiotic regimen for more than 3 to 5 days has no clinical benefits, provided

Step 8	Shorten the treatment duration.	that initial therapy was appropriate, the clinical course evolves favorably, and microbiological data exclude difficult-to-treat microorganisms. Shorter antibiotic administration has achieved good outcomes with less antibiotic consumption. Prolonged therapy leads to colonization with antibiotic-resistant bacteria, which may precede recurrent episodes.
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ESBL, extended- spectrum β -lactamase; GNB, Gram-negative bacilli.

TABLE 2: VARIOUS TYPES OF ANTIBIOTICS AND THEIR MECHANISM OF ACTION USED IN THE ITU

Antibiotic Type	Type of Action	Effect
D-cycloserine (oxamycin)	Inhibits racemase transforming L to D alanine	Prevents synthesis of peptide side chain on muramic acid
Vancomycin	Inhibits growth of glycopeptides polymer	Prevents synthesis of murein
Risocetin		
Bacitracin		
Penicillin	Inhibits transpeptidation of side chain to bridge	Prevents crosslinking of chains of glycopeptide
Methicillin		
Ampicillin		
Cephalosporin		
Lysostaphin	Hydrolyzes peptide side chain and cleaves muramic acid- glucosamine polymer	Lysis of staphulococci
Tyrocidine	Damage to membrane	Leakage of cell contents
Gramicidine	Uncouples oxidative phosphorylation; binds to membrane	Leakage of cell contents
Polymicin	Releases protein from membrane	Leakage of cell contents
Colistin		

In the most recent literature on the topic describes use of polymyxin B or E (colistin) (intravenous, intramuscular, or inhaled) for treatment of *Acinetobacter* species. This is largely because some nosocomial isolates are only susceptible to colistin due to increasing resistance.

Principle of De-escalation practice of antibiotics:

Antibiotic de-escalation therapy is thus the practice of using more powerful or broader spectrum of antibiotics, earlier in treatment, i.e. empirically, for a short period of time – and then switching to a less powerful or narrower spectrum of antibiotic (if possible stopping the antibiotic therapy) once the infection is accurately diagnosed and under control. De-escalation of antibiotics may be also defined as a switch to or discontinuation of an antibiotic resulting in a less broad spectrum of coverage.

De-escalation practice; its importance:

Rapid spread of antibiotic resistance problem is emerging as a challenge to the physicians as well as a threat to the available antibiotics and an important factor influencing patient's length of stay in hospital, patient's overall healthcare costs as well as patient's outcome. Though a number of factors are at root cause of the problem the core factor is surely correlated with the extensive and extensively inappropriate use of antibiotics in hospitals

specially in the Critical Care Units, where infections are common day-to-day problem. This has thus led to intense focus on optimization of antibiotic therapy. Various strategies have been developed to optimize the antibiotic usage in Critical Care Units in order to prevent resistance. However these strategies should provide a balance between the need to provide adequate initial antibiotic therapy in the severely ill patients who are at high risk to infections and the need to prevent the spread of antibiotic resistance.

The strategy of de-escalation practice also minimizes the overall healthcare cost of the patient, lessens risk of drug related adverse events and most importantly reduces the pressure on bacterial ecology, which in turn diminishes the chance of spread and emergence of antibiotic resistant pathogens along with simultaneous goal of improving patient outcome and the chance of turning an available antibiotic absolute.

CONCLUSIONS: The high antibiotic resistance observed in ICU patients who develop infections limits treatment options and justifies using regimens combining several broad-spectrum antibiotics, even when the presumed infection probability is low, because initial inappropriate therapy has been linked to poor prognoses. More

than its economic impact, this 'spiraling empirical' practice increasingly leads to undue antibiotic administration to many ICU patients without true infections, paradoxically causing the emergence of more antibiotic-resistant microorganisms causing infections those, in turn, are associated with heightened mortality and morbidity.

Therefore, antibiotic therapy for ICU patients with infections should be viewed as a two-stage process: the first involves administering broad-spectrum antibiotics to avoid inappropriate treatment of true bacterial infections, and the second focuses on trying to achieve the first without antibiotic overuse or abuse. In general, the first goal can be accomplished by rapidly identifying patients with infection and starting empirical therapy likely to treat the institution's most common etiological agents. This strategy requires that initial antibiotic choices be guided by local antibiotic resistance patterns and laboratory test results (including Gram staining), rapidly yielding identities of likely responsible pathogens.

The second aim involves stopping therapy when the probability of infection is low, focusing and narrowing treatment once the microorganism is known, switching to monotherapy after day 3 whenever possible, and shortening treatment to 7 to 8 days for most patients, based on the clinical response and bacteriology findings. Therefore, every effort should be made to obtain reliable specimens from the specific suspected infection site in each patient for direct microscope examination and cultures in order to de-escalate antibiotics.

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How to cite this article:

Sharma J, Kosey S and Kumar R: Antibiotic de-Escalation in the Intensive Therapy Unit- a Review. *Int J Pharm Sci Res* 2016; 7(9): 3596-01. doi: 10.13040/IJPSR.0975-8232.7(9).3596-01.

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