Antibiotic Dose Optimization at Critically Ill Patient

Essay

Submitted for Partial Fulfillment of Master Degree
in **Critical Care**

By

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2017

Abstract

Introduction: Antimicrobial management in the intensive care unit (ICU) represents an ongoing challenge for critical care clinicians. In the ICU setting broadspectrum antibiotic consumption is often unavoidably high, and antimicrobial resistance rates are increasing in many parts of the world**.**

Early and appropriate antimicrobial administration is paramount in critically ill patients with suspected or confirmed infection and sepsis**.**

Aims: To achieve prompt and appropriate management of infections in critically ill patients in order to limit mortality and morbidity to adjust antibiotic dosing and be able of therapeutic monitoring to achieve maximal efficacy, decrease the risk of antimicrobial resistance and minimize toxicity.

Summary: Successful prediction of a patient's infecting pathogen is the most important initial treatment consideration for critically ill individuals. Considerations before implementing treatment regimens include typical bacterial pathogens for disease states, local susceptibility patterns and antibiogram data, and risk stratification for MDR organisms.

Keywords: Antibiotic Dose, Critically Ill Patient, Mortality and morbidity

بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgments

*First and forever, thanks to **Allah**, Almighty for giving me the strength and faith to complete my thesis and for everything else.*

I would like to express my sincere gratitude to **Prof. Dr. Amr Essam Eldin Abd Elhamid,** *Professor of Anesthesia and ICU, Faculty of Medicine – Ain Shams University, under his supervision, I had the honor to complete this work, I am deeply grateful to him for his professional advice, guidance and support.*

My deep gratitude goes to **Dr. Ayman Ibrahim Tharwat,** *Assistant Professor of Anesthesia and ICU, Faculty of Medicine – Ain Shams University, for his great support, tireless guidance and meticulous supervision throughout this work.*

Words fail to express my thanks and appreciation to **Dr. Hany Maher Salib,** *Lecturer of Anesthesia and ICU, Faculty of Medicine – Ain Shams University, for the efforts and time he has devoted to accomplish this work.*

I can't forget also to thank all the staff in the laboratory of Obstetrics and Gynecology Hospital and the Microbiology Department, Faculty of Medicine, Ain Shams University, for their cooperation and great help.

*Last but not least, I like to thank all my **Family**, especially my **Parents,** for their kind care, help and encouragement.*

Hassan Abo Bakr Ali Darweesh

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List of Abbreviations

Abbr.	Full-term
AAG	Alpha acid glycoprotein
ADM	adrenomedullin
AKI	Acut kidney injury
AMS	Antimicrobial stewardship
ANG	angiopoietin
APACHE II	Acute physiology and chronic health evaluation II
AUC0-24	Area under the concentration/time curve
AUROC	Area under the receiver operating characteristic curve
CDC	Centers for Disease Control and Prevention
CL	Clearance
CDI	Clostridium deffecile infection
CLSI	Clinical Laboratory Standards Institute
cMAX	Maximum drug concentration
cMIN	Minimum drug concentration
Cr.Cl	Create clearance
CRP	C-reactive protein
ETA	Endotracheal aspiration
EPIC II	European Prevalence of Infection in Intensive Care II
ESBL	Extended spectrum β-lactamase
fT	Free drug plasma concentration
GAS6	Growth arrest specific protein 6
GFR	Glomerular filtration rate
GIT	Gastrointestinal tract
HAP	Hospital Acquired Pneumonia
HD/CVVHD	Hemodiaysis / Continuous Venovenous Hemodialysis
hVISA	Heterogeneous vancomycin intermediate Staph. aureus
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IL	Interleukin
IM	Intramuscular
KPC	Klebsiella pneumoniae carbapenemase
MDR	Multidrug resistant
MIC	Minimum inhibitory concentration
MRSA	Methicillin resistant S. aureus

ODIN	Organ dysfunction and infection
PAF	Prospective audit and feedback
PBP	Penicillin-binding protein
PCR	Polymerase chain reaction
PCT	Procalcitonin
PD	Pharmacodynamics
PK	Pharmacokinetics
REMS	Risk evaluation and mitigation strategies
SOFA	Sequential organ failure assessment
soUPAR	Soluble Urokinase type plasminigen receptor
sTREM-1	Soluble Triggering Receptor Expressed on Myeloid Cells-1
TNF	Tumor necrosis factor
TRCE	Time resolved amplified cryptate emssion
UPAR	Urokinase type plasminigen receptor
UTI	Urinary tract infection
VAP	Ventilator associated pneumonia
VD	Volume of distribution
VISA	Vancomycin intermediate S. aureus
VRE	Vancomycin resistant Enterococcus
WHO	World health organization

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Introduction

Antimicrobial management in the intensive care unit (ICU) represents an ongoing challenge for critical care clinicians. In the ICU setting broadspectrum antibiotic consumption is often unavoidably high, and antimicrobial resistance rates are increasing in many parts of the world ***(Brusselaers et al., 2011).***

Early and appropriate antimicrobial administration is paramount in critically ill patients with suspected or confirmed infection and sepsis ***(Kumar et al., 2006).***

However, in hospitals with high rates of multi-drug-resistant pathogens, appropriate antimicrobial choices are limited to few options like carbapenems, colistin and tigecycline. Moreover, critically ill patients present profound pathophysiological changes, altering the pharmacokinetics of the administered antimicrobials, and failure to achieve target serum concentrations ***(Roberts and Lipman, 2009).***

Antimicrobial resistance is strongly associated with adverse patient outcomes and increased resource utilization ***(Kollef, 2000).***

The effective clinician in today’s hospital environment must utilize all available laboratory and clinical data in the selection of the optimal antibiotic therapy for the critically ill patient. Antibiotics must, be utilized in a manner that ensures not only a maximally favorable outcome for the individual patient but, also, the minimization of subsequent antimicrobial resistance ***(Paterson and Rice, 2003).***

As the microbiological data and evolving clinical information become available, antibiotic therapy must be appropriately adjusted, often allowing a narrowing of its spectrum. Such de-escalation of therapy (i.e, discontinuation of therapy as soon as maximum benefit has been achieved) and assurance of the heterogeneity of antibiotic use, allows for the establishment of balance between the competing tensions of the individual patient and the public health consequences of antibiotic use ***(Craven et al., 2004).***

Perhaps the most important principle is the understanding that any delay in the initiation of adequate antibiotic therapy is potentially lethal. In addition, inappropriately prolonged antibiotic therapy may adversely affect both the individual patient and the more general bacterial ecology. Multiple studies have demonstrated that survival is significantly improved when the initial choice of antibiotics is “appropriate,” defined as indicating that all isolated pathogens are susceptible to more than one of the administered antibiotics***(Craven et al.,2004).***

Considered more broadly, however, both empirical and definitive antibiotic therapy, to be considered appropriate, require timely initiation, administration in appropriate dosages consistent with pharmacokinetic and pharmacodynamic (PK/PD) information, and appropriate alteration of therapy in response to clinical responses and microbiological data as they become available ***(Kollef, 2000).***

Aim of the Work

To achieve prompt and appropriate management of infections in critically ill patients in order to limit mortality and morbidity to adjust antibiotic dosing and be able of therapeutic monitoring to achieve maximal efficacy, decrease the risk of antimicrobial resistance and minimizetoxicity.

Chapter (1)
General Principles of Antimicrobial Therapy

Antimicrobial agents are some of the most widely and often injudiciously used therapeutic drugs worldwide. Important considerations when prescribing antimicrobial therapy include obtaining an accurate diagnosis of infection, understanding the difference between empiric and definitive therapy, identifying opportunities to switch to narrow spectrum, cost effective oral agents for the shortest duration necessary, understanding drug characteristics that are peculiar to antimicrobial agents (such as pharmacodynamics and efficacy at the site of infection), accounting for host characteristics that influence antimicrobial activity and in turn, recognizing the adverse effects of antimicrobial agents on the host (***Surbhi et al., 2011).***

I. Selecting and Initiating an Antibiotic Regimen

An infectious disease diagnosis is reached by determining the site of infection, defining the host (eg, immunocompromised, diabetic, of advanced age)and establishing when possible a microbiological diagnosis. When a patient does not benefit from antimicrobial therapy chosen on the basis of clinical presentation, additional investigations are needed to determine the etiologic agent or exclude noninfectious diagnoses. To optimize an accurate microbiological diagnosis, clinicians should ensure that diagnostic specimens are properly obtained and promptly submitted to the microbiology laboratory, preferably before the institution of antimicrobial therapy. Infectious disease diagnoses also frequently rely on a detailed exposure history. Although the microbiological diagnosis is ideally based on data such as bacterial or fungal culture or serologic testing, frequently the "most likely" microbiological etiology can be inferred from the clinical presentation***(Mandell et al., 2007).***

- **Normal Flora and Endogenous Infection**

Many areas of the human body are colonized with bacteria this is known as normal flora. Infections often arise from one's own normal flora (called an endogenous infection). Endogenous infection may occur when there are alterations in the normal flora (eg, recent antimicrobial use may allow for overgrowth of other normal flora) or disruption of host defenses (eg, a break or entry in the skin). Knowing what organisms reside where can help guide empirical antimicrobial therapy (Figure 1). In addition, it is beneficial to know what anatomic sites are normally sterile. These include the cerebrospinal fluid, blood, and urine ***(Catherine, 2016).***

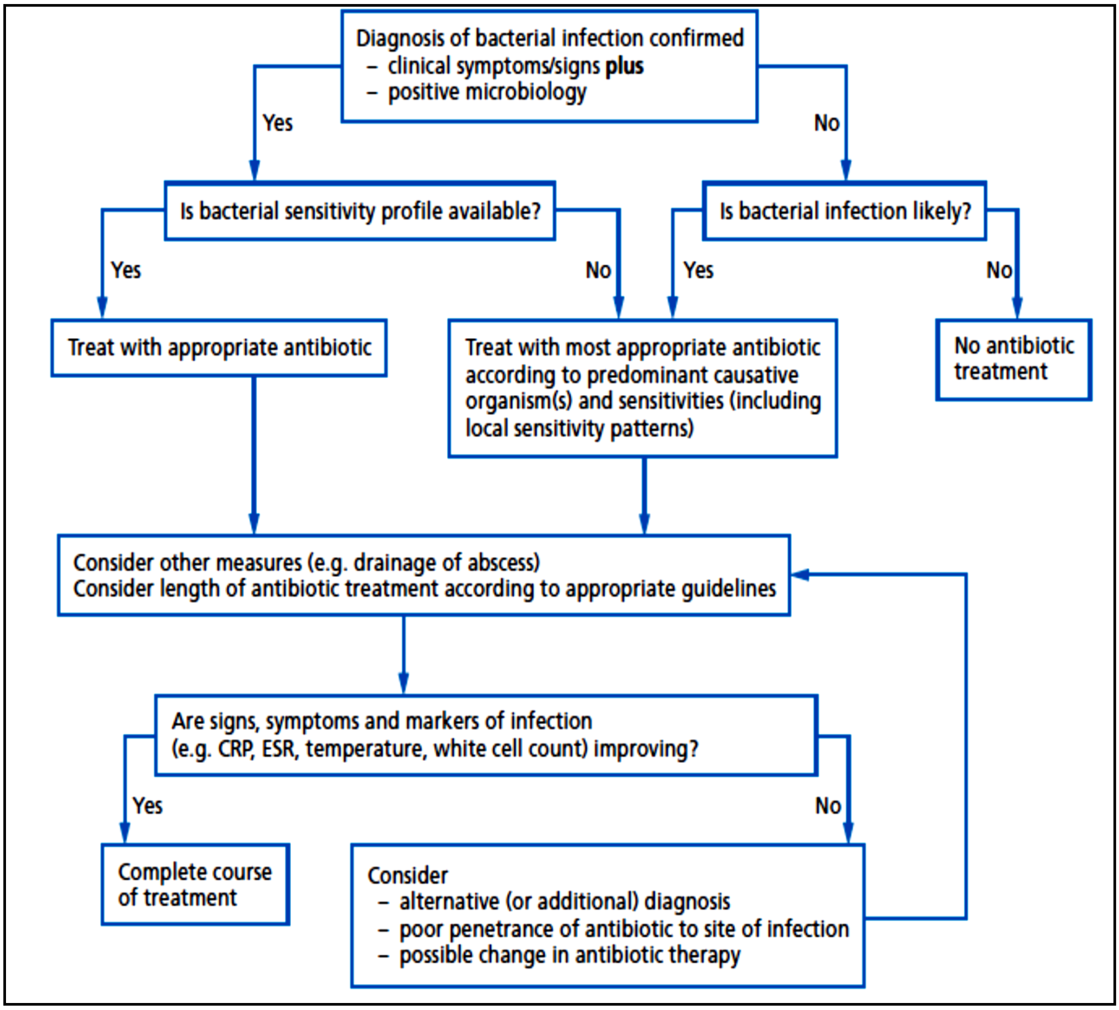

Figure (1): General algorithm for the treatment of bacterial infections *(James et al., 2008).*

- **Determining Colonization versus Infection**

Infection refers to the presence of bacteria that are causing disease (eg, the organisms are found in normally sterile anatomic sites or in nonsterile sites with signs/symptoms of infection). Colonization refers to the