CME article

Empirical antibiotics in the intensive care unit

Souvik Chaudhuri

Email: souvikchaudhuri1207@gmail.com

Abstract

Patients with complex medical and surgical issues are often admitted to the intensive care unit (ICU). In such patients, prompt administration of broad spectrum empirical antibiotics is mandatory to control the infection. Antibiotic therapy should be instituted as soon as possible after the relevant culture specimens of blood, urine, endotracheal secretions or cerebrospinal fluid are sent. Ideally, empirical antibiotic therapy should be initiated within the first hour of admission of patients with suspected sepsis in ICU. While selecting the empirical antibiotic therapy, the patient's clinical history along with the probable source of infection, previous antibiotic history and most likely pathogens according to the prevalence in the particular intensive care unit (ICU) should be taken into account. A delay in initiating empirical antibiotic therapy is associated with a higher risk of progression to severe sepsis, more days on ventilator and ultimately an adverse outcome. However, empirical therapy should be de-escalated as soon as the culture and sensitivity reports are available to the clinician.

Keywords: Catheter-related infections, empirical antibiotics, infections, intensive care unit.

Introduction

Empirical antibiotic therapy is used when antibiotics are given to a patient without prior information of the specific bacteria causing the infection. It is based on the principle that controlling the infection as early as possible significantly reduces both morbidity and mortality. Combination antimicrobial therapy to cover both Gram-positive and Gram-negative organisms is commonly practised as it has been proven that inadequate coverage leads to longer hospital stays and deterioration of patient's condition.[1,2] Antibiotics should be chosen with utmost sagacity, keeping in mind the local epidemiology and resistance patterns. If a wrong choice of antibiotic is made initially, it increases mortality significantly, even if the antibiotic is changed later to an appropriate one after the availability of cultures reports.[3] The presence of critical illness patients necessitates the use of broad spectrum antibiotics frequently.[4]

Souvik Chaudhuri, MD

FNB Trainee in Critical Care Medicine, National Board of Examinations. Apollo Hospitals, Bhubaneswar. Odisha.

Principles of antibiotic therapy

Following principles should be kept in mind while administering empirical antibiotics in the intensive care unit (ICU).[5]

1. Antibiotics should be selected for maximum coverage initially, and then de-escalated later. Overaggressive therapy should be avoided to prevent emergence of antibiotic resistance.
2. We should avoid using the same antibiotics persistently and select astutely depending on the probable organism involved in a particular outbreak.
3. Antibiotic cycling by withdrawing an antibiotic from use for a certain period of time to prevent emergence of resistance against the particular antibiotic is essential.

The source of infection is not always evident in patients who are critically ill in ICU. Empirical antibiotics must be started intravenously (IV) within the first hour of recognition of severe sepsis and septic shock. The probability of survival reduces by 7.6% with every hour of delay in starting antibiotic therapy and thus the saying "time is tissue"

How to cite this article: Chaudhuri S. Empirical antibiotics in the intensive care unit. Ind J Resp Care 2015; 4(2): 651-6.

is apt.[3,6] Most patients admitted to ICU with severe sepsis or septic shock often do not have an obvious focus of infection.[4]

Surviving Sepsis Guidelines recommends the administration of effective IV antimicrobials within the first hour of recognition of septic shock and severe sepsis without septic shock as the goal of therapy. [7] The antibiotics should be selected not only on the basis of patient's clinical condition at that point of time but also after analysing the past infection and antibiotic history, hospital admissions in the recent past and the prevalence of particular organisms in the ICU. Gram-positive bacteria are most commonly incriminated to cause septic shock in hospitalised patients, followed by Gram-negative and mixed bacterial microorganisms. [7]

Recently used antibiotics should be avoided. Clinicians should also be aware of the emerging prevalence of oxacillin (methicillin)-resistant Staphylococcus aureus and resistance to broad-spectrum beta-lactams and carbapenem among Gram-negative bacilli in ICUs. [7]

Consideration should also be given to possibility of fungal infections, and if likely, the particular candida species likely to cause the infection, as the antifungal therapy is different based on the candida species. Candida albicans is mostly responsive to fluconazole, whereas non-albicans Candida such as C. glabrata and C. krusei are fluconazole resistant, and require echinocandin therapy.[7] Certain risk factors for fungal infections such as immunosuppressed or neutropenic conditions, previous prolonged antibiotic therapy, or multiple site infections, should also be envisaged while selecting initial therapy.[7] Empiric antimicrobial therapy must include one or more agents that have adequate coverage against all likely organisms as well as sufficient penetration in adequate concentrations into infected tissues likely to be the source of sepsis.[7] Antimicrobial regimen should be reviewed regularly for possible de-escalation. Decreasing procalcitonin levels or other similar biomarkers may be used as evidence of diminishing infection and therefore may be useful in de-escalation or discontinuation of antibiotics.[7] Combination empirical therapy is also recommended for neutropenic patients with severe sepsis and suspected multi-drug resistant bacteria such as Acinetobacter and Pseudomonas species.

Empiric combination therapy must be given for maximum period of 3–5 days or till specific culture -sensitivity reports are unavailable.

A regimen of empirical antibiotic therapy in ICU in adults with severe sepsis, without an obvious focus of infection but with normal renal function is as follows.[4,8] Antibiotic doses referred are all IV doses with their hourly schedule.

Immunocompetent adult : Not allergic to beta lactams

Pipericillin-tazobactam 3.375 g q 4-6 h (In India 4.5 g) or
Imipenem-cilastatin 500mg q 6 h or
Meropenem 1 g q 8 h or

Immunocompetent adult : Allergic to beta lactams

Levofloxacin 750 mg q 12 h + Clindamycin 600 mg q8 h + Vancomycin 1 g q 12 h (15 mg/kg)

Neutropenia < 500 neutrophils/μL

Meropenem 1 g q 8 h or
Imipenem-cilastatin 500 mg q 6 h or
Cefepime 2 g q 8h

Vancomycin 1 g q 12 h (15 mg/kg q 12 h) should be added if the patient has indwelling central vascular catheter, MRSA is suspected, or if the patient is on chemotherapy.

Empirical antifungal therapy should be added if the patient has haemodynamic instability, febrile neutropenia, has been on broad spectrum antibiotic agents over a prolonged duration but still having severe sepsis or having long term central venous catheter.

Empirical antifungal therapy in severe sepsis is as follows:

Caspofungin 70 mg stat, then 50 mg once daily or
Lipid formulation of Amphotericin B,5 mg/kg/day.

Splenectomy

Cefotaxime 2 g q 8 h or ceftriaxone 2 g q 12 h

IV Drug user

Vancomycin 15 mg/kg q 12 h

Acquired Immune Deficiency Syndrome (AIDS)

Pipericillin-tazobactam 3.375 g q 4-6 h (In India 4.5 g) plus Tobramycin 5 mg/kg q 24 h.

Combination antibiotic therapy is used in critically ill patients due to widespread emergence of multidrug resistance (MDR) organisms. MDR is defined as lack of susceptibility to at least one agent in three or more antibiotic categories.[9] Carbapenem resistant enterobacteriaceae (CRE) has emerged as one of the most notorious groups of MDR organisms.[10]

Combination therapy is useful in empirical regimens when the culprit organism is unidentified, and improves survival in high risk life-threatening infections, but may not be useful in low risk patients.[10]

The six most common MDR pathogens in ICU can be remembered by the pneumonic 'ESKAPE' as Enterococcus faecium, Staphyloccus aureus, Klebsiella pneumoniae, Acinetobacter species, Pseudomonas aeruginosa, Enterobacter species.[4] Combination therapy is practised when MDR organism is suspected where polymicrobial infections are common as in intra-abdominal infections or in the following situations.[3]

1. Antimicrobial therapy in the last three months
2. Present hospitalisation of 5 days or more
3. Persistence of antibiotic resistance in the ICU
4. Chronic dialysis within 30 days
5. Immunosuppressive disease or therapy

Combination therapy ensures that at least one agent will invariably cover the infecting organism. It covers polymicrobial infections such as skin and soft tissue infection, intra-abdominal infections, prevents emergence of resistant organisms and also has synergistic effect.[10]

Treatment options for suspected MDR Gram – negative bacteria.[4,11]

Monomicrobial infection –

Meropenem1 g q 8 h + Tigecycline 100 mg stat then 50 mg q 12 h.

Polymicrobial infection –
Meropenem1 g q 8 h + Vancomycin 1 g q 12 h or
Tigecycline+ Antipseudomonal agent (Carbapenems/Pipericillin-Tazobactam)
MDR Pseudomonas aeruginosa – Meropenem 1 g q 8 h + Colistin 9 million units (mu) stat, then 3 mu q 8 h

CRE – Meropenem + Colistin

OrTigecycline + Colistin

Treatment options for suspected MDR Gram – positive bacteria.
Vancomycin resistant Staphylococcus aureus – Linezolid 600 mg IV q 12 h
Vancomycin resistant Enterococcus - Linezolid 600 mg IV q 12 h
Streptococcus pneumonia – Ceftriaxone 2 g q12 h

Empirical antibiotic therapy in sepsis with an identified focus of infection.[4,12]

Ventilator-associated Pneumonia (VAP)

The diagnosis of VAP requires the presence of a new infiltrate in the chest X-ray with two of the following: Fever, leukocytosis, purulent tracheal secretions VAP can be classified as:

Early: Infection within five days of hospital admission.
Late: Infection after five days of hospital admission.

Empirical therapy for early VAP is recommended using a single agent which can be any one of the following drugs:

Ceftriaxone 1-2 g IV q12 h
Levofloxacin 750 mg IV q12 h
Ampicillin + Sulbactam 1.5-3 g IV q 6 h

Combination therapy is advised for late VAP and when VAP is suspected to be due to a multidrug-resistant (MDR) pathogen.

The drugs used are:

Ceftazidime 1-2 g IV q12 h /Cefepime 1-2 g IV q12 h
Imipenem-cilastatin 500mg IV q 6 h /Meropenem1g IV q 8 h
Piperacillin-Tazobactam 4.5 g IV q 6 h + an Aminoglycoside (Amikacin 1 g IV q 24 h)
Fluoroquinolone + Vancomycin/Linezolid.

Catheter-related Bloodstream Infections (CRBSIs)

The diagnosis of CRBSIs depends on the validation, by culture, of the same organism from the catheter tip and blood culture. A colony count at least

three-fold greater for blood obtained from the catheter hub or a differential time to positivity (DTP) of at least two hours at the catheter hub also indicates CRBSI.[4,13]

CRBSI is treated with the combination of a fourth generation cephalosporin/carbapenem plus vancomycin to cover MRSA.[4,13]

An aminoglycoside is added if Pseudomonas is suspected. The duration of therapy depends on the infecting pathogen. Complicated CRBSI (*i.e.*, CRBSI-associated with suppurative thrombophlebitis, endocarditis) requires at least 28 days of antibiotic therapy.[4,13]

Sepsis due to blood stream infections (BSIs)

BSIs are quite prevalent in ICU and is a major cause of morbidity and mortality worldwide. It is a poor prognostic factor for severe sepsis.[14]

They may be primary when no focus is identified, or secondary to a localised infection at a specific site. Hospital acquired BSIs are associated with increased incidence of Methicillin-resistant Staphyloccocus aureus, Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa.

Following is the suggested empirical antimicrobial treatment of blood stream infections according to source of infection and common pathogens.[14]

Urinary tract infection (UTI) with sepsis/ Urosepsis/catheter associated UTI

Catheter-associated UTIs are diagnosed when bacteriuria (10^3 colony forming units/ml) is associated with symptoms associated with UTI. These infections are often polymicrobial and are caused by MDR pathogens. Catheter has to be replaced if it has been in place for more than two weeks.[4,11,15] If UTI is suspected, empirical treatment may be with

Ceftriaxone 1-2 g IV q 24 h + Gentamycin 80 mg IV q 8 h /Pipericillin-tazobactam/Meropenem

We should not use tigecycline for the treatment of UTI as the penetration of tigecycline into renal tissues is poor.[4] So, the penetration ability of the antibiotics should also be kept in mind while prescribing for a particular infection which is suspected.

Intra-abdominal sepsis

The successful treatment of intr-abdominal sepsis requires a combination of both source control and antibiotics.[16] Common organisms causing intra-abdominal sepsis are Escherichia coli, Pseudomonas aeruginosa, Enterococcus species, Bacteroides species.[4]

Antimicrobials used for the initial empiric treatment of complicated intra-abdominal infections are as follows.

Table 1: Empirical antibiotic therapy based on site and likely pathogens.[4,17]

Site	Likely Pathogens	Suggested empirical antibiotic
Community acquired and health-care associated pneumonia	Streptococcus pneumoniae Staphylococcus aureus	Third generation cephalosporins
Hospital acquired pneumonia	Streptococcus pneumoniae Staphylococcus aureus Pseudomonas aeruginosa Enterobacteriaceae	Piperacillin-Tazobactam + Aminoglycoside+ Linezolid if Methicillin-resistant Staphylococcus aureus suspected.
Ventilator- associated pneumonia	Streptococcus pneumoniae Staphylococcus aureus Haemophilus influenza	Third generation cephalosporins + Aminoglycoside/ Fluoroquinolones
Intra-abdominal sepsis	Gram-negative bacilli Escherichia coli Enterobacteriaceae Enterococcus, Anaerobes Bacteroides	Piperacillin-Tazobactam Meropenem/Imipenem-Cilastatin + Aminoglycoside
Urinary tract infection	Escherichia coli Enterobacteriaceae Enterococcus Pseudomonas aeruginosa	Ceftriaxone/Ceftazidime+ Aminoglycosides

Single agent – Tigecycline IV 100 mg stat, then 50 mg IV q 12 h or Cefoxitin 1 g IV q 8 h – mild to moderate severity
Meropenem 1 g IV q 8 h – high risk or severity

Combination therapy –
Ceftazidime1-2 g IV q 12 h + Metronidazole 500 mg IV q 6 h
Cefepime1-2 g IV q 12 h + Metronidazole 500 mg IV q 6 h

Skin and soft tissue infections[4,15]

Streptococcus species	β-lactam + β-lactamase inhibitor (Tazobactam)
Staphylococcus species	Piperacillin-Tazobactam
Gram-negative bacilli	Carbapenem

Ideally, empirical therapy for life-threatening infections in ICU should cover all likely pathogens. Combination therapy is frequently used as it is not possible to cover all likely organisms with monotherapy. The duration of empirical antibiotic therapy with broad spectrum antibiotics must be optimised and de-escalation is extremely essential after culture reports are available to prevent the emergence of MDR pathogens.

The most common cause for failure of empirical antibiotic therapy is the fact that often the causative organism is resistant to the antibiotic administered.[17] In at least 20% cases in ICU, the administered antibiotic is ineffective against the causative pathogen.[17] In such scenarios, the emergence of MDR pathogens is inevitable, which then increases the mortality rates upto 70%.[18] Therefore selection of empirical antibiotics requires astute clinical judgement and sound knowledge of the microbiological flora persisting in the particular community and ICU.

References

1. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections onpatient outcomes in the ICU setting. *Chest* 2000;**118**:146-55.
2. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. *Mayo ClinProc* 2011; **86**:156-67.
3. Todi S, Chawla R. Antibiotic stewardship. In:Chawla R, Todi S. Editors. ICU Protocols :A stepwise approach. Springer: India. 2012.p. 389-93.
4. Sarin MSK, Vadivelan M, Bammigatti C. Antimicrobial therapy in the intensive care unit. *Indian Journal of Clinical Practice* 2013;**23**:601-9.
5. Paterson DL, Rice LB. Empirical antibiotic choice for the seriously ill patient: Are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive? *Clinical Infectious Diseases* 2003;**36**:1006-12.
6. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. 2008 *Crit Care Med* 2008;**36**:296-327.
7. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock:2012. *Crit Care Med* 2013;**41**:580-637.
8. Munford RS. Severe sepsis and septic shock. In: Longo DL, Kasper DL, Jameson JL, Fauci AS, Hauser SL, Loscalzo J. Editors. Harrison's Principles of Internal Medicine. 18thed. New York. The McGraw-Hill Companies(USA); 2012.p.2223-32.
9. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas NE, Giske CG. Multidrug-resistant, extensively drug resistant and pan drug resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. ClinMicrobiol Infect 2012;18:268-81.
10. Ahmed A, Azim A,Gurjar M, Baronia AK. Current concepts in combination antibiotic therapy for critically ill patients. *Indian Journal of Critical care Medicine* 2014;**18**:310-4.
11. Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS. Treatment options for systemic infection due to selected multi-drug resistant Gram-negative bacilli. In: Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS. Editors. The Sanford Guide to Antimicrobial Therapy 2015. 45th

Edition. Sperryville. Antimicrobial Therapy, Inc. (USA);2015.p.78.

12. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare associated pneumonia. *Am J RespirCrit Care Med* 2005;**171**(4):388-416.
13. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, *et al.* Clinical practice guidelines for the diagnosis and management of intravascular catheter related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;**49**(1):1-45.
14. Timsit JF, Soubirou JF, Voiriot G, Chemam S, Neuville M, Mourviller B *et al.* Treatment of blood stream infections in ICUs.*BMC Infectious Diseases* 2014;**14**:489
15. Textoris J, Wiramus S, Martin C, Leone M. Overview of antimicrobial therapy in intensive care units. *Expert Rev Anti Infect Ther* 2011;**9**(1):97-109.
16. Sawyer RG, Claridge JA, Nathens AB, Rostein OD, Duane TM, Evans HL. Trial of short-course antimicrobial therapy or intraabdominal infection. *N Engl J Med* 2015;**372**:1996-2005.
17. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJC, Baron EJ *et al.* Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Disease Society of America. *Clinical Infectious Diseases* 2010;**50**:133-64.
18. Tamma PD, Cosgrove SE, Maraqakis LL. Combination therapy for treatment of infections with gram-negative bacteria. *ClinMicrobiol Rev* 2012;**25**:450-70.