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'Antibiotic Cycling' – Learn to Avoid Multidrug Resistance!

Dr. Amanat Kang[1], Dr. Manpreet Singh[2], Dr. Dheeraj Kapoor[3]

[1]MD, Senior Resident, [2]MD, FACEE, FIMSA, FCCP, MNAMS, FSASS, Professor

[3]MD, FACEE, FCCP, FSASS, DESA, Professor

Affiliation: Department of Anaesthesia and Intensive Care, Government Medical College and Hospital, Chandigarh, India

Corresponding Author: Dr Manpreet Singh

Department of Anaesthesia and Intensive Care,
Government Medical College and Hospital, Chandigarh, India
Email- manpreetdawar@gmail.com
Ph.: +91-9646121503

Abstract

Antibiotics are often used rampantly in patients in critical care settings. Sepsis, trauma, ventilator associated pneumonias, adult respiratory distress syndrome and multiorgan failure are difficult to treat .Thus, multiple antibiotics are used to treat the infections. The judicious and rationale use of these antibiotics help in decrease of morbidity and mortality of the critical patients.This case hereby presents the judicious use of the antibiotics and its advantages to treat a case.

Keywords: Antibiotics; cycling; Resistant ; morbidity

Introduction

Antibiotic cycling or 'crop rotation of antibiotics' is to regularly substitute antibiotics with same or different class agent with equivalent spectrum.[1] Increase in emergence of multi drug resistant pathogens in critical care units is worrisome in modern practice. Sepsis, ventilator associated pneumonias, adult respiratory distress syndrome and multiorgan failure are difficult to treat and translate into higher mortality and cost leading to increased length of hospital stay.[2] We hereby describe a patient with severe sepsis and multi drug resistant and multiorgan failure managed with appropriate antibiotic therapy and supportive treatment.

Case History

A 29-year-old male presented to GMCH emergency with complaints of pain abdomen for 25 days localized to right hypochondrium and epigastrium which was sudden in onset, gradually progressive and later became diffuse over entire abdomen. There was history of fever documented at 100-101° F associated with chills and it relieved with medication. There was associated decrease in appetite. The patient was a beedi smoker and chronic alcoholic, taking 10 beedi/day for last 7 years and 250 ml alcohol/day and had left them both about a month back.

Investigations included complete blood count, liver and renal function tests, serum electrolytes, arterial blood gases were sent. Total leucocyte count had risen from 8000 to 18000/dl over two days. Arterial blood gases (Table-1) revealed acute respiratory acidosis; arterial pH- 7.242, with acute rise in arterial PCO^2 to 64.2 mmHg, arterial PO^2 was 90 mm Hg while breathing room air and arterial oxygen saturation was 92.7% and bicarbonate levels,ultrasound abdomen and contrast enhanced computed tomography (CECT) chest and abdomen. Ultrasound Abdomen showed signs of subcapsular collection of 14.3 x 13.6 cm in size in right lobe of liver with liquified contents. In CECT; findings of ultrasound were corroborated and it showed a right liver abscess of 12x8 cm size. In the chest- the CT findings showed right sided massive pleural effusion with estimate of more than 450 ml pleural fluid and showed significant pleural separation. Provisional diagnosis of ruptured liver abscess with right sided massive pleural abscess was formed and planned for pigtail insertion.

On post-operative day-1, he developed sudden dyspnea and desaturation. Chest X-Ray (Figure 1 A-C) showed right cardiopulmonary angle blunting with pleural effusion and pleural separation of 1.4 cm was seen. Right ICD 32 FR was inserted, and 250 ml serous fluid was drained. Patient was then shifted to ICU for

management of persistent respiratory distress.

Patient was admitted in the ICU in view of sudden onset of dyspnea, falling oxygen saturation. He was initially managed using non-invasive ventilation via NIV mask with continuous positive pressure ventilation. After initial resolution of symptoms, his condition deteriorated again with sudden onset respiratory distress and because of which he was later intubated and kept on Synchronized intermittent mandatory ventilation (SIMV)- Pressure controlled mode of ventilation.

He was given multiple weaning trials over a period of a month but unfortunately due to failure of weaning, eventually, he was tracheostomized and required increasing mechanical ventilator support. During his prolonged 45-day stay in the ICU, the patient developed ventilator associated pneumonia following which he went in fulminant sepsis.

Multidrug resistant Acinetobacter was isolated from blood, abscess, tracheal cultures and Klebsiella pneumoniae in urine culture. The resistance potential of the pathogens was alarming with the organism and antibiotic cycling regime with Injection Polymyxin B and Injection Cefoperazone-Sulbactam was started. Henceforth, drastic resolution of septicemia was seen that also translated to pathogen eradication in cultures. Patient was decannulated and discharged from ICU after 30 days.

Discussion

Antibiotic resistance develops naturally in bacteria, but it is accelerated by the selective pressure produced by widespread antibiotic use. The World Health Organization (WHO) said in 2014 that primary bacteria species such as E. coli, Klebsiella pneumoniae, and Staphylococcus aureus had considerable antibiotic resistance in at least 50% of isolates (WHO, 2014). More people might face life-threatening resistant bacterial infection if no proper steps were taken, according to the WHO.[5] Many circumstances, such as long-term hospitalization, can make chronically ill individuals more prone to infection with drug-resistant bacteria. Furthermore, other factors like invasive surgery, immunodeficiency and endemic microbial flora, poor asepsis, failure in barrier nursing, all predispose to developed of ICU sepsis.

Hand hygiene, chlorhexidine baths, limitations of ineffective medications, treatment duration, antibiotic-cycling strategy, and antibiotic mixing strategy are few of the measures that have arisen to combat the establishment or spread of antibiotic-resistant bacteria. A specific antibiotic is empirically administered as a preferred option for a predetermined period in patients whose pathogenic microorganisms are unknown in the cycling method (also known as rotation strategy).[7] After that time, another antibiotic, generally from a different class of antibiotics, becomes the first line of defense for all patients who require antibacterial therapy. In future patients, the first-line antibiotic will be switched using the mixing strategy's predetermined regimen.[6]

When compared to non-interventional (or baseline period) antibiotic prescriptions, when the attending physician chooses the antibiotic for empirical use, the two measures are thought to improve antibiotic variety. Christiane and colleagues discovered that switching structurally similar medications helped restore resistant bacteria's sensitivity to antibiotics.[8] "Cycling," or changing the primary antibiotic in a ward or hospital on a regular basis. The second is "mixing," which involves randomly assigning patients to various antibiotics so that numerous antibiotics are used in about equal quantities at any one time. It was seen that when bacteria identified during the baseline period showed a low average number of resistance genes to the medications used in the cycling regimen, clinical cycling lowered the number of overall infections.[9]

In this case, after switching therapy to different drugs of same class that is switch over from Colistin-Polymyxin E against which the organism was resistant; to Polymyxin B proved effective in controlling septicemia in the patient resulting in drastic recovery clinically as well as in terms of laboratory evidence. Cycling may not directly lead to reduced resistance among ICU pathogens, but it may help in decreasing the selection pressure that drives resistance in pathogens.[3] Cycling can be used in ICUs and areas with high risk of resistance in empiric stage.[4] The cycling regime should be institutionalized as per prevalence and is to be strictly followed to achieve maximum benefit.[4] The cycling practice serves to keep the total drug consumption below the critical level that may cause resistance against that drug.[4] It is pertinent to identify similar resistance patterns among drugs and

not to reuse any drug with same resistance pattern for example; cycling between different aminoglycosides can be done as their mechanism of resistance is different but this cannot be done with Beta lactams or fluoroquinolones.[4] Antibiotic 'crop rotation' also reduces the cost burden for the patient and resource conservation for the hospital.[2] This works optimally if infection control measures are also strictly followed such as hang hygiene, barrier nursing.[3] However, no clear benefit of using cycling as a measure of reducing the resistance among various organisms across various hospitals has been noted. It has been shown as a useful practice in certain institutions keeping in cost and resource benefit and added advantage of mitigating selection pressure by withdrawing indiscriminate usage of antibiotics.[3]

The difficulty of implementing and ensuring compliance with the protocol is the first challenge that limits such a programme. It can be done in the community or in an academic environment with the support of a pharmacist, nurses and appropriate knowledge teaching.[10] The duration and medications to use for antibiotic cycling are yet unknown. For suspected Gram-negative infections in the ICU, Evans et al. compared dual antibiotic rotation (DAR) with single antibiotic rotation (SAR). Empirical cycling regimens for pneumonia and peritonitis were included in the DAR. They discovered that SAR was related with enhanced resistance among Gram-negative bacteria as compared to DAR, albeit data are difficult to interpret due to low protocol compliance (71%) during SAR. [11]

Before using these regimens, any negative consequences of antibiotic cycling must be evaluated. During the research period, antibiotic cycling is not always successful in preventing the establishment of antibiotic resistance. Van Loon et al. studied the acquisition of resistance to three antibiotics during a cyclic protocol and discovered that bacteria were less susceptible to levofloxacin and piperacillin-tazobactam during cycling periods of exposure to each of these antibiotics, which was likely due to the antibiotic's homogeneous pressure, but they did not find a significant increase in cross-resistance between antibiotics that were not on the cycle. An increase in the number of Gram-positive (enterococcal) infections has been linked to cycling.[12]

Conclusion

Antibiotic cycling should be incorporated into the ICU care strategies to reduce antibiotic exposure and consequentially reduce the emergence of antimicrobial resistance in due time with diligent practice in congruence with other asepsis measures. Institutional cycling protocols can be made depending upon local epidemiology and prevalence of resistance. It requires strict adherence from all team members and becomes a pivotal part of antibiotic stewardship protocols. There are no recommendations for order, duration or outcomes to

Figure 1 (A- C) shows X-Ray chest of day 1 and successive days



(A) (B) (C)

Figure 2 shows all the investigations of the patient with antibiotics that were administered at different moments of time

Antibiotics	Inj piperacillin-tazobactam 4.5 gm x 6hrly Inj metronidazole 200mg x 8 hrly	Inj Linezolid 600mg x 8 hrly Inj Meropenem 1gm x 8hrly Inj Fluconazole 200mg x 12 hrly	Inj colistin 9mu loading f/b 3 mu 8hrly Inj Linezolid 600mg x 8 hrly Inj Fluconazole 200mg x 12 hrly	Inj cefoperazone-sulbactam 1.5gm x 8hrly Inj polymyxin b 5 lakh units once daily
Blood	Candida spp	sterile	sterile	sterile
Tracheal	Acinetobacter – sensitive to Imipsnem/meropenem/tetracyclines	sterile	Acinetobacter – MDR, resitant to linezolid/colistin	sterile
Urine	sterile	sterile	Klebsiella- sensitive to fosfomycin	sterile
HB	10.0	9.5	8.1	9.5
TLC	13.4	12.26	15.5	8.94
NEUTROPHILS	84.6	74.2	80	56.4
LYMPHOCYTES	11.8	16.5	16.1	27.5
BASOPHILS	4.6	7.8	2	9.1
EOSINOPHILS	2.4	1.4	2	6.8
MONOCYTES	2.0	0	0	0.0
PLATELET COUNT	139	445	245	214
TEMPERATURE (^{0}F)	101-101.4^{0}F	afebrile	100.7-101.2 ^{0} F	afebrile
P/F ratio	116	216	255	305

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