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Increasing Resistance to Vancomycin; A Myth Or Reality -A Review

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Abstract
Vancomycin is used against certain infections caused by MRSA, for patients allergic to penicillin and endocarditis. Adverse effects of vacomycin include erythma, pseudomembranous colitis, and skin rash. Vancomycin is also used empirically in various hospitals. Off label use is also associated with vancomycin. Use of vancomycin in hospitals reduced prominently due to its increasing resistance and inappropriate prescribing. Supervision under pharmacist played important role in decreasing the resistance which is caused by vancomycin utilization in those hospitals which do not have pharmacist based vancomycin management system
Keywords: *MRSA, endocarditis, off-label*

INTRODUCTION

Vancomycin was first isolated by Dr .E. C. Kornfield from a sample of soil from the jungle of Borneo in discovering the agents against staphylococci and proves to be safe and effective when administered to patients with staphylococcal infections. [1].

It is a glycopeptide antibiotic used for the treatment of gram-positive bacteria. In last 20 years its use became more due to prevention against methicillin resistant strains. [2]

Elimination half life of vancomycin is from four to six hours. Mean plasma clearance is 0.058 L/kg/hr and mean renal clearance is 0.048 L/kg/hr. It is indicated for the treatment of penicillin-allergic patients, used in infections resistant to other antibiotics, in endocarditis, and bone infections. Vancomycin is a lyophilized powder reconstituted before use .The pH ranges from 2.5 to 4.5. It should be administered intravenously. [3][4][5]

Vancomycin shows adverse effects i.e. pseudomembranous colitis, sore throat, fever, chills, hives, skin rash, itching, difficulty breathing or swallowing, red neck and tinnitus etc. [6]

Inappropriate use

A study was conducted in order to check the vancomycin utilization in pediatric hospitals either it was consistent with the guidelines according to the centers for disease control. Inappropriate use of vancomycin was found in most of the patients which suppressed significantly by conducting educational programmes. These education relevant programmes about vancomycin utilization were important and should be continued. [7]

Therapeutic use of vancomycin considered to be matched with the guidelines but its total use decreased. So after these guidelines inappropriate prescribing of vancomycin was significantly increased, as compared to those patients who were utilizing it by inappropriate prescribing by physicians that result in prolonged duration of course. By introducing educational programmes and some therapeutic guide lines, reduced its utilization in hospitals that were designed to restrict its inappropriate us in concern with VRE awareness programmes and its implementation for patient care. [8]

Empiric use

There are many drugs and procedures influencing the risk of gram negative bacteremia among the children who are victim of bacteremia. Main and strong cause of gram negative bacteremia is empiric use of vancomycin. Its use, in children who are suspected of bacteremia, is safe and may not be warranted. [9]

Vancomycin is initiated to use in patients who has certain compromised host factors. In some children's hospitals, only few resistant organisms were isolated at the time after vancomycin prescribing. Efforts are done to improve the empiric use of vancomycin there. To decrease length of therapy and days of therapy before laboratory results may lessens the exposure toward vancomycin. [10]

The use of vancomycin has become an issue as part of initial antibiotic therapy of febrile neutropenic patients. Some studies support it while some are against it. In a prospective study it has been shown that vancomycin is not an important component of

the initial empiric treatment regimen for patients receiving ceftazidine. [11]

Off- label use

Patients hospitalized in tertiary care units must receive at least one medication which is outside the FDA regulations. Frequency of off-label use was observed. Despite this frequency we cannot determine the treatments which are safe or unsafe to the patients. [12]

Many drugs used for children mostly are unlicensed or used off-label. Various risks are associated with this off-label use such as increased risk of ADR's and various medication errors. These risks are most likely to occur in newborns and infants. Inspite of various initiatives taken to promote awareness there is still a high percentage of off-label drugs used in neonatology. [13]

Restriction policies

Most Of the hospitals showed a restriction policy about use of antimicrobials. Some of them restrict the use of vancomycin while others restricted not only vancomycin but also other antibiotics such as amphotericin B and cefotaxime. Out of these policies some required provision of justification from clinician while ordering that restricted antibiotic and some required the improvement of order by physicians before it was filling up by pharmacist. Some of the policies clarified the stop orders for those antibiotics which are specified i.e. vancomycin: 72 hrs. Only few policies proposed therapeutic alternate to the prescribed antibiotics. Half of them specified the presence of pharmacy and therapeutic committee. [14]

RESISTANCE IN BACTERIAL INFECTION

MRSA which is known as "methicillin-resistant Staphylococcus aureus", are strains of the bacterium which are resistant to beta-lactam antibiotics. It has shown resistance not to beta-lactam antibiotics, but also to different classes of antibiotics .MRSA is resistant to antibiotics, predominantly found to vancomycin-resistant. [15]

After description of VRE (vancomycin resistant enterococci) in late 1980's, the emergence of S.aureus with decreased vancomycin susceptibility was predicted. This was the first description of VISA (vancomycin intermediate S.aureus). The expected mechanism of vanA gene was latterly observed in 2002; i.e. plasmid-mediated transfer from enterococci to S.aureus, which was preliminary introduction of VRSA (vancomycin resistant S.aureus). [16][17][18]

Although vancomycin adverse effects are greatly reduced now a day using new preparations but a number of problems remain. Adverse effects with use of teicoplanin such as nephrotoxicity, found to be much less than vancomycin, although they have same efficacy. [19]

VRE BSI is a risk factor of VRE as a result of VRE colonization. Development of VRE BSI in patients was calculated by comparing it with the patients who did not develop VRE BSI. Further more risk factors of only BSI among colonized patients were infection seen at body and exposure of it to vancomycin, while for death these factors were VRE BSI and immunosupperession [20]

It has become clear that vancomycin is losing its potency against S.aureus including MRSA. Serious infections caused by MRSA in the laboratory are not responding well to vancomycin. This is shown by increased mortality seen with MRSA infection and markedly weekend efficacy of vancomycin caused by vancomycin heteroresistance in S.aureus. So the definition of vancomycin susceptibility requires more scrutiny when applied to serious MRSA infection such as bacteremia. [21]

PREVENTION OF RESISTANCE

With the growing resistance of high level enterococcal resistance to penicillin and amino glycosides, vancomycin resistance in enterococci has coincided; thus it presents a challenge for physicians who treat patients suffering from infections caused by the microorganisms.[22][23] Choice for treatment is limited to those antimicrobials or experimental compounds that have unproven efficacy. [24][25]

A supervised and efficient intervention against infection control, including the collection of surveillance cultures and separating the infected patients, can suppress or reduce the spread of VRE in the health care system of a community. [26]

Strategies for control of infection include risk assessment and developing methods for controlling MRSA and VRE rates in ICU's; developing compliance toward hand hygiene, guaranteeing adequate environmental cleaning. [27]

GUIDELINES FOR VANCOMYCIN UTILIZATION

Practical guidelines were developed in order to strengthen vancomycin utilization. Patients taking vancomycin previously had shown marked improvement. The guidelines included

appropriateness of use. These guidelines serve as educational tool and provide surveillance to patients receiving vancomycin. [28]

In addition, the pharmacodynamic properties of vancomycin had not been evaluated at the time these recommendations were made. Because the AUC/MIC has been found to correlate with efficacy in experiments conducted with in vitro or animal models, this evidence has led some clinicians to question the relevance of monitoring peak serum vancomycin concentrations. [29]

Assessment of therapeutic monitoring of vancomycin treating staphylococcus aureus was done through practical guidelines. Basic premise of monitoring serum vancomycin concentration depends upon need to get concentration above MIC, and to avoid certain adverse effects such as ototoxicity and nephrotoxicity. A significant AUC/MIC has been developed on basis of animal and human data, to achieve this significant value larger dose of vancomycin are required. This increase in dosage is the risk of adverse events which are experienced with vancomycin administration. [30]

PHARMACIST MANAGED VANCOMYCIN THERAPY: ROLE OF PHARMACIST

Hospitals that lack pharmacist-managed vancomycin therapy suffered from increased death rates lengthen hospital stay; increased cost of therapy, increased laboratory charges, greater hearing loss, a high account of renal impairment, also the death rate of patients was higher as compared to those hospitals which had pharmacists to cope with these problems and complications. So all the major problems regarding health of patients, which were hospitalized and receiving vancomycin therapy, improved their condition and get health benefits only by applying pharmacist managed vancomycin therapy. [31]

Thus role of pharmacists there to check prescription orders of vancomycin and to suggest therapeutic alternates, when it did not comply with the limits for vancomycin utilization. Pharmacist or physicians assessed those prescription orders that required more clinical attention to control infectious disease [32]

Many years ago pharmacist did not question why a drug was prescribed and either it was used for unapproved by FDA, but now pharmacists realize that they must ask why a medication prescribed and either it was used appropriately. [33]

CONCLUSION

It is becoming clear that vancomycin is losing its potency against *S. aureus*, including MRSA. Serious infections due to MRSA defined as susceptible in the laboratory are not responding well to vancomycin. This is determined by increased mortality seen in patients with MRSA infection and markedly weekend efficacy caused by vancomycin heteroresistance in *S. aureus*. Therefore, it shows that definition of vancomycin susceptibility requires further investigation and exploration when applied to serious MRSA infections, such as bacteremia.

Vancomycin use guidelines play an important role as these provide surveillance to patients.

Acquired resistance to vancomycin therapy is becoming common. Vancomycin has certain side effects, as every other drug, so its use was restricted in most hospitals and also the inappropriate use of vancomycin was there but that can be minimized under vigilant supervision of a pharmacist. Pharmacists also must realize that a prescription for an off-label use does not produce an automatic refusal to dispense.

Initiatives to decrease length of therapy by decreasing the number of surgical prophylaxis doses and days of therapy before laboratory results may decrease vancomycin exposure.

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