Original Research Article

A study on ESKAPE pathogens the bad bug with no drug

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Abstract

Introduction: ESKAPE pathogens include Enterococcus faecium, Staphylococcus aureus, Klebsiella pnuemonia, Acienetobacter baumanii, Pseudomonas aeruginosa and Enterobacter species. Currently all these organisms are the main cause of hospital infections globally and they have the property to effectively escape the effect of antibacterial drugs. Unstoppable success of these superbugs will lead to unwinnable war. The success of these pathogens is mainly because of the mutations, modifications of LPS. As the crisis for the antibiotic resistance continues to grow, the latest IDSA (infectious disease society of America) "Bad Bugs, No Drugs" reports the urge for new antibiotics in the research and development pipeline and proposes steps to tackle the shortage. **Objective:** The aim of the study was to characterize the antimicrobial resistance in ESKAPE pathogens isolated from 330 culture positive clinical sample. **Method:** Antibiotic resistance was determined by VITEK 2 and manual method was done on Kirby baurer method. MIC was determined by VITEK 2 and E-Test according to CLSI guidelines. **Result:** Out of the total cases 63 percent of the culture has ESKAPE pathogens. Except for S. aureus multidrug resistance index of ESKAPE pathogens revealed on increasing trend. **Conclusion:** ESKAPE pathogens are commonly identified in alarming frequency and knowledge of antimicrobial resistance will be aided for empirical treatment.

Keywords: ESKAPE pathogens, Multi drug resistance, Infections, Antibiotics

Introduction

Nosocomial infections are caused by a variety of organisms, including bacteria, fungi, viruses, parasites, and other agents. Infections can be derived from exogenous or endogenous sources and are transferred by either direct or indirect contact between patients, healthcare workers, contaminated objects, visitors, or even various environmental sources. A survey of hospital-acquired infections (HAI) in the United States in 2011 reported a total of about 722,000 reported cases, with 75,000 deaths associated with nosocomial infections [1].

A second study conducted in 2002 estimated that when taking into account all types of bacterial infections, approximately 1.7 million patients suffered from HAIs, which contributed to the deaths of 99,000 patients per year [2]. From the last decade antibiotic resistance bacteria continue to be a challenge to the physicians. The growing numbers of antimicrobial-resistant pathogens, which are increasingly associated with nosocomial infection, place a significant burden on healthcare systems and have important global economic costs. There is steady increase in the curve of resistance development among the Gram Positive and Gram negative pathogens that cause infection in the hospital and community [3]. IDSA (Infectious Disease Society of America) reported these as the ESKAPE pathogens Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumanii, Pseudomonas aeruginosa, Enterobacter species) these are responsible for the majority of hospital acquired infections and they also effectively "ESCAPE" the effects of antibacterial drugs. Data from the centre for disease control and preventions show a rapid increase in the rate of infection due to Methicillin– resistant S.aureus (MRSA), Vancomycin– resistant E.faecium, and fluoroquinolone-resistant P.aeruginosa [4].

There has been an increase in reporting of infections caused by Multi Drug resistant organisms, thereby limiting the choice of effective antimicrobial agents available to clinicians. The addition of aging population and frequent referral of patients to acute care facilities also add for the prevalence of multi drug resistant organisms.

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Multidrug resistant (MDR) organisms especially gram-negative bacilli have become a pivotal of long term care facilities in the hospital and vice-versa [5]. In contemporaneous the aging population and frequent referrals of patients from and to acute care facilities also add as the reservoir for the MDR [3]. The unstoppable success of these SUPERBUGS will lead to the crisis called "UNWINNABLE WAR" [6]. Data from the National Nosocomial Infection Surveillance (NNIS) System (2003 versus 1998-2002) showed that, in the nine selected antimicrobial- resistant pathogens associated with nosocomial infections in intensive care unit patients, there is increase in the prevalence of resistance to third-generation cephalosporins (either ceftriaxone, cefotaxime or ceftazidime. The emergence of resistant organisms to other drugs serves to bring the therapeutic importance of polymyxins such as colistin. No new antibiotic classes against multi drug resistant Gram-negative bacteria are expected to be commercially available within the next several years. Even more worrying, the emergence of resistance to colistin, the only available active antibiotic against multidrug-resistant Gram-negative bacteria [7].

Our therapeutic options for these pathogens are so extremely limited that clinicians are forced to use older, previously discarded drugs, such as colistin, that are associated with significant toxicity and for which there is a lack of robust data to guide selection of dosage regimen or duration of therapy [1].

The growing number of elderly patients and patients undergoing surgery, transplantation, and chemotherapy and dramatic increases in population in neonatal intensive care units will produce an even greater number of immunocompromised individuals at risk of these infections [2].

Antimicrobial resistance pattern of ESKAPE Pathogens- Antimicrobial resistance genes may be carried on the bacterial chromosome, plasmid, or transposons [8].

Mechanisms of drug resistance fall into several broad categories, including drug inactivation/ alteration, modification of drug binding sites/ targets, changes in cell permeability resulting in reduced intracellular drug accumulation, and biofilm formation [11–12].

- Drug Inactivation or Alteration
- Modification of Drug Binding Sites
- Reduced Intracellular Drug Accumulation
- Biofilm Formation

Materials and Methods

Type of study: The research done is an applied, analytical type of case study research. The samples were collected by direct observational method.

To avoid multiple entries from a single patient, only the first positive MDR culture for a given patient was included. The patients Identification number, age, sex, type of sample, recent significant treatment history with antibiotics, provisional diagnosis, duration of hospital stays and any other history related to the research was collected in observational design from the adminis-trative data base.

All the clinical samples received for Bacteriological culture in Microbiology section of the laboratory were processed and analyzed for the research. All clinical samples were inoculated in the respective media and methods as per standard guidelines and incubated. The blood culture bottles will be placed in Bac T/ Alert 3 D and the positive culture bottle will be processed by Grams stain and in routine bacteriological media for inoculation and incubated. All the ESKAPE pathogens isolated from all the clinical samples will be subjected for determining the MIC and Sensitivity by Vitek 2 and Kirby Bauer method as per CLSI.

Isolates that were collected within 2 days after admission were considered to be acquired prior to the hospitalization, or non-nosocomial; Isolates acquired after day 2 were considered nosocomial. Total of 1000 samples were included in the study after the ethical committee approval by the institution.

Inclusion criteria: All culture positive samples

Exclusion criteria: Any organism isolated from the same patient with same sensitivity

Statistical method: All the ESKAPE PATHOGENS isolated samples where included in the study (probability sampling).

Results

In total 1000 samples, 430 culture positive clinical sample. Among 430 Positive samples, 271 pathogens were identified as ESKAPE pathogens. The Enterococcus faecium accounted for 28, 72 samples isolated MRSA. In 64 and 39 samples Pseudomonas aeruginosa and Acinetobacter were isolated respectively.46 samples isolated Klebsiella pneumonia and 22 isolated Enterobacter.

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The samples which were resistant to more than 3 groups of antibiotics were considered as Multidrug Resistant Organisms (MDRO). Out of 1000 samples 6.9% were MDR.

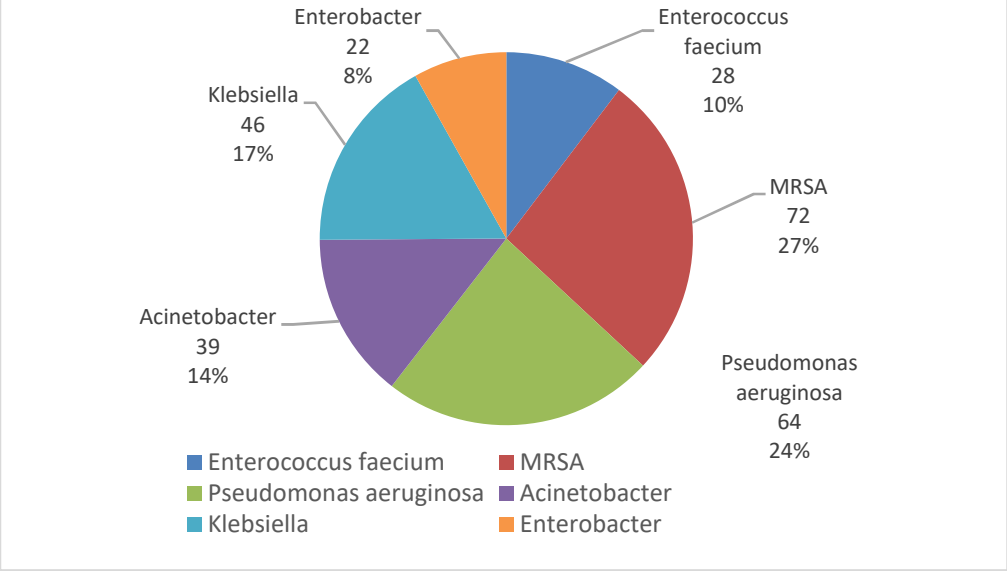

Figure-1: Distribution of ESKAPE

Discussion

The importance of ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) to the establishment and promotion of antimicrobial resistance in hospitalized patients was first recognized in a 2008 publication by Rice [13]. The morbidity and mortality associated with Gram-negative ESKAPE pathogens is particularly concerning as new antimicrobial agents, with spectra of activity that reliably encompass multidrug-resistant and pan-resistant Gram-negative isolates, have not appeared in as timely a manner as hoped [14] and nosocomial infections remain a constant concern for patient health, particularly for critically ill inpatients as well as for patients requiring placement of invasive devices or surgical procedures.

ESKAPE pathogens frequently present clinicians with serious therapeutic dilemmas because of their complex resistance profiles [13,15]. Given that ESKAPE pathogens account for a majority of the antimicrobial resistance encountered in the nosocomial setting [13-15] surveillance describing the resistance profiles of these organisms provides an important gauge of regional antimicrobial resistance present in hospitalized patients. The bacteria have the ability to rapidly gain resistance along with overuse and misuse of antibiotics, we are now living in the age of multidrug resistant (MDR) and Pan-drug resistant(PDR) bacterial pathogens leading to the situation like the pre-antibiotic era.the development of number of antibacterial in phase 2or 3 clinical development have left to a disappointment so far, this leads to the Danger in treating the Gram - negative bacilli. Ph RMA have although reported 388 medicines and vaccines in testing, out of which only 83 was little significant to antibiotics and only less than 83 antibiotics are available for advanced clinical treatment. Only 5 major pharmaceutical companies- Glaxo Smith Kline, Novartis, Astra Zeneca, Merck, and Pfizerstill have active antibacterial discovery programs, and the number of antibacterial trials registered at Clinical Trials. gov decreased between 2005 and 2007 [16,17]. This is due to the improper use of antibiotics and the free availability of antibiotics to public.

We live in a period where even though people are well educated they refuse to consult a Doctor for the disease and purchase the antibiotics from the pharmacy counter freely without a valid physician prescription. One more consent for the development of MDR bacteria is that most of the reserved antibiotics have now come to the market for day today use and now we don't have a reserve antibiotic to take care of the resistant bugs. Most of the broad-spectrum antibiotics have now come in simple tablet and injection form adding to vow of MDR bacteria. The patients too donot take the antibiotics as prescribed by the physicians and they discontinuetheir course leading to the development of MRD. The increased burden of antimicrobial resistance has been due to the increased days of stay in hospital, mortality, and the cost of Hospital care [10]. Of more recent concern is the emergence of MDR Gram negative bacilli (GNB) in long term care facilities;

several studies have shown that the carriage prevalence of MDR GNB has far exceeded that of methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin- resistant enterococci (VRE) [4]. Acinetobacter baumannii, Pseudomonas and Entero bacteriaceae were considered to be Pan drug resistant (PDR) if isolates were resistant to all classes of anti pseudomonalagents [11,12].

There is some small sign of success as certain drugs like Doripenem is been approved.There has been an increase in the potency of this drug against P. aeruginosa with positive result in phase 3 studies for teavancin, ceftobiprole and cethromycin are encouraging. And recently there has been several drugs in the Phase 2 trial which is promising.

We found evidence of potentially increased interest among large pharmaceutical companies in the recent announcements of collaborations between Mpex Pharmaceuticals and GlaxoSmithKline, Novexel and Forest Laboratories, and Protez and Novartis [18,19,20].

This study focuses on the resistance pattern of the most commonly isolated MDR organism and emergence of antimicrobial stewardship to be followed by the physicians. The slowness to market of novel antimicrobial agents with reliable activity against Gram-negative ESKAPE pathogens suggests efforts to identify optimal strategies for infection control and prevention as well as antimicrobial use/stewardship need to intensify, especially in ICUs [15].

Ongoing surveillance data is crucial as it provides guidance for empiric antimicrobial agent selection by identifying the most common pathogens and their antimicrobial susceptibility profiles. In addition to ongoing surveillance efforts, data on the impact of clinical interventions to decrease the prevalence of resistance are required.

As resistance to parenteral broad-spectrum antimicro-bial agents continues to increase, combination empiric therapies for infections potentially attributable to Gram-negative ESKAPE pathogens may become routine and will be driven by surveillance initiatives [21].

The limitation of this study was that this study was done to a small number of population in our country. Furthermore, it was difficult to follow the patient as patients frequently move between wards during a single admission. The publication of such surveillance study data describing regional antimicrobial susceptibility/ resistance rates in clinical isolates of Gram-negative ESKAPE pathogens is essential to stimulate antimicrobial stewardship efforts as well as to identify emerging resistance trends and geographic diversity over time.

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References

1. Giske CG, Monnet DL, Cars O, Carmeli Y; ReAct-Action on Antibiotic Resistance. Clinical and economic-impact of commonmultidrug-resistantgram-negativebacilli. Antimicrob Agents Chemother. 2008 Mar; 52 (3): 813-21. Epub 2007 Dec 10.

2. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis. 2008 Apr 15;197(8):1079-81. doi: 10.1086/533452.

3. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, Bartlett JG, Edwards J Jr; Infectious Diseases Society of America. The epidemic of antibiotic-resistantinfections: a call to action for the medicalcommunity from the Infectious Diseases Society of America.Clin Infect Dis. 2008 Jan 15; 46 (2): 155-64. doi: 10.1086/524891.

4. National Nosocomial Infections Surveillance System Report, data summary from January 1992 through June (2004) issued October 2004. Am J Infect Control 2004; 32:470-85.

5. Lim CJ, Cheng AC, Kennon J, Spelman D, Hale D, Melican G, Sidjabat HE, Paterson DL, Kong DC, Peleg AY. Prevalence of multidrug-resistant organisms and risk factors for carriage in long-term carefacilities: a nested case-control study. J Antimicrob Chemother. 2014 Jul; 69 (7):1972-80. doi: 10.1093/jac/ dku 077. Epub 2014 Apr 7.

6. Federico Perez, Andrea M. Hujer, Kristine M. Hujer, Brooke K. Decker, Philip N. Rather, and Robert A. Bonomo. Global Challenge of Multidrug-Resistant Acinetobacter baumannii ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. (2007), p. 3471–3484 Vol. 51, No. 10 0066-4804/07/$08.000 doi:10.1128/ AAC. 01464-06 Copyright © 2007, American Society for Microbiology.

7. Poudyal A, Howden BP, Bell JM, Gao W, Owen RJ, Turnidge JD, Nation RL, Li J.In vitropharmaco-dynamics of colistinaga instmultidrug- resistant Klebsiella pneumoniae. J Antimicrob Chemother. 2008 Dec; 62 (6): 1311-8. doi: 10.1093/jac/dkn 425. Epub 2008 Oct 15.

8. Magill S. S., Edwards J. R., Bamberg W., et al. Multistate point-prevalence survey of health care-associated infections. The New England Journal of Medicine. 2014; 370 (13):1198–1208. doi: 10.1056/ nejmoa 1306801. [PMC free article] [PubMed] [Cross Ref]

9. Klevens RM, Edwards JR, Richards CL Jr, Horan TC, Gaynes RP, Pollock DA, Cardo DM. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep. 2007 Mar-Apr;122 (2): 160-6.

10. Giedraitienė A, Vitkauskienė A, Naginienė R, Pavilonis A. Antibiotic resistance mechanisms of clinically important bacteria. Medicina (Kaunas). 2011; 47 (3): 137-46.

11. Wright G. D. Bacterial resistance to antibiotics: enzymatic degradation and modification. Advanced Drug Delivery Reviews. 2005; 57 (10): 1451–1470. doi: 10. 1016/j. addr. 2005. 04. 002. [PubMed] [Cross Ref]

12. Wilson DN. Ribosome- targeting antibiotics and mechanisms of bacterial resistance. Nat Rev Microbiol. 2014 Jan; 12(1):35-48. doi: 10.1038/nrmicro3155.

13. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis. 2008 Apr 15;197(8):1079-81. doi: 10.1086/533452.

14. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009 Jan 1;48(1):1-12. doi: 10.1086/595011.

15. Rice LB.Progress and challenges in implementing the research on ESKAPEpathogens. Infect Control Hosp Epidemiol. 2010 Nov;31 Suppl1:S7-10. doi: 10. 1086 /655995.

16. Taubes G. The bacteria fight back. Science. 2008 Jul 18; 321(5887):356-61. doi: 10.1126/science. 321. 5887. 356.

17. Karlberg JP. Trends in disease focus of drug development. Nat Rev Drug Discov. 2008 Aug;7 (8): 639-40. doi: 10.1038/nrd2618.

18. Traczewski M, Brown S. PTK0796: in vitro potency and spectrum of activity compared to ten other antimicrobial compoundsProceedings of the 43rd Inter science Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL), 2003 Washington, DC American Society of Microbiology

19. Karlberg JPE. Trends in disease focus of drug development, Nat Rev Drug Discov, 2009, vol.7 (pg.639-40)

20. Glaxo Smith Kline and Mpex Pharmaceuticals form alliance to develop novel efflux pump inhibitors for use against serious gram-negative infections, 2009London, and San Diego Glaxo Smith Kline

21. Jones RN, Guzman-Blanco M, Gales AC, et al. Susceptibility rates in Latin American nations: report from a regional resistance surveillance program. Braz J Infect Dis. 2013;17:672-81.

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