Effect of Antimicrobial Stewardship Program on Carbapenems Consumption and Klebsiella Resistance in the Intensive Care Units

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March 30, 2022

Abstract

Introduction: The prevalence of carbapenem-resistant Klebsiella strains and their related mortality are increasing worldwide. These pandemics impose optimizing antibiotic consumption through the application of the antibiotic stewardship programs. We aimed to evaluate the impact of applying antibiotic stewardship programs on carbapenem consumption and the klebsiella resistance pattern in critically ill patients of a large Egyptian hospital. Method: We retrospectively evaluated critically ill patients with isolated Klebsiella species from the ICU of Elaraby hospital, Egypt during the period from April 2017 to January 2019. We collected data related to carbapenem consumption (expressed as defined daily dose /1000 patient-days) and Klebsiella clinical isolates and their antimicrobial susceptibility pattern. Based on Klebsiella sensitivity, as sensitive to ceftriaxone and cefotaxime, resistant to ceftriaxone/cefotaxime, or resistance to meropenem/imipenem, Klebsiella isolates were classified as grades 1, 2, or 3, respectively. Our primary outcome was the change in carbapenem consumption after implementing the program, while the secondary outcomes were the change in the incidence of carbapenem-resistant Klebsiella. Results: The study included 205 patients with isolated Klebsiella species during the study period. The antibiotic stewardship program started in March 2018. Out of the 205 patients, 61 patients (29.8%) represented the pre-intervention sample, and 144 patients (70.2%) represented the post-intervention sample. Applying the antibiotic stewardship program was associated with a significant decrease in the carbapenem consumption from 38.9 to 26.6 defined daily dose /1000 patient-days (P=0.02). The incidence of carbapenem-resistant Klebsiella was decreased from 85.25% of total Klebsiella isolates to 48.6% (P<0.001). Klebsiella species were more likely to be in a lower category of resistance after applying the program with an odds ratio (OR) = 6.3 (2.88-13.73) using ordinal logistic regression. Conclusion: Applying the antibiotic stewardship program could reduce the unnecessary carbapenems use in the ICU with a subsequent decrease in the emergence of the Klebsiella resistant strains.

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Keywords: carbapenems, Klebsiella, intensive care unit, resistance, defined daily dose.

INTRODUCTION

Emerging multidrug-resistant (MDR) and extensively-drug-resistant (XDR) gram-negative bacteria have become one of the major threats to human health worldwide (Sherry & Howden, 2018). A striking increase in the occurrence of antibiotic-resistant gram-negative organisms, including carbapenem-resistant Enterobacteriaceae (CRE) was reported during the last decades (S. L. Solomon & Oliver, 2014). Considering that only a few novel antibiotics are in the pipeline, antibiotic resistance should be considered as a global health problem(America, 2011; Bassetti, Merelli, Temperoni, & Astilean, 2013). Gram-negative bacteria were seen to be associated with higher rates of septic shock and mortality compared to other bacteria (Abe et al., 2010). Gram-negative MDR bacteria were found in 93.6% of 126 nonduplicate gram-negative isolates from hospitalized patients in Egypt (Khalifa et al., 2019).

The increased antibiotic consumption and inappropriate antibiotic use were reported by many authors to be associated with more antibiotic resistance (Bell, Schellevis, Stobberingh, Goossens, & Pringle, 2014; Costelloe, Metcalfe, Lovering, Mant, & Hay, 2010; McNulty, 2012; Van De Sande-Bruinsma et al., 2008). The inappropriate use of antibiotics was also found to be a significant mortality predictor (Maeda et al., 2016).

It was estimated in one study that about 70 % of intensive care units (ICU) patients had antibiotics prescribed to them during their hospitalization (Vincent et al., 2009). In addition to this high prevalence of antibiotic use, the poor outcomes of ICU patients from resistant gram-negative infections (Hidron et al., 2008; Shorr, Zilberberg, Micek, & Kollef, 2014) render them an important population target for rationalized antibiotic use.

A Chinese study reported a 20.8% incidence of carbapenem-resistant *Klebsiella* (CRK) in ICU patients (Shu et al., 2019). Similarly, a high incidence of extended-spectrum beta-lactamase (ESBL) and*Klebsiella* pneumoniae carbapenemase (KPC) producing *Klebsiella* was reported in middle east countries including Egypt (Abdallah et al., 2015; Al-Agamy, Shibl, & Tawfik, 2009; Amer, Khalil, & Abd EL Wahab, 2016; Metwally, Gomaa, Attallah, & Kamel, 2013). However, the interventional programs reduced the prescribed antibiotics to hospitalized patients, decreased cost and bacterial resistance, and improved clinical outcomes (Davey et al., 2013; Yong, Buising, Cheng, & Thursky, 2010).

A guideline released by the Infectious Diseases Society of America (IDSA) and supported by the American Academy of Pediatrics, American Society of Health-System Pharmacists, and other Societies recommended the establishment of a multidisciplinary antimicrobial stewardship team including a physician, clinical pharmacist, and other members. The core task of the team is a prospective audit with intervention, feedback, formulary restriction, and preauthorization (Dellit et al., 2007). The implementation of the antimicrobial stewardship program (ASP) decreased rates of *Clostridium difficile* , methicillin-resistant*Staphylococcus aureus* , and vancomycin-resistant enterococci nosocomial infection and reduced the antimicrobial expenditure (Nowak, Nelson, Breidenbach, Thompson, & Carson, 2012).

The resistance pattern of gram-negative bacteria *Klebsiella*species in Egypt was not adequately studied especially in rural areas. This study was intended to evaluate the impact of an antibiotic stewardship program on the carbapenem consumption and *Klebsiella*resistance pattern in critical care areas of an Egyptian rural hospital. Also, to study the relationship between carbapenems use and the development of *Klebsiella* resistance.

2. MATERIALS AND METHOD:

2.1. Study design:

A retrospective observational study was conducted in the ICU of Elaraby hospital, Ashmoun, Menoufia, Egypt from April 2017 to January 2019. The inclusion criteria were *Klebsiella* isolates obtained from the clinical specimen of ICU patients aged more than 12 years during the study period. The data of the bacterial isolates were collected from the hospital laboratory records and the data of carbapenem consumption were obtained from the main pharmacy records. The ASP was started on 1 March 2018.

2.2. Carbapenems consumption:

The carbapenem consumption data in ICU over the study period including meropenem and imipenem expressed as a daily defined dose (DDD) / 1000 patient-days, a unit recommended from WHO, were daily collected during the study period. It was calculated as the amount of meropenem and imipenem consumed in each day by the gram, divided by 2, and the number of patients then multiplied by 1000 (Sketris et al., 2004).

2.3. Antimicrobial stewardship program:

The program consists of three main parts: (1) Interventional part including preauthorization of restricted antibiotics list by clinical pharmacy specialists and primary physician, antibiotic timeout to reassess empiric antibiotics use 48-72 hours after their initiation, dosing optimization (based on patient-specific drug clearance, the volume of distribution, infection site, and microbiological factors), and managing the antibiotics-related problems, (2) Designing and implementing hospital-specific guidelines and antimicrobial policies, (3) Educational part including education of health-care professionals regarding antibiotics administration and handling.

2.4. Bacterial isolates:

Blood samples were transferred into brain heart infusion broth, incubated at 35 C^{o} for 5 days, and if any turbidity was observed, it was transferred into MacConkey agar and blood agar. Sputum samples were inoculated in MacConkey agar, blood agar, and chocolate agar. Swab samples were inoculated in MacConkey agar and blood agar.

2.5. *Klebsiella* identification:

The *Klebsiella* isolates obtained in MacConkey agar showed large, highly mucoid, and pink colonies. Microscopic examination with gram stain showed short gram-negative rods. Confirmation for*Klebsiella* was performed using biochemical reactions (Hansen, Aucken, Abiola, & Podschun, 2004). These include Kligler's Iron Agar (KIA) test, Lysine iron agar (LIA) test, Motility indole ornithine (MIO) test, Citrate test, and Urease test.

2.6. Antibiotic susceptibility:

The antibiotic susceptibility using the disc diffusion method was performed with Mueller Hinton agar and discs from Oxoid®, United Kingdom and based on Kirby-Bauer technique (Bauer, 1966) and the cut-off values for clear zones set by The Clinical & Laboratory Standards Institute (CLSI) recommendations and standards 2018 (In, 2018). The test discs were ceftriaxone 30 ηg, cefotaxime 30 ηg, ceftazidime 30 ηg, meropenem 10 ηg, and imipenem 10 ηg.

Klebsiella isolates were classified into three grades according to antibiotics susceptibility: grade 1 which are sensitive to ceftriaxone and cefotaxime, grade 2 which resist ceftriaxone/cefotaxime, and grade 3 including strains resistant to meropenem/imipenem (carbapenem-resistant *Klebsiella* (CRK))

2.7. Study outcomes:

The primary outcome was the pre- and post-intervention carbapenem consumption as a direct measure of the ASP efficacy, while the secondary outcomes was the pre- and post-intervention prevalence of the*Klebsiella* isolates and their resistance.

The study protocol was approved by the institutional review board of the hospital. The requirements for informed consent were waived for this retrospective medical records review. Patient privacy and confidentiality of medical records and data were maintained all through the study.

2.8. Statistical methods :

Data were collected and coded before analysis using the statistical package of social science (SPSS version 25). Normal distribution of different variables was tested using the z-value of skewness and kurtosis between -1.96 and +1.96 (Doane & Seward, 2011) and the p-value of Shapiro-Wilk's test > 0.05 (Razali & Wah, 2011;

Shapiro & Wilk, 1965). The post-intervention was compared to pre-intervention carbapenems consumption using the independent sample t-test. Chi-Square test and odds ratio with 95% confidence interval (95% CI) were used for comparison of qualitative data. One-way ANOVA (Analysis of Variance) test was used to compare carbapenem consumption among the three*Klebsiella* resistance grades. Two ordinal logistic regression models were used to study the effect of each of carbapenem consumption and the intervention program on *Klebsiella* resistance ordinal grades. Statistical significance was considered at p-value [?] 0.05.

RESULTS:

A total of 472 patients with positive culture results were initially evaluated during the study period of 22 months. After excluding 267 patients with culture results with non-*klebsiella* organisms, the remaining 205 patients represented our study sample. The initial 11 months from April 2017 till February 2018 represented the pre-intervention control period and included 61 patients (29.8 %), while the following 11 months from March 2018 till January 2019 represented the post-intervention period and included 144 patients (70.2 %). Sputum samples were the most common representing 95 samples (46.3 %). Other samples included 38 for urine (18.5 %), 32 for wound swabs (15.6 %), 23 for blood cultures (11.2 %), and 17 for other samples (8 %).

Primary outcomes:

The applied ASP interventions in March 2018 was associated with a significant decrease in carbapenem consumption as indicated by a shift of the mean DDD from 38.9 $\pm$ 12.8 DDD /1000 patient-days during the pre-intervention period to 26.6 $\pm$ 9.98 DDD / 1000 patient-days in the post-intervention period with 31.6 % decrease by the implementation of the intervention (Figure 1). This change in the carbapenem use was seen to be statistically significant, $P = 0.02$.

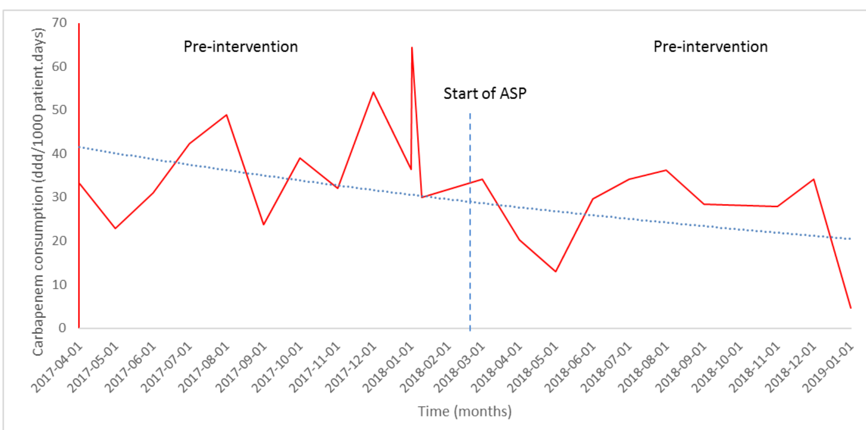

Figure 1: Average monthly carbapenem consumption (DDD / 1000 patient-days) over the study period

Secondary outcomes:

Out of the 205 patients with isolated *Klebsiella* organisms in the ICU during the study duration, 122 (59.5 %) were carbapenem-resistant (CRK). Those CRK were resistant to imipenem in 97 patients, to meropenem in 62 patients, or resistant to both in 51 patients.

The pre-intervention CRK isolates was reported in 52 isolates (85.2 %) compared to 70 isolates (48.6 %) in the post-intervention period. These differences were statistically significant with OR (95% CI) of 0.164 (0.075-0.357), P $<$ 0.001.

Among the 61 patients in the pre-intervention period, no patients were in grade 1 (0 %), while 9 (14.8 %) and 52 patients (85.2 %) had grade 2 and 3 resistance respectively compared to 13 (9 %), 61 (42.4 %) and 70 (48.6 %) of the 144 of the post-intervention periods had resistance of grade 1, 2, and 3 respectively (P $<$

0.001). This pattern showed a decreased prevalence of CRK (grade 3) at the expense of increased grades 1 and 2 *Klebsiella* species.

One-way ANOVA (Levene's Test of equality of error variances p-value > 0.05) showed that the difference in carbapenem consumption reported with the different *Klebsiella* grades was significant (F=4.8, P=0.009). It was 31.9 ± 3 DDD / 1000 patient-days with grade 1 compared to 31.7 ± 10.1 and 36.5 ± 11.8 DDD / 1000 patient-days with grades 2 and 3 respectively. Moreover, post-hoc analysis using Turkey's test for pairwise comparison found a significant difference between grade 2 and 3 (P=0.01) (Figure 2).

Figure 2: The relationship between *Klebsiella* resistance grades and carbapenems consumption.

Two ordinal logistic regression models were used. The first model with a fit parallel line test (χ^2 = 1.97, P = 0.16) showed that *Klebsiella* species were more likely to be in a lower category of resistance significantly after implementation of the ASP with OR (95 % CI) of 6.3 (2.88 – 13.73). The second model with a fit parallel line test (χ^2 = 0.275, P = 0.6) showed that that *Klebsiella* species were more likely be in a lower category of resistance with a decrease in carbapenems use with OR (95 % CI) of 1.04 (1.012 – 1.07).

4. DISCUSSIONS:

Multidrug-resistant bacteria are shown to be caused by antibiotics abuse in the healthcare facilities (Cantón, Horcajada, Oliver, Garbajosa, & Vila, 2013) especially in ICUs (Prabaker & Weinstein, 2011). We hypothesized that the application of ASP within the ICU including the preauthorization of restricted antibiotics list, the timeout for de-escalation, and the timeout for early discontinuation with other different elements can decrease the consumption of different antibiotics especially carbapenems, and consequently decrease the prevalence of the CRK species. We conducted an observational study to measure the carbapenem consumption within the ICU of a tertiary hospital in an Egyptian rural area after the implementation of ASP elements and compared this consumption with that prior to the program implementation. We also evaluated the impact of the carbapenem consumption on the*Klebsiella* species resistance pattern.

The implementation of the ASP in our study significantly decreased the carbapenem utilization, where it caused a decrease in the carbapenem use by 31.6 % compared to 22% in another study (Elligsen et al., 2012). A previously reported stewardship program decreased carbapenem utilization from 300 to 20 DDD / month (Simmons, Sherman, & Crosmun, 2016), which is not like our results that could be because of the different units used for carbapenem consumption. Another study found that the ASP decreased the consumption of meropenem from 90.5 to 24.96 and imipenem from 6.5 to 2.3 in terms of DDD / 1000 patients-days (Jaggi, Sissodia, & Sharma, 2012).

Other impacts of ASP were studied, and it was concluded that the application of the program caused a significant decrease in the inappropriate antibiotic use from 18.5 % to 11.4 % (Maeda et al., 2016) and the implementation of antibiotic restriction policy decreased the total broad-spectrum antibiotic days. (Rimawi, Mazer, Siraj, Gooch, & Cook, 2013). Moreover, the prospective audit and feedback elements of the ASP were seen to be of utmost importance in applying of the program in many studies (Lesprit, Landelle, & Brun-Buisson, 2013; D. H. Solomon et al., 2001). One study applied an easy-to-use electronic preauthorization system within ASP that was seen to significantly decrease the cephalosporins use by 39 % (Buising et al., 2008). Other earlier programs that restricted the use of cephalosporins caused an 18 % decrease in hospital prescription of cephalosporins (Hanberger, Skoog, Ternhag, & Giske, 2014).

Appropriate antibiotics selection and time to de-escalation from carbapenems or antipseudomonal antibiotics was studied after ASP implementation and it was found that ASP significantly improved time to de-escalation and appropriateness of antibiotics (Bookstaver et al., 2017). We didn't however analyze the impact of the different program elements separately due to the small sample size. The decrease in carbapenem consumption in our study might indicate compliance to restricted antibiotics policy, shorter time to antibiotics de-escalation, appropriate duration, and optimum dosing.

We reported a 59.5 % prevalence of CRK in our study. Other studies in Egypt reported similar prevalence ranging from 44 % up to more than 63 % (Amer et al., 2016; El Kholy & El Manakhly, 2018; Metwally et al., 2013). Additionally, out of 80 *Klebsiella pneumoniae* isolates obtained from hospitalized patients at Menoufia University Hospitals, the resistance to imipenem and meropenem was observed in 62.5 and 56.2 respectively(Melake et al., 2016).

We reported a significant decrease in the prevalence of the CRK after the implementation of the ASP interventions. Viñau Lopez et al. found a decrease in resistance of *Klebsiella pneumoniae* after ASP implementation in a tertiary hospital from 46 % to 38 % (Jaggi et al., 2012). Other studies reported that the applying of ASP with a shorter antibiotic course was shown to decrease antibiotic-resistant superinfection from 38 % to 14 % (Srinivasan, 2017). Others showed that interventions that decreased excessive antibiotic use, decreased the antibiotic resistance pattern, and even improve clinical outcomes (Davey et al., 2013). Despite that Elligsen et al showed that the ASP interventions decreased meropenem resistance, they didn't show a significant difference in the clinical outcome in terms of mortality or length of stay (Elligsen et al., 2012).

We also found that higher*klebsiella* resistance grades were associated with higher carbapenem consumption. Horikoshi et al showed a positive correlation between days on carbapenems and carbapenems resistance in the pediatric population (Horikoshi et al., 2017). Another case-control study involving *Klebsiella pneumoniae* bloodstream infection found that carbapenem use caused 9.98 fold increase in the odds of acquiring carbapenem resistance (Yuan et al., 2020). Carbapenem exposure within one month before the onset of bloodstream infection was found by other authors to be the only risk factor for developing CRK infection (Liu et al., 2019).

Despite that the reduced antibiotic consumption could be the direct outcome of applying ASP, its long-term impact might include several clinical and economic impacts. Mortality reduction and decrease hospital length of stay as outcomes to ASP had been also studied. The ASP implementation caused up to a 54 % reduction in mortality with an OR of 2.17 (Conway et al., 2017) and decreased length of hospitalization (Horikoshi et al., 2017). These results were, however, not reproduced in a meta-analysis including 11 studies (Lindsay et al., 2019).

Our study was limited by the small sample size. We did not study the impact of the program on clinical outcomes in terms of mortality and length of stay. The authors considered that changes related to the clinical outcome may require a longer duration to be evident. It is of significance to study a sub-analysis of the effect of the different elements of the ASP. This, however, requires a larger sample size, and accordingly, the authors studied the impact of the program as a bundle.

CONCLUSION

Applying antibiotic stewardship programs including preauthorization of restricted antibiotics, timeouts of de-escalation and discontinuation, and implementing hospital-specific guidelines could reduce the unnecessary carbapenems use in the ICU with a subsequent decrease in the emergence of the Klebsiella resistant strains.

Acknowledgements:

We gratefully thank Dr. Mamdouh Elaraby, the general manager of the Elaraby hospital group for his help and support. Also, we acknowledge the critical care and clinical pathology medical staff in Elaraby Hospital, Menoufia, Egypt for their support.

Ethics Statement:

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The US National Research Council's guidelines for the Care and Use of Laboratory Animals were followed

Funding

None.

Conflict of Interest Statement

The authors do not have a conflict of interest to disclose.

Data availability statement information:

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES:

Abdallah, H., Wintermans, B., Reuland, E., Koek, A., Al Naiemi, N., Ammar, A., . . . Vandenbroucke-Grauls, C. (2015). Extended-spectrum β-lactamase-and carbapenemase-producing Enterobacteriaceae isolated from egyptian patients with suspected blood stream infection. *PloS one, 10* (5), e0128120.

Abe, R., Oda, S., Sadahiro, T., Nakamura, M., Hirayama, Y., Tateishi, Y., . . . Hirasawa, H. (2010). Gram-negative bacteremia induces greater magnitude of inflammatory response than Gram-positive bacteremia.*Critical Care, 14* (2), 1-7.

Al-Agamy, M. H., Shibl, A. M., & Tawfik, A. F. (2009). Prevalence and molecular characterization of extended-spectrum β-lactamase-producing Klebsiella pneumoniae in Riyadh, Saudi Arabia. *Annals of Saudi medicine, 29* (4), 253.

Amer, W. H., Khalil, H. S., & Abd EL Wahab, M. (2016). Risk factors, phenotypic and genotypic characterization of carbapenem resistant Enterobacteriaceae in Tanta University Hospitals, Egypt. *Int J Infect Control, 12* (2), 1-11.

America, I. D. S. o. (2011). Combating antimicrobial resistance: policy recommendations to save lives. *Clinical Infectious Diseases, 52* (suppl_5), S397-S428.

Bassetti, M., Merelli, M., Temperoni, C., & Astilean, A. (2013). New antibiotics for bad bugs: where are we? *Annals of Clinical Microbiology and Antimicrobials, 12* (1), 22. doi:10.1186/1476-0711-12-22

Bauer, A. (1966). Antibiotic susceptibility testing by a standardized single disc method. *Am J clin pathol, 45* , 149-158.

Bell, B. G., Schellevis, F., Stobberingh, E., Goossens, H., & Pringle, M. (2014). A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC infectious diseases, 14* (1), 13.

Bookstaver, P., Nimmich, E., Smith, T., Justo, J., Kohn, J., Hammer, K., . . . Al-Hasan, M. (2017). Cumulative effect of an antimicrobial stewardship and rapid diagnostic testing bundle on early streamlining of antimicrobial therapy in gram-negative bloodstream infections.*Antimicrobial agents and chemotherapy, 61* (9), e00189-00117.

Buising, K., Thursky, K., Robertson, M., Black, J., Street, A., Richards, M., & Brown, G. (2008). Electronic antibiotic stewardship—reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting.*Journal of Antimicrobial Chemotherapy, 62* (3), 608-616.

Cantón, R., Horcajada, J. P., Oliver, A., Garbajosa, P. R., & Vila, J. (2013). Inappropriate use of antibiotics in hospitals: the complex relationship between antibiotic use and antimicrobial resistance.*Enfermedades infecciosas y microbiologia clinica, 31* , 3-11.

Conway, E. L., Sellick, J. A., Horey, A., Fodero, K., Ott, M. C., Krajewski, M. P., & Mergenhagen, K. A. (2017). Decreased mortality in patients prescribed vancomycin after implementation of antimicrobial stewardship program. *American journal of infection control, 45* (11), 1194-1197.

Costelloe, C., Metcalfe, C., Lovering, A., Mant, D., & Hay, A. D. (2010). Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *Bmj, 340* .

Davey, P., Brown, E., Charani, E., Fenelon, L., Gould, I. M., Holmes, A., . . . Wilcox, M. (2013). Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database of Systematic Reviews* (4).

Dellit, T. H., Owens, R. C., McGowan, J. E., Gerding, D. N., Weinstein, R. A., Burke, J. P., . . . Carpenter, C. F. (2007). Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clinical Infectious Diseases, 44* (2), 159-177.

Doane, D. P., & Seward, L. E. (2011). Measuring skewness: a forgotten statistic? *Journal of statistics education, 19* (2).

El Kholy, A., & El Manakhly, A. (2018). *2300. Molecular Epidemiology of Carbapenem-Resistant Klebsiella pneumoniae (CRKP) Causing Central Line Associated Blood Stream Infections (CLABSI) in Three ICU Units in Egypt.* Paper presented at the Open Forum Infectious Diseases.

Elligsen, M., Walker, S. A., Pinto, R., Simor, A., Mubareka, S., Rachlis, A., . . . Daneman, N. (2012). Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients a controlled interrupted time series analysis. *Infection Control & Hospital Epidemiology, 33* (4), 354-361.

Hanberger, H., Skoog, G., Ternhag, A., & Giske, C. G. (2014). Antibiotic consumption and antibiotic stewardship in Swedish hospitals. *Upsala Journal of Medical Sciences, 119* (2), 154-161.

Hansen, D. S., Aucken, H. M., Abiola, T., & Podschun, R. (2004). Recommended test panel for differentiation of Klebsiella species on the basis of a trilateral interlaboratory evaluation of 18 biochemical tests. *Journal of clinical microbiology, 42* (8), 3665-3669.

Hidron, A. I., Edwards, J. R., Patel, J., Horan, T. C., Sievert, D. M., Pollock, D. A., . . . Facilities, P. N. H. S. N. (2008). Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infection control and hospital epidemiology, 29* (11), 996-1011.

Horikoshi, Y., Suwa, J., Higuchi, H., Kaneko, T., Furuichi, M., Aizawa, Y., . . . Shoji, T. (2017). Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality. *International Journal of Infectious Diseases, 64* , 69-73.

In, C. (2018). Performance standards for antimicrobial susceptibility testing: Wayne, PA: Clinical and Laboratory Standards Institute.

Jaggi, N., Sissodia, P., & Sharma, L. (2012). Impact of antimicrobial stewardship programme on carbapenem resistance in gram negative isolates in an Indian tertiary care hospital. *American Journal of Infectious Diseases, 8* (2), 106-111.

Khalifa, H. O., Soliman, A. M., Ahmed, A. M., Shimamoto, T., Nariya, H., Matsumoto, T., & Shimamoto, T. (2019). High prevalence of antimicrobial resistance in gram-negative Bacteria isolated from clinical settings in Egypt: recalling for judicious use of conventional antimicrobials in developing nations. *Microbial Drug Resistance, 25* (3), 371-385.

Lesprit, P., Landelle, C., & Brun-Buisson, C. (2013). Clinical impact of unsolicited post-prescription antibiotic review in surgical and medical wards: a randomized controlled trial. *Clinical microbiology and infection, 19* (2), E91-E97.

Lindsay, P. J., Rohailla, S., Taggart, L. R., Lightfoot, D., Havey, T., Daneman, N., . . . Muller, M. P. (2019). Antimicrobial stewardship and intensive care unit mortality: a systematic review. *Clinical Infectious Diseases, 68* (5), 748-756.

Liu, J., Wang, H., Huang, Z., Tao, X., Li, J., Hu, Y., . . . Zou, M. (2019). Risk factors and outcomes for carbapenem-resistant Klebsiella pneumoniae bacteremia in onco-hematological patients. *The Journal of*

Infection in Developing Countries, 13 (05), 357-364.

Maeda, M., Takuma, T., Seki, H., Ugajin, K., Naito, Y., Yoshikawa, M., . . . Shoji, H. (2016). Effect of interventions by an antimicrobial stewardship team on clinical course and economic outcome in patients with bloodstream infection. *Journal of Infection and Chemotherapy, 22* (2), 90-95.

McNulty, C. A. (2012). European Antibiotic Awareness Day 2012: general practitioners encouraged to TARGET antibiotics through guidance, education and tools. *Journal of antimicrobial chemotherapy, 67* (11), 2543-2546.

Melake, N. A., Mahmoud, A. B., Elraghy, N. A., Labib, A. Z., Hassan, D. M., & Elbrolosy, A. M. (2016). Detection of Klebsiella pneumoniae carbapenemases and metallo-β-lactamases among Klebsiella pneumoniae isolates from hospitalized patients at Menoufia University Hospitals, Egypt. *Menoufia Medical Journal, 29* (4), 801.

Metwally, L., Gomaa, N., Attallah, M., & Kamel, N. (2013). High prevalence of Klebsiella pneumoniae carbapenemase-mediated resistance in K. pneumoniae isolates from Egypt. *Eastern Mediterranean Health Journal, 19* (11).

Nowak, M. A., Nelson, R. E., Breidenbach, J. L., Thompson, P. A., & Carson, P. J. (2012). Clinical and economic outcomes of a prospective antimicrobial stewardship program. *American Journal of Health-System Pharmacy, 69* (17), 1500-1508.

Prabaker, K., & Weinstein, R. A. (2011). Trends in antimicrobial resistance in intensive care units in the United States. *Current opinion in critical care, 17* (5), 472-479.

Razali, N. M., & Wah, Y. B. (2011). Power comparisons of shapiro-wilk, kolmogorov-smirnov, lilliefors and anderson-darling tests. *Journal of statistical modeling and analytics, 2* (1), 21-33.

Rimawi, R. H., Mazer, M. A., Siraj, D. S., Gooch, M., & Cook, P. P. (2013). Impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial utilization and patient outcome. *Critical care medicine, 41* (9), 2099-2107.

Shapiro, S. S., & Wilk, M. B. (1965). An analysis of variance test for normality (complete samples). *Biometrika, 52* (3/4), 591-611.

Sherry, N., & Howden, B. (2018). Emerging Gram negative resistance to last-line antimicrobial agents fosfomycin, colistin and ceftazidime-avibactam–epidemiology, laboratory detection and treatment implications. *Expert review of anti-infective therapy, 16* (4), 289-306.

Shorr, A. F., Zilberberg, M. D., Micek, S. T., & Kollef, M. H. (2014). Predictors of hospital mortality among septic ICU patients with Acinetobacter spp. bacteremia: a cohort study. *BMC infectious diseases, 14* (1), 572.

Shu, L.-b., Lu, Q., Sun, R.-h., Lin, L.-q., Sun, Q.-l., Hu, J., . . . Zhang, R. (2019). Prevalence and phenotypic characterization of carbapenem-resistant Klebsiella pneumoniae strains recovered from sputum and fecal samples of ICU patients in Zhejiang Province, China.*Infection and drug resistance, 12* , 11.

Simmons, M., Sherman, B., & Crosmun, C. (2016). *Decrease in Daily Defined Doses of Carbapenems Using Minimal Impact Interventions, Suppression of Sensitivities and Utilization.* Paper presented at the Open Forum Infectious Diseases.

Sketris, I. S., Metge, C. J., Ross, J. L., MacCara, M. E., Comeau, D. G., Kephart, G. C., & Blackburn, J. L. (2004). The use of the World Health Organisation anatomical therapeutic chemical/defined daily dose methodology in Canada. *Drug information journal: DIJ/Drug Information Association, 38* (1), 15-27.

Solomon, D. H., Van Houten, L., Glynn, R. J., Baden, L., Curtis, K., Schrager, H., & Avorn, J. (2001). Academic detailing to improve use of broad-spectrum antibiotics at an academic medical center. *Archives of internal medicine, 161* (15), 1897-1902.

Solomon, S. L., & Oliver, K. B. (2014). Antibiotic resistance threats in the United States: stepping back from the brink. *American family physician, 89* (12), 938-941.

Srinivasan, A. (2017). Antibiotic stewardship: why we must, how we can. *Cleveland Clinic journal of medicine, 84* (9), 673.

Van De Sande-Bruinsma, N., Grundmann, H., Verloo, D., Tiemersma, E., Monen, J., Goossens, H., . . . System, E. A. R. S. (2008). Antimicrobial drug use and resistance in Europe. *Emerging infectious diseases, 14* (11), 1722.

Vincent, J.-L., Rello, J., Marshall, J., Silva, E., Anzueto, A., Martin, C. D., . . . Sakr, Y. (2009). International study of the prevalence and outcomes of infection in intensive care units. *JAMA, 302* (21), 2323-2329.

Yong, M., Buising, K. L., Cheng, A., & Thursky, K. (2010). Improved susceptibility of Gram-negative bacteria in an intensive care unit following implementation of a computerized antibiotic decision support system. *Journal of Antimicrobial Chemotherapy, 65* (5), 1062-1069.

Yuan, Y., Wang, J., Yao, Z., Ma, B., Li, Y., Yan, W., . . . Xu, J. (2020). Risk Factors for Carbapenem-Resistant Klebsiella pneumoniae Bloodstream Infections and Outcomes. *Infection and drug resistance, 13* , 207.