Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Benchmarking of antibiotic usage: An adjustment to reflect antibiotic stewardship program outcome in a hospital in Saudi Arabia

Hisham Momattin a, Anfal Y. Al-Ali b, Khurram Mohammed a, Jaffar A. Al-Tawfiq c,d,∗

a Pharmacy Services Division, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia
b Department of Pharmacy Services, Dhahran Eye Specialist Hospital, Dhahran, Saudi Arabia
c Specialty Internal Medicine, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia
d Indiana University School of Medicine, Indianapolis, IN, USA

A R T I C L E   I N F O

Article history:
Received 21 April 2017
Received in revised form 11 August 2017
Accepted 12 August 2017

Keywords:
DDD
Antibiotic stewardship
Benchmarking
Days of therapy
DOT

A B S T R A C T

Antimicrobial stewardship program aims to reduce antibiotic use. Periodic measurement and monitoring of antibiotic use and comparison within the institution as well as with other organizations are important indicators. We analyzed antibiotic usage in a general hospital in Saudi Arabia. Antibiotic data were collected retrospectively for 2011 and from 2013 to 2015, and only adult patients (>15 year of age) were included in the study. Data were presented as days of therapy (DOT) and defined daily dose (DDD). DDD was adjusted per 100 bed-days and according to the case mix index (CMI). The total DDD was 37,557 in 2013, 36,550 in 2014 and 38,738 in 2015. The DDD per 100 patient-days was 90.7–94.5. There was a discordant findings of antibiotic measurements based on the DDD compared to DOT, and DDD/100 bed-days compared to DOT/100 bed-days. There was a negative correlation between CMI and DDD per 100 bed days (r = −0.696), but a positive correlation of CMI with DOT (r = 0.93). Adjusted DDD/100 bed-days showed decrease in the usage of antibiotics, reflecting activities of the antibiotic stewardship program. The increase in DOT/100 bed-days may indicate the favorable utilization of combination therapy. Antibiotic usage needs to be adjusted per 100 bed-days and correlated with CMI for better reflection of optimal antibiotic use, activities of the antibiotic stewardship program, and to allow benchmarking.

© 2017 The Authors. Published by Elsevier Limited on behalf of King Saud Bin Abdulaziz University for Health Sciences. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

It is estimated that 20–50% of antibiotic use is inappropriate or unnecessary in acute care hospitals [1]. Inappropriate antimicrobial use has a negative impact on patients and the entire community [2,3]. Misuse of antibiotics leads to an increase in antibiotic resistance and additional healthcare costs [1,4]. Unfortunately, we are facing a dramatic increase in bacterial resistance with the obvious drop in the number of antibiotics discovered and approved each year [5,6]. Therefore the antimicrobial stewardship program (ASP) was developed to ensure the proper use of antibiotics, reduce overutilization of antimicrobial agents, and halt the development of resistance [3,4].

At Johns Hopkins Aramco Health (JHAH), we started an ASP in 2011 with an educational program of physicians and pharmacist.

The program was enhanced mid-2012 with the following interventions: a re-designed antibiotic sensitivity report [2], intravenous to oral conversion program, vancomycin pharmacokinetic program [7], automatic renal dosing, antibiotic de-escalation, pre-operative antibiotic protocols utilizing adapted orders, and a multi-facteted approach to decrease antibiotics for respiratory tract infections [8]. The program incorporated “if you cannot measure it, you cannot improve it,” and thus included periodic measurement and monitoring of antibiotic use, and comparing data within the institution and with other institutions [1,9].

To standardize the units for comparison, we used the most common definitions: defined daily dose (DDD), and days of therapy (DOT). DDD is as an average of the maintenance dose of a single antibiotic in its main indication for adults per day [10]. According to the World Health Organization (WHO), each drug has an anatomical therapeutics chemical (ATC) code and a DDD value in grams [10]. To define the exact consumption rate, it was recommended to express DDD per 100 bed-days in hospitals and DDDS per 1000 inhabitant-days for out-patients [11–13]. DOT is the number of days that a patient receives an antibiotic regardless of the dose [1]. DDD has
better estimation than DOT, especially in patients receiving a combination of antibiotics or one dose only (e.g., surgical prophylaxis), and it can be calculated even in the absence of a computerized pharmacy system [1].

A better measure for comparing DDD with an external hospital, is the quantitative assessment of antibiotics use, with adjustment for severity of illness among hospitalized patients, using the case mix index (CMI) [11,14]. There are limited studies of antibiotic utilization in Saudi Arabia [15]. In this study, we compare the DDD, DOT, DDD per 100 bed-days, and the adjusted DDD according to CMI.

**Materials and methods**

The study was carried out at Dhahran Health Center as a part of Johns Hopkins Aramco Healthcare (JHAR), which serves a population of approximately 370,000 patients [16]. Dhahran Health Center is the main general hospital with a 380-bed capacity and five intensive care units (cardiac, medical, surgical, pediatric, and neonatal) [16]. The hospital provides acute, general medicine and surgery, intensive care services, and management of hematological and solid organ malignancies [16].

A computerized database was generated for all prescribed antibiotics. Antibiotic data were collected for 2011 to have a baseline, and then retrospectively for 2013–2015. All data were collected for the first 6 months of 2011, 2013–2015. To minimize the drawback of using DDD, only adult patients (above 15 years of age) were included in the study. The data were transferred to an Excel spreadsheet. The World Health Organization 2013 Guidelines for Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) were utilized for the calculation of DDD. DDD for each antibiotic was calculated separately, the total number of grams administered for each antibiotic per year was divided by the WHO DDD in grams [10]. Thus, the DDD is an estimate of the number of days of antibiotic therapy. Data of day surgery was not included in calculating the bed days. Antibiotic usage was adjusted per 100 bed-days by dividing DDD by daily occupied days and multiplied by 100. A direct measure of the number of days of therapy (DOTs) is a common method of antibiotic usage evaluation. DOT is simply the sum of the total number of days of all used antibiotics. Thus, when the same patient receives more than one antibiotic, more than one DOT was counted.

The case mix index (CMI), an economic surrogate marker, was calculated by dividing total cost weights for all inpatient in specific period by the number of admission [17], as provided by the hospital information department. CMI describes the average patients’ morbidity of individual hospitals [17].

**Results**

Antibiotic data were collected for 2011 as a baseline, and for subsequent years 2013, 2014, and 2015. The collected data were expressed as DDD and DOT and were adjusted per 100 patient-days.

**Defined daily dose (DDD) and days of therapy (DOT)**

The total DDD was 38,270 in 2011, 37,557 in 2013, 36,550 in 2014, and 38,738 in 2015 (Fig. 1). However, there was no significant increase in the DDD overtime with an correlation coefficient ($R^2$) trend of 0.006. A reduction in the DDD was more pronounced if we excluded antimicrobials given to suspected MERS-CoV patients during the 2014 outbreak [18] where the DDD decreased from 38,738 to 35,942. On the other hand, days of therapy (DOT) were 35,218, 36,958, 38,945 and 42,326 days at base line and in the years 2013–2015, respectively (Fig. 1) with a significant $R^2$ trend of 0.973.

**Adjusted DDD per 100 bed-days and based on case mix index (CMI)**

DDD showed a non-significant increase in 2015 compared to baseline. To avoid variation between different hospital settings and to allow comparison with similar hospitals, we reported DDD and DOT per 100 bed-days, as well as the adjustment of DDD/100 bed-days in relation to CMI. Data for DDD/100 bed-days showed a slight negative correlation with an $R^2$ of $-0.775$ whereas there was a clear positive correlation in the case of DOT/100 bed-days with an $R^2$ of 0.918. Adjusted for the bed-days and the CMI, the DDD/100 bed-days is shown in Fig. 2. The correlation between DDD/100 bed-days and CMI was −0.696. A plot of the DDD/100 bed-days against the CMI showed that DDD/100 bed-days falls within the benchmark in relation to the CMI, based on data by Kuster et al. [17]. A total reduction in antibiotic usage after adjustment using 100 bed-days
and CMI was 5.13% (from 95.6 to 90.7 between the baseline in 2011 and year 2015) (Fig. 2).

Discussion

Evaluation of antimicrobial usage is standardized using the DDD as a recommended strategy for comparison with similar hospitals [13]. The use of risk adjustment is needed to overcome the challenge of benchmarking. Two patient characteristics are associated with clinical outcomes and use of the healthcare system. These factors are: patient mix and severity of illness [19,20]. Direct comparison of the quantity of antibiotic consumed between hospitals is flawed, due to multiple factors, such as severity of illness, structures, and missions [17]. We reported antibiotic consumption per 100 bed-days for inpatients, to overcome the variation in hospital size and occupancy rate. We also adjusted antibiotic usage using the case mix index (CMI), to reduce the variation of patient morbidity among hospitals. CMI is a tool for comparison and had been shown to have a moderate correlation with antibiotic use [17,21].

The use of DDD estimates indirectly the actual DOT [19,20]. The measurement of DOT is insensitive to the actual dosages administered. And DOT measurement favors those situations where broad spectrum monotherapy is used. One of the drawbacks of DDD measurement is related to patients with renal or hepatic dysfunction needing adjustment [22]. In this report, we observed a discordant findings of antibiotic measurements based on the DDD and DOT and a discordant findings of antibiotic measurements based on DDD/100 bed-days compared to DOT/100 bed-days. Similarly, previous studies showed discordant measurements between DDD and DOT [22–26]. The DDD method is useful for benchmarking, but not for evaluation of the number of DOTs or relative use for antibacterial agents [27]. And that DOT is more difficult to measure, but is a superior measurement methodology [27].

Reporting DDD data could be misleading and may not reflect the activity of the ASP, because other factors may interfere, such as hospital days and the morbidity of admitted patients. This findings is obvious in this report where DDD increased and the DDD per 100 bed days decreased in 2015 compared to the baseline. The adjusted DDD/100 bed-days showed a decrease in the usage of antibiotics, reflecting activities of the antibiotic stewardship program. Measuring DDDs per 100 patient-days and DOTs per 1000 patient-days (or 100 patient-days) may be required especially in relation to antimicrobial resistance [27]. Further adjustment of DDD/100 bed-days based on CMI in our study showed a negative correlation with increasing CMI, reflecting the efficacy of ASP activities in our institute. The reduction of 5.13% of DDD adjusted to 100 bed-days, and correlation with CMI, gave us an indicator of the ASP’s success. Similarly, previous studies showed a strong correlation between CMI and antibacterial usage expressed as DDD/100 patient days [17]. However, increasing CMI may lead to increased combination therapy as shown by an increase in the DOT and DOT/100 bed-days. This increase in combination therapy could be also the target of future antimicrobial stewardship program, particularly targeting deescalation from combination therapy to monotherapy.

In conclusion, antibiotic usage needs to be adjusted per 100 bed-days, and correlated with CMI, for better reflection of ASP activities, and to allow benchmarking with other organizations. It is important to monitor DDD and the addition of DOT monitoring may also shed light on the pattern of antibiotic usage in the form of combination versus monotherapy.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Approved by the JHAH IRB.

References

[1] Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. Clin Infect Dis 2014;59(Suppl 3):S97–100. http://dx.doi.org/10.1093/cid/ciu542.
[2] Al-Tawfiq JA, Momattin H, Al-Habboubi F, Dancer SJ. Restrictive reporting of selected antimicrobial susceptibilities influences clinical prescribing. J Infect Public Health 2015;8:234–41. http://dx.doi.org/10.1016/j.jiph.2014.09.004.
[3] Owens RC. Antimicrobial stewardship: concepts and strategies in the 21st century. Diagn Microbiol Infect Dis 2008;61:110–28, http://dx.doi.org/10.1016/j.diagmicrobio.2008.02.012.

[4] MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. Clin Microbiol Rev 2005;18:638–56, http://dx.doi.org/10.1128/CMR.18.4.638-656.2005.

[5] Society for Healthcare Epidemiology of America N, Infectious Diseases Society of America, Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol 2012;33:322–7, http://dx.doi.org/10.1086/655010.

[6] Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1–12, http://dx.doi.org/10.1086/595011.

[7] Momattin H, Zogheib M, Homoud A, Al-Tawfiq JA. Safety and outcome of pharmacy-led vancomycin dosing and monitoring. Chemotherapy 2016;61:1–7, http://dx.doi.org/10.1159/000440607.

[8] Al-Tawfiq JA, Alawami AH. A multifaceted approach to decrease inappropriate antibiotic use in a pediatric outpatient clinic. Ann Thorac Med 2017;12:51–4, http://dx.doi.org/10.4103/1817-1737.197779.

[9] Chen I-L, Lee C-H, Su I-H, Tang Y-F, Chang S-J, Liu J-W. Antibiotic consumption and healthcare-associated infections caused by multidrug-resistant gram-negative bacilli at a large medical center in Taiwan from 2002 to 2009: implicating the importance of antibiotic stewardship. PLoS One 2013;8:e65621, http://dx.doi.org/10.1371/journal.pone.0065621.

[10] World Health Organization. WH0CC: definition and general considerations; 2016. http://www.who.int/norms/definition_and_general_considerations/ [Accessed 7 January 2017].

[11] Hutchinson JM, Patrick DM, Marra F, Ng H, Bowie WR, Heule L, et al. Measure https://www.who.int/ddd/definition_and_general_considerations/ [Accessed 7 January 2017].

[12] Pope SD, Delitt TH, Owens RC, Hooton TM. Infectious Diseases Society of America, Society for Healthcare Epidemiology of America. Results of survey on implementation of Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Infect Control Hosp Epidemiol 2009;30:97–8, http://dx.doi.org/10.1086/592579.

[13] Delitt TH, Owens RC, McGowan JE, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159–77, http://dx.doi.org/10.1086/510393.

[14] Kanerva M, Ollgren J, Lyytikainen O, Agthe N, Mottonen T, Kauppinen M, et al. Benchmarking antibiotic use in Finnish acute care hospitals using patient case-mix adjustment. J Antimicrob Chemother 2011;66:2651–4, http://dx.doi.org/10.1093/AC/MR18.4.618-656.2005.

[15] Al-Tawfiq JA. Changes in the pattern of hospital intravenous antimicrobial use in Saudi Arabia. 2006–2008. Ann Saudi Med 2012;32:517–20.

[16] Al-Tawfiq JA. Distribution and epidemiology of Candida species causing fungemia at a Saudi Arabian hospital, 1996–2004. Int J Infect Dis 2007;11:239–44.

[17] Kuster SP, Rief C, Bollinger AK, Ledergerber B, Hinternann A, Deplazes C, et al. Correlation between case mix index and antibiotic use in hospitals. J Antimicrob Chemother 2008;62:837–42, http://dx.doi.org/10.1093/jac/dks275.

[18] Al-Tawfiq JA, Hinedi K, Ghandaour J, Khairalla H, Musleh S, Ujaliy A, et al. Middle East Respiratory Syndrome–Coronavirus (MERS-CoV): a case-control study of hospitalized patients. Clin Infect Dis 2014;59:160–5, http://dx.doi.org/10.1093/cid/ciu226.

[19] Ibrahim OM, Polk RE. Benchmarking antimicrobial drug use in hospitals. Expert Rev Anti Infect Ther 2012;10:445–57, http://dx.doi.org/10.1586/eri.12.18.

[20] Ibrahim OM, Polk RE. Antimicrobial use metrics and benchmarking to improve stewardship outcomes. Infect Dis Clin North Am 2014;28:195–214, http://dx.doi.org/10.1016/j.clinid.2014.01.006.

[21] Mylotte JM, Keagle J. Benchmarks for antibiotic use and cost in long-term care. J Am Geriatr Soc 2005;53:1117–22, http://dx.doi.org/10.1111/j.1532-5415.2005.53351.x.

[22] Mandy B, Routy E, Cornette C, Woronot-Lernis M-C, Talon D. Methodological validation of monitoring indicators of antibiotics use in hospitals. Pharm World Sci 2004;26:90–5.

[23] Muller A, Monnet DL, Talon D, Hémon T, Bertrand X. Disparities between prescribed daily doses and WHO defined daily doses of antibacterials at a university hospital. Br J Clin Pharmacol 2006;61:585–91, http://dx.doi.org/10.1111/j.1365-2125.2006.02605.x.

[24] Kern WV, Steib-Bauert M, de With K, Reuter S, Berfiz H, Frank U, et al. Fluoroquinolone consumption and resistance in haematology-oncology patients: ecological analysis in two university hospitals 1999–2002. J Antimicrob Chemother 2005;55:57–60, http://dx.doi.org/10.1093/jac/dki510.

[25] Zagorski BM, Trick WE, Schwartz DN, Wisniewski MF, Hershcov RC, Fridkin SK, et al. The effect of renal dysfunction on antimicrobial use measurements. Clin Infect Dis 2002:35:1491–7, http://dx.doi.org/10.1086/344753.

[26] Shekta M, Pastor J, Phelps P. Evaluation of the defined daily dose method for estimating anti-infective use in a university hospital. Am J Health Syst Pharm 2005;62:2288–92, http://dx.doi.org/10.2146/ajhp050140.

[27] Polk RE, Fox C, Mahoney A, Lefcavage J, MacDougall C. Measurement of adult antibiotic drug use in 130 US hospitals: comparison of defined daily dose and days of therapy. Clin Infect Dis 2007;44:664–70, http://dx.doi.org/10.1086/511640.