Journal of Infection and Public Health xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Retrospective evaluation of piperacillin–tazobactam, imipenem–cilastatin and meropenem used on surgical floors at a tertiary care hospital in Saudi Arabia

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ARTICLE INFO

Article history:
Received 16 November 2016
Received in revised form 26 August 2017
Accepted 9 September 2017

Keywords:
Microbial drug resistance
Surgical
Antimicrobial stewardship
De-escalation
Imipenem–cilastatin
Piperacillin–tazobactam
Meropenem

ABSTRACT

Background: The appropriate use of broad-spectrum antibiotics, including appropriate de-escalation, is essential to reduce the emergence of antibiotic resistance. In surgical floors antibiotics are prescribed for prophylaxis (mostly, single dose), empirical treatment (started if infection is suspected till bacteria are identified with its sensitivity to antibiotics), or treatment of well-defined infection of previously isolated bacteria with its sensitivity to antibiotics. In this study, we aimed to evaluate the use of broad-spectrum antibiotics based on requests for cultures and de-escalation based on sensitivity results of culture tests at tertiary care hospital.

Method: A retrospective cohort study was conducted to evaluate the utilization of broad-spectrum antibiotics on surgical floors at a tertiary care center in Jeddah, Saudi Arabia. Patients who are admitted to surgical floors were included if they received any of three broad-spectrum antibiotics (piperacillin–tazobactam, imipenem–cilastatin or meropenem) from 1 June 2014 to 31 August 2014. Data were collected on whether culture and sensitivity test requests were made within 24 h of starting antibiotics, the duration of antibiotic therapy and the number of days to de-escalation after receiving culture and sensitivity results.

Results: Of the 163 patients who received broad-spectrum antibiotics, culture tests were requested in 112. Before receiving culture results, one patient was discharged and one died. The results of culture tests justified continuation of broad-spectrum antibiotics in only 22 patients, whereas 24 showed no microbial growth in any culture. De-escalation was delayed >24 h after culture results became available in 33 out of 64 eligible patients. On the other hand, 51 patients continued receiving broad spectrum antibiotics without any culture test during the whole treatment course.

Conclusion: The use of broad-spectrum antibiotics in surgical floors at a tertiary care hospital in Saudi Arabia was largely unjustified by culture-test result. Interventions are needed to enforce culture and sensitivity test requests within 24 h of starting the broad spectrum antibiotics therapy with further follow up to ensure appropriate de-escalation and discontinuation whenever indicated.

Introduction

According to the Center for Disease Dynamics, Economics and Policy (CDDEP), the overuse of antibiotics and the ensuing development of bacterial resistance are issues of significant global concern [1]. The first 'superbug' with resistance to colistin (a last-resort antibiotic for use against several multidrug-resistant bacteria) was isolated in the USA in 2016 [2]. The 2015 CDDEP report on the State of the World's Antibiotics recommended that, to achieve maximum benefit to human health, reductions in the inappropriate usage of antibiotics should be combined with improved access to them when they are needed [1].

The duration of therapy is an important aspect of the appropriate use of antibiotics, but it is not typically a priority in decisions regarding initial therapy. Guidelines for the treatment of bacterial infections highlight the importance of prompt antimicrobial treatment to save lives. Mortality is reduced when antimicrobials are initiated within the first hour after diagnosis; thereafter, culture-guided treatment should be performed, with escalation

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http://dx.doi.org/10.1016/j.jiph.2017.09.001

Please cite this article in press as: Youssif E, et al. Retrospective evaluation of piperacillin–tazobactam, imipenem–cilastatin and meropenem used on surgical floors at a tertiary care hospital in Saudi Arabia. J Infect Public Health (2017), http://dx.doi.org/10.1016/j.jiph.2017.09.001

or de-escalation of antibiotics as appropriate [3,4]. Antibiotic de-escalation refers to the process of converting patients from a broad-spectrum antibiotic, which covers several different types of disease-causing bacteria to a narrow spectrum antibiotic that targets a specific infecting organism. Appropriate use of antibiotics includes termination of antimicrobial treatment when no bacterial infection is present [5,6]

Guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America recommend the de-escalation of empirical antimicrobial therapy and elimination of redundant therapy on the basis of culture-test results, to decrease antimicrobial exposure and generate substantial cost savings [7]. Limiting antimicrobial exposure has the potential to reduce adverse drug effects, the incidence of secondary infections and the development of resistance, which is currently outpacing the development of new antibiotics [1].

However, the Centers for Disease Control and Prevention (CDC) highlighted that up to 50% of all in-hospital antimicrobial use is inappropriate. In a study determining the incidence of antibiotics misuse in a community hospital in Saudi Arabia; 72% of the antibiotics were judged to be misused [8].

Antimicrobial stewardship aims to combat the emergence of resistance, improve clinical outcomes, decrease adverse effects and control costs by improving the use of antimicrobials. This strategy involves restriction of antibiotic prescriptions in hospitals and the development of local guidelines controlling antibiotic use, to ensure appropriate duration of antibiotic treatments and guide treatment through the results of culture tests [7]. Antimicrobial stewardship includes de-escalation of therapy, and can potentially reduce unnecessary costs of antimicrobial agents, which account for up to 30% of total hospital pharmacy budgets [7,11]. Yet, data relating to the cost-effectiveness of de-escalation or discontinuation of antibiotics in case of negative microbiology culture results are limited in both quantity and quality. From the perspective of drug acquisition and administration, the potential for de-escalation to produce savings is compelling. Clinical benefits of de-escalation and decrease of redundant use can be associated with cost reductions through the occurrence of fewer complications and shorter length of stay, both in the intensive care unit (ICU) and in the hospital. Conversely, inappropriate and unnecessary antimicrobial use leads to selection of resistant pathogens, necessitating the use of expensive broad-spectrum or combination antibiotics. Evidence suggests that appropriate de-escalation has positive effects on resistance patterns and health-care costs [5,7]. It is well known that the administration of therapeutic doses of antibiotics may cause disturbance of the normal micro flora which can result in diminishing the natural defense mechanisms provided by the microbial ecosystem. That may lead to overgrowth of opportunistic organisms such as *Candida* spp. and *Clostridium difficile* [10].

The exact timing for de-escalation or discontinuation has not been definitively established, but evidence suggests that microbiology results available within 48–72 h of treatment initiation should be considered in addition to clinical judgment to determine the proper time to begin de-escalation [5]. Factors that can affect the decision to de-escalate treatment include fear of relapse in patients with clinical improvement, or fear of colonization by multidrug-resistant strains.

Results of a retrospective study evaluating antibiotics use in a university hospital in Manisa showed that antibiotic in surgical floors is inappropriately used. Inappropriate antibiotics use was statistically higher in those patients receiving prophylactic or empiric treatment compared to patients from whom specimens had been taken for culture [9].

The objective of our study is to assess the use of broad-spectrum antibiotics on surgical floors at a tertiary care center in Saudi Arabia, and to measure to what extent the inappropriate use of broad-spectrum antibiotics can result in unnecessary expense, or emergence of secondary infection.

Method

We conducted a retrospective study. This study design was considered appropriate, because it maintained the prescriber's autonomy and did not interrupt patient care.

Primary end points were: receipt of broad-spectrum antibiotics without culture request; continuation of antibiotic treatment despite a negative culture; and delay of de-escalation (administration of broad-spectrum antibiotic >24 h after the availability of culture-sensitivity results). Secondary end points were: identification of antibiotics that are highly associated with misuse in relation to culture requests and results; calculation of the costs of delays in de-escalation and delays in discontinuation of broad-spectrum antibiotics; and quantitation of the incidence of secondary infections by *Candida* spp. and *Clostridium difficile*.

This research was conducted at King Abdul Aziz Medical City/Ministry of National Guard Health Affairs in Jeddah, Saudi Arabia and approved by King Abdullah International Medical Research center (IRB approval date is 24 march 2015).

Study design and subjects

We reviewed the records of all adult patients who were admitted to surgical floors from 1 June 2014 to 31 August 2014 and received any of three broad-spectrum antibiotics (piperacillin–tazobactam, imipenem–cilastatin and meropenem) as empirical treatment. Exclusion criteria; were the use of broad-spectrum as a single prophylactic dose prior to a surgical procedure and/or administration of a shortened post-operative course of antimicrobials involving a single dose or continuation for less than 24 h post-operative[17].

A retrospective cohort study was conducted through chart-review. Broad-spectrum antibiotics were categorized as anti-pseudomonal β-lactams (formulary item piperacillin–tazobactam 4 g/0.5 g by injection) and carbapenems (formulary items meropenem 1 g by injection and imipenem–cilastatin 500 mg/500 mg by injection).

Medication profiles were reviewed to identify microbiology culture requests made within 24 h of suspected infection, along with the relative timing of sample collection and initiation of antibiotic treatment. For patients to whom microbiology culture was requested, we recorded follow-up of broad-spectrum antibiotic discontinuation if no microorganisms were isolated or de-escalation if the results showed sensitivity to a narrow-spectrum antibiotic. The timing of de-escalation was evaluated, as well as the timing of discontinuation along with subsequent exposure to broad-spectrum antibiotics, the cost of which was calculated in US Dollars by referring to hospital acquisition costs.

The incidence of secondary infection or colonization was assessed by counting the cases of *Candida albicans* isolated from cultures after starting the antibiotic treatment. Such isolate were considered secondary when *C. albicans* was only isolated from a patient's cultures after antibiotic use, and not from their initial cultures. In addition, we counted the number of positive *Clostridium difficile* toxin tests.

Data analysis

Analysis was performed using SPSS software version 23. Continuous data are expressed in mean or median; as appropriate. Statistical significance was defined as $P \leq 0.05$. Differences between

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