Diagnostic Microbiology and Infectious Disease 88 (2017) 41–46

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Clinical Studies

Necessity of carbapenem use when prescribed per infectious diseases specialists

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ARTICLE INFO

Article history:
Received 17 November 2016
Received in revised form 8 February 2017
Accepted 21 February 2017
Available online 27 February 2017

Keywords:
Stewardship
Preauthorization
Restriction
Antimicrobial
Resistance

ABSTRACT

Preauthorization strategies, including restricting broad-spectrum antimicrobials such as carbapenems to infectious diseases physicians (ID) are commonly employed by stewardship programs. The appropriateness, or "necessity" of empiric carbapenem therapy by ID, defined as an isolated organism sensitive to the carbapenem and resistant to cefepime, was evaluated over a 6 month span and included 84 patients. Additionally, 30 patients followed by ID who were not prescribed a carbapenem until final susceptibilities were included as a definitive therapy group. Differences in multi-drug resistant organism (MDRO) risk factors between groups were non-significant. Carbapenem therapy was necessary for only 6 (7%) empiric therapy patients, while four times as many definitive group patients required a carbapenem but did not receive one empirically. Overall, ID's ability to accurately gauge which patients required carbapenems appeared poor in this study. Alternative risk stratification strategies may better guide broad-spectrum antimicrobial use than ID judgment alone.

1. Introduction

Managing and maintaining robust antimicrobial stewardship programs in the era of increasing antimicrobial resistance is a continued challenge for clinicians. Globally, up to 16% of all Enterobacteriaceae isolated from hospitalized patients have been molecularly confirmed as extended-spectrum β-lactamase (ESBL) producers, with similar rates of multi-drug resistant *Pseudomonas aeruginosa* (Castanheira et al., 2015; Farrell et al., 2013). For patients at significant risk for infection with multi-drug resistant organisms (MDRO), patients may be appropriately initiated on broad-spectrum antimicrobial agents empirically, with subsequent de-escalation of therapy to the most narrow-spectrum agent with activity against the causative pathogen as culture results become available.

Guidelines by the Infectious Diseases Society of America (IDSA) advocate for antimicrobial preauthorization, whereby clinicians are required to obtain approval prior to prescribing certain antimicrobials designated as restricted by the stewardship team, hailing it as an effective method for reducing the initiation of inappropriate broad-spectrum antibiotics (Barlam et al., 2016). Previous studies have shown decreases in the overall use of broad-spectrum agents and their associated costs following the implementation of preauthorization interventions (Buising et al., 2008; Lewis et al., 2012; Metjian et al., 2008; Pakyz et al., 2009; White et al., 1997). However, a significant limitation of these studies is that the appropriateness of empiric broad-spectrum therapy pre- and post-implementation was not evaluated, with the overall utilization of broad-spectrum agents being less important clinically than the proportion of cases where broad-spectrum empiric therapy was truly indicated.

An alternative methodology recommended by IDSA guidelines is to restrict broad-spectrum antimicrobial use to certain indications outlined in institution-specific protocols (Barlam et al., 2016). However, since all patient scenarios necessitating use of a restricted antimicrobial cannot always be anticipated, many hospitals allow for use by infectious diseases physician (ID) approval to account for unique circumstances. Carbapenems have traditionally been regarded as first-line agents for the treatment of documented or suspected MDRO (Paterson, 2006). At Hartford Hospital, carbapenem use is restricted to urinary tract infection (UTI) for select high-risk patients (ESBL identified in the urine within 12 months), selected ventilator associated pneumonia (VAP) patients in the medical intensive care unit (ICU) per protocol, use in cystic fibrosis patients, and infectious diseases physician or infectious diseases pharmacist approval for any other indication. Despite the ubiquity among hospitals of an ID prior authorization strategy, no studies to date have investigated the appropriateness of carbapenem use as empiric therapy when per ID. The objective of this study was to assess the frequency at which ID accurately predict which patients require carbapenem therapy, specifically in cases where the primary pathogen is cephalosporin-resistant. This objective will be measured by answering two questions: 1) "How often does ID empirically prescribe a carbapenem to a patient who ultimately grows a bacterium that is resistant to extended-spectrum cephalosporins (i.e., cefepime)?" and 2) "How

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http://dx.doi.org/10.1016/j.diagmicrobio.2017.02.013
0732-8893/

often does ID need to escalate therapy to a carbapenem after cultures reveal a bacterium resistant to extended-spectrum cephalosporins?" Time to de-escalation was also evaluated as a secondary outcome.

2. Methods

2.1. Study design and patient population

This retrospective, single-center, descriptive chart review included patients aged 18–88 years with medical or surgical admissions to Hartford Hospital from January 1st, 2014, to June 30th, 2014, inclusive, and was approved by the institutional review board of Hartford Hospital. Patients with one or more orders for an antibiotic of the carbapenem class (doripenem, ertapenem, imipenem-cilastatin, and meropenem) were screened for inclusion in one of two designated patient groups: the empiric therapy group or definitive therapy group. Patients were included in the empiric therapy group if they had received one or more doses of a carbapenem as empiric antimicrobial therapy with ID approval. Patients were included in the definitive therapy group if they received one or more doses of a carbapenem per ID as definitive therapy following the reporting of antimicrobial susceptibilities (i.e. required escalation of antimicrobial therapy as a result of the isolation of a bacterium non-susceptible to the empiric antimicrobial selected by ID). Patients were only included in this group if ID was following for >48 hours prior to the finalization of culture results and had received no prior carbapenem doses dosing their admission. Patients with carbapenem orders during multiple admissions during the study period were included only once during their index admission. Patients with UTI listed as the sole infection source were excluded from the empiric therapy group as Hartford Hospital's UTI protocol allows for empiric carbapenem use without ID approval in select patients following the completion of a surveillance study of pathogen epidemiology and risk factors for resistant pathogens within our hospital's population (Cardwell et al., 2016). Patients with VAP were included despite empiric carbapenem use being allowed on select ICU floors per protocol as long as an ID physician consult was present, as the protocol provides strict instructions for de-escalation with ID involvement uncommon, and patients with VAP and ID consultation were believed to represent more complicated patients falling outside of the protocol. Cystic fibrosis patients, and patients with ertapenem ordered for the purpose of regimen simplification for planned outpatient therapy were also excluded.

2.2. Definitions

For the purposes of study inclusion, empiric therapy was defined as the receipt of carbapenem therapy prior to the final reporting of antimicrobial susceptibilities. Carbapenems were determined to be ordered with ID approval through the presence of an ID physician consult note or a listed ID care provider before or during the span of the carbapenem order, or if notation was made on the order or in medical progress notes documenting ID's involvement.

The first study question of the primary outcome examines the necessity of carbapenem therapy when used by ID empirically. In this study, "necessary" carbapenem use was defined as the presence of an organism on culture susceptible to the prescribed carbapenem and resistant to cefepime per antimicrobial susceptibility testing. Cefepime resistance was chosen as the marker for carbapenem necessity as it is the agent of first choice at the study facility for patients with recent healthcare exposure or other risk factors for antimicrobial resistance, with 82% of *P. aeruginosa* isolates and ≥90% of Enterobacteriaecae and Amp-C producing Gram-negative rods susceptible per the 2014 institutional antibiogram (Table 1). Bacterial susceptibilities were determined using the MicroScan system and the results were interpreted according to the pre-2014 breakpoints for cefepime set by the Clinical and Laboratory Standards Institute (CLSI). Secondary outcomes of this study included time to de-escalation, with any de-escalation to a narrow-spectrum antimicrobial within 24 hours of the reporting of final susceptibilities counting as zero days to de-escalation, 24–48 hours counting as 1 day, and so forth.

Table 1
Hartford Hospital 2014 susceptibility profile (percent susceptible).

Organism	#	ERT	PIM	TAZ	ZOS	MER
Enterobacter aerogenes	85	100	95	84	89	100
Enterobacter cloacae	208	98	90	75	80	99
Escherichia coli	2701	100	93	92	92	100
Klebsiella oxytoca	104	100	95	95	92	100
Klebsiella pneumoniae	662	100	95	81	94	100
Pseudomonas aeruginosa	495	-	82	87	87	90

Definitions: ERT = ertapenem; PIM = cefepime; TAZ = ceftazidime; ZOS = piperacillin-tazobactam; MER = meropenem.

Comorbid conditions were assessed using the Charlson Comorbidity Index (CCI). Immunosuppression was defined as AIDS, chemotherapy in the past 30 days, ≥20 mg of prednisone or equivalent daily for a minimum of 2 weeks, or receipt of other immunosuppressive agents (e.g. TNF-α inhibitors) within 3 months. History of MDRO was defined as the isolation of, or known colonization with, *Serratia spp*., *Pseudomonas spp*., *Acinetobacter spp*., *Citrobacter spp*., *Enterobacter spp*., indole-positive *Proteae*, or an ESBL producer.

2.3. Statistical analysis

Baseline categorical variables were compared between the empiric and definitive groups by $\chi 2$ or 2-tailed Fisher exact test, when appropriate. Continuous variables were compared using Student's *t* test or Mann–Whitney *U* test. A *P* value of <0.05 was considered statistically significant.

3. Results

3.1. Patient population

During the study time frame, 235 patients received a carbapenem. Of those screened, 84 (35.7%) were included in the empiric therapy group and 30 (12.8%) were included in the definitive therapy group (Fig. 1). Ten different ID physicians were involved in the carbapenem prescribing for the included encounters. Although our hospital also allows for approvals per ID pharmacist, all patients meeting inclusion criteria were managed by ID physicians during the study time period.

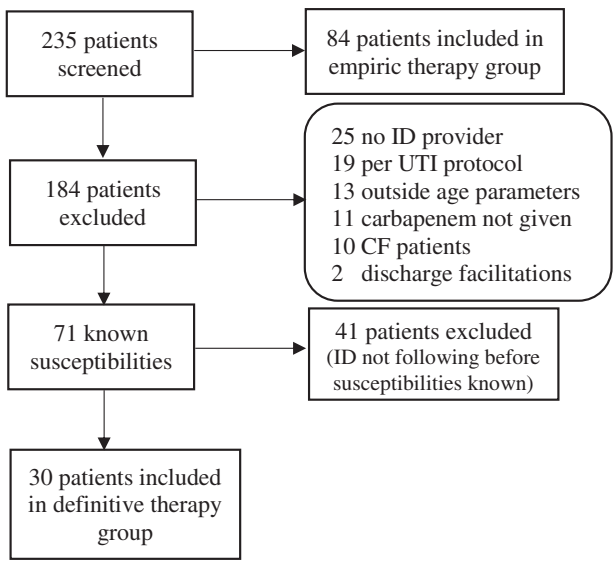

Fig. 1. Patient screening.