International Journal of Antimicrobial Agents 49 (2017) 650–654

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Short Communication

Implementation of a cefazolin-based stewardship pathway for methicillin-susceptible *Staphylococcus aureus* bloodstream infections paired with infectious diseases consultation

Benjamin J. Lee [a,1], Sonia N. Rao [a,2], Sheila K. Wang [b,c], Jane Y. Lee [a], Irfana Y. Lakada [a], Elise M. Gilbert [d,e,3], Viktorija O. Barr [d,f], Michael J. Postelnick [d], Sarah H. Sutton [g], Teresa R. Zembower [g], Maureen Bolon [g], Marc H. Scheetz [b,d], Nathaniel J. Rhodes [b,d,*]

[a] *Chicago College of Pharmacy, Midwestern University, Downers Grove, IL, USA*
[b] *Department of Pharmacy Practice, Chicago College of Pharmacy, Midwestern University, Downers Grove, IL, USA*
[c] *Department of Pharmacy, Rush University Medical Center, Chicago, IL, USA*
[d] *Department of Pharmacy, Northwestern Memorial Hospital, Chicago, IL, USA*
[e] *Department of Pharmacy Practice, Chicago State University College of Pharmacy, Chicago, IL, USA*
[f] *Department of Pharmacy Practice, College of Pharmacy, Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA*
[g] *Division of Infectious Diseases, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA*

ARTICLE INFO

Article history:
Received 9 May 2016
Accepted 20 December 2016

Keywords:
Methicillin-susceptible *Staphylococcus aureus*
Bloodstream infection
Oxacillin
Cefazolin
Infectious diseases consultation
Antimicrobial stewardship

ABSTRACT

Methicillin-susceptible *Staphylococcus aureus* (MSSA) infections have been successfully treated both with cefazolin and antistaphylococcal penicillins; cefazolin appears effective in MSSA bloodstream infections (BSIs). Thus, our antimicrobial stewardship programme (ASP) implemented a clinical pathway supporting cefazolin use in MSSA-BSIs and restricting oxacillin use to infectious diseases (ID) consultation due to cefazolin's lower cost and more convenient dosing. This before and after quasi-experimental study was conducted to describe the impact on outcomes and process of care measures associated with implementing this pathway among patients with MSSA-BSI. Definitive treatment with cefazolin increased over the study period from 17.3% to 69.8% post-implementation. Clinical failure (5.8% vs. 2.3%; $P = 0.62$) and in-hospital mortality (3.8% vs. 0%; $P = 0.50$) were rare pre- and post-implementation. Median hospital length of stay among survivors was similar between pre- and post-implementation periods ($P = 0.31$). Duration of bacteraemia [median (IQR) 3 (2–4) days vs. 2 (2–3) days; $P = 0.002$] and rates of re-infection after culture clearance (9.6% vs. 0%; $P = 0.06$) were reduced post-implementation. Frequency of source control ($P = 0.71$) and time to source control ($P = 0.52$) were similar between study periods. Significant increases in ID consultations (33.3% [3/9] vs. 73.3% [22/30]; $P = 0.047$) and median (IQR) 24-h daily doses [2 (1–3) g vs. 6 (3–6) g; $P < 0.01$] were seen for patients treated with cefazolin post-implementation. ASPs may find implementation of a similar pathway to be an effective means of improving the care of patients infected with MSSA.

1. Introduction

Infections caused by *Staphylococcus aureus* remain a leading cause of healthcare-associated and community-onset bloodstream infections (BSIs) [1,2]. Whilst hospital-onset infections caused by methicillin-resistant *S. aureus* (MRSA) are declining, infections caused by methicillin-susceptible *S. aureus* (MSSA) strains remain common [2]. MSSA-BSI is of great concern to clinicians owing to the incidence of systemic complications, their association with prolonged and costly treatment, and high rates of patient morbidity and mortality [2–4]. Despite an increase in the number of treatment options for MRSA [5,6], few agents have been developed to address serious or deep-seated MSSA infections [7–11]. Whilst antistaphylococcal penicillins such as oxacillin have long been considered the gold standard in the treatment of MSSA, they are frequently associated with adverse events and higher daily costs compared with first-generation cephalosporins [7,9,11–13]. We previously found cefazolin to be effective for a variety of MSSA-BSIs [11]. As a result, our antimicrobial stewardship programme (ASP) developed and implemented a clinical pathway to increase both cefazolin use and the rate of infectious diseases (ID) consultations in MSSA-BSI. The pathway promoted

* Corresponding author. Department of Pharmacy Practice, Chicago College of Pharmacy, Midwestern University, 555 31st St., Downers Grove, IL 60515, USA. Fax: +1 630 515 6958.
E-mail address: nrhode@midwestern.edu (N.J. Rhodes).
[1] Present address: Department of Pharmacy, University of California Irvine Health, Orange, CA, USA.
[2] Present address: Allergan, Plc, Irvine, CA, USA.
[3] Present address: Janssen Scientific Affairs, Titusville, NJ, USA.

http://dx.doi.org/10.1016/j.ijantimicag.2016.12.021
0924-8579/

interchange of cefazolin for oxacillin in MSSA-BSI in the absence of central nervous system (CNS) involvement. Oxacillin use was restricted to treatment of MSSA-BSI with CNS involvement and/or recommendation by an ID consultation. Unit-based clinical pharmacists were responsible for interfacing with the prescribing team to make the therapeutic exchange or recommend ID consultation. The purpose of this study was to assess the impact of the pathway.

2. Materials and methods

2.1. Study design, setting and pathway development

This before and after quasi-experimental retrospective study was conducted at Northwestern Memorial Hospital (NMH), a tertiary-care academic medical centre in Chicago, IL. Oxacillin was preferentially used in MSSA-BSI prior to implementation of the clinical pathway at this centre, unless intolerance was observed, according to consensus guidelines [4]. These historical data defined the pre-implementation period. The ASP developed a clinical pathway to increase the use of cefazolin in non-CNS MSSA infections based on an evaluation of cefazolin's safety and efficacy [11] and the favourable cost and convenient dosing for cefazolin. The pathway was implemented in August 2013 after it was approved by the Division of Infectious Diseases and NMH Pharmacy and Therapeutics Committee. During the post-implementation period, oxacillin use was restricted to use under the direction of ID consultation or for CNS-MSSA infections. Details of the clinical pathway were disseminated to all hospital physicians and pharmacists. Unit-based pharmacists were responsible for implementing the interchange or recommending ID consultation with case review conducted by the ASP. The study was approved by the Institutional Review Boards at Northwestern University and Midwestern University.

2.2. Study population and data elements

Similar to our initial study [11], BSI cases were screened for study inclusion if patients were: (i) treated with cefazolin or oxacillin within 48 h of a finalised MSSA blood culture; and (ii) admitted between 1 January 2010 and 31 June 2014. The first positive blood culture growing MSSA was considered the index culture for patients during the study period. Subsequent positive cultures were considered evidence of sustained infection if interim cultures were negative for ≤24 h and as re-infection if cultures had been negative for >24 h. Patients were excluded if they: (i) presented with polymicrobial infection; (ii) received any antibiotics other than cefazolin or oxacillin as definitive therapy for MSSA-BSI; (iii) received any antibiotic for ≥5 days prior to switching to a β-lactam; (iv) had a documented penicillin or cephalosporin allergy; or (v) were <18 years old. Isolate susceptibilities were determined using VITEK®2 (bioMérieux, La Balmes-les-Grottes, France) and were classified according to interpretive criteria in place at the time [14].

2.3. Study definitions

Similar to our previous study, clinical failure was defined as persistent positive blood cultures growing MSSA or a change in MSSA-directed therapy with documented clinician opinion that cefazolin or oxacillin treatment was ineffective [11]. Thus, the outcome of clinical failure was a composite of objective laboratory results documented in the medical record (i.e. duration of bacteraemia) and clinical findings (i.e. growth of abscesses, new embolic events, worsening of pain, and lack of response to therapy on imaging). Source control was defined by source removal (e.g. central line, port, arteriovenous graft), abscess drainage, wound debridement or any other interventions used to mitigate the infection. Patients for whom an intervention was not appropriate at the time of index positive culture were not considered evaluable for source control. Definitions for infection source, deep-seated infection, intensive care unit onset of infection, and 24-h daily dose of antibiotics were the same as our previous study [11]. At NMH, the recommended cefazolin dose for severe infections was 2 g every 8 h over 30 min or the renal dose-adjusted equivalent, whilst the oxacillin dose was 2 g every 4 h over 30 min irrespective of renal function. Severity of illness was quantified using the modified Acute Physiology and Chronic Health Evaluation II (m-APACHE II) score [15,16], which was calculated on infection Day 0 (i.e. index culture date). Adverse drug events (ADEs) were defined as documented renal, hepatic, dermatological or systemic reactions that were consistent with ADEs reported in the product labelling of each agent [17,18]. ADEs were considered to be treatment-related if they occurred while the patient was receiving cefazolin or oxacillin.

2.4. Outcomes and statistical analyses

We sought to evaluate the impact of the clinical pathway on (i) clinical outcomes and (ii) process of care measures among patients with MSSA-BSI. The difference in clinical outcomes before and after implementation of the pathway was evaluated. Outcomes of interest in this preliminary analysis included: rates of clinical failure; in-hospital mortality; hospital length of stay (LOS) among survivors; frequency of re-infection; and duration of bacteraemia. Several process of care measures were also evaluated, including: rates of source control; time to achieve source control; frequency of ID consultation; rates of institutional guideline-concordant dosing of the protocol agents; and occurrence of ADEs. Data analysis was performed using Intercooled Stata v.14.1 (StataCorp, College Station, TX). Descriptive statistics were calculated for patient demographics and clinical outcomes. Continuous variables were evaluated using Student's *t*-test or Wilcoxon rank-sum test, and categorical variables were evaluated using the χ^2 or Fisher's exact test as appropriate. Kaplan–Meier curves were constructed for time-to-event data, and differences in time-to-event endpoints were analysed using log-rank tests.

3. Results

A total of 95 patients met the study inclusion criteria, with 52 patients identified before and 43 patients identified after implementation of the pathway. Baseline characteristics were comparable between the two groups (Table 1). As expected, definitive treatment with cefazolin increased over the study period from 17.3% (9/52) pre-implementation to 69.8% (30/43) post-implementation. Conversely, definitive treatment with oxacillin decreased from 82.7% (43/52) pre-implementation to 30.2% (13/43) post-implementation ($P < 0.001$).

3.1. Clinical outcomes

Clinical outcomes of patients treated according to the clinical pathway are presented in Table 2. Overall, clinical failure was rare both before and after implementation of the clinical pathway (5.8% vs. 2.3%; $P = 0.62$). Two patients died during the pre-implementation period, and no deaths were observed after the pathway was implemented ($P = 0.50$). The median [interquartile range (IQR)] hospital LOS among survivors was similar between the pre- and post-implementation periods [9 (6–12) days vs. 8 (6–13) days; $P = 0.31$]. The median (IQR) duration of bacteraemia, however, was significantly reduced after protocol implementation [3 (2–4) days vs. 2 (2–3) days; $P = 0.002$] (Fig. 1). The rate of re-infection after initial clearance was also markedly, although not significantly, reduced after protocol implementation (9.6% vs. 0%; $P = 0.06$).