Society of Infectious Diseases Pharmacists newsletter

Spring 2014

823 CONGRESS AVE., SUITE 230, AUSTIN, TX 78701
PH: (512) 479-0425 FAX: (512) 495-9031 WWW.SIDP.ORG

PRESIDENT'S COLUMN

Joseph L. Kuti, Pharm.D.
Associate Director, Clinical and Economics Studies
Center for Anti-Infective Research and Development
Hartford Hospital

Spring is in the air. Actually, where I am sitting, it is more like Summer. As I write this, I am attending the Annual Infectious Diseases Fellowship Forum here in Captiva, Florida. It is a balmy 80 degrees, but don't be too jealous – I am working.

The Fellowship Forum is put on each year to bring together all of the current Pharmacy Fellows in Infectious Diseases to 1) provide a venue for all of tomorrow's researchers to meet their peers and develop lasting friendships, and 2) to showcase some of the projects Fellows are working on. Each Fellow has to give a 10 minute stand-up presentation of their research project, and then there is a 5 minute Q&A where Fellowship coordinators, mentors, and Fellows themselves can ask questions and provide constructive feedback. By the way, I am confident the Fellows don't call this latter part "constructive feedback". We have the folks from Wayne State University (Rybak, Davis, Cha), University of Chicago Illinois (Danziger, Rodvold), and the University of Minnesota (Rotschafer) to thank for this wonderful opportunity. And that's what it truly is… opportunity.

If you provide multiple opportunities for Infectious Diseases Pharmacists in training, great minds will take advantage of these opportunities and shine. As part of SIDP's Strategic Plan (you can find a link to it on the Home Page), our first goal is to support the advancement of pharmacists in ID clinical practice. One of our strategic directions in this area is to provide opportunity by supporting/funding ID training program for residents. This year, thanks to a generous grant from Cubist Pharmaceuticals, I am thrilled to report that SIDP will support two ID training programs. Unique to these programs is that Fellowships will also be included along with PGY-2 residencies, and that the program must meet specific criteria in Antimicrobial Stewardship with a strong focus on outcome-based endpoints. The RFP for these programs went out last month, and as you read this newsletter, the Board will be reviewing applications with a decision to be made by June 1st. We'll announce the recipients of these exciting opportunities at the Annual Meeting.

Speaking of the Annual Meeting, I apologize if there was any recent confusion on where or when the Annual Meeting is going to be held: ICAAC versus ID Week. In current tradition, the Annual Meeting will be held the day before ICAAC, so mark your calendars for Friday, September 5th 2014, and plan on joining us in Washington DC. The Program's Committee has put together an amazing group of speakers and topics this year to provide us opportunity for education and for part of our keynote, a bit of entertainment as well. However, as many of our members also attend ID Week, we are also putting a plan together for a SIDP reception with a Meet-the-Experts-in-Stewardship format for those making their way to Philadelphia this year also. Stay tuned for more information.

Since the theme of this column is opportunity, I am pleased to announce SIDP will also be funding two Young Investigator Research Awards this year. This is in line with Goal 2 in our strategic plan: to support the advancement of pharmacists in ID research. Research funding, especially for young faculty members and clinical pharmacists, has become more challenging to acquire in recent years. The Board appreciates that these awards, although small, are often the catalyst needed to spark a successful research career. That is why we have decided to offer two awards this year. The Research Committee is currently preparing the RFP, and it will be announced shortly. I encourage you to bring your best ideas forward, whether they are bench-top, translational, or clinical research, and apply.

Finally, in an effort to reward and recognize certain individuals in our membership who have consistently dedicated their time and effort to SIDP, the Board is exploring a Fellowship status for the Society. Please fill out the survey that is currently up to help us figure out where this acknowledgement best fits. I can't say I know if adding 4 or 5 more letters at the end of one's name will provide additional opportunity, but it certainly sounds nice and is the right path for our growing Society.

Opportunities for Employment

Job listings; Spring 2014 (current on website as of 4/8/14)

Clinical Pharmacy Specialist - Infectious Disease
Location: Mid-West
Contact: Bob Costa, C.P.C., bob.costa@sierrastaffing.com
Details: Clinical Pharmacy Specialist

Assistant Professor, Pharmacy Practice
Location: St. Louis College of Pharmacy
Contact: Ryan Moenster, Pharm.D., BCPS-ID, Ryan.Moenster@stlcop.edu
Details: Assistant Professor

Director, Infectious Diseases, Global Health Science
Location: The Medicines Company, Several positions throughout the USA (Field-Based) for Qualified Applicants; Immediate Hiring
Contact: Jill Massey, PharmD, MBA, Jill.Massey@themedco.com
Details: Director, Infectious Diseases

Deputy Director PharmD Medical Science Liaison
Location: Minneapolis
Contact: Mary Kate Reeves-Hoche, MaryKate.Reeves-Hoche@sanofipasteur.com
Details: Deputy Director

Pharmacist, Clinical Specialist Infectious Diseases
Location: University of Texas MD Anderson Cancer Center; Houston, TX
Contact: Judy Chase, PharmD; jchase@mdanderson.org
Details: Clinical Specialist ID

Outpatient Infectious Diseases Clinical Pharmacy Specialist
Location: Parkland Health and Hospital System, Dallas, TX
Contact: Steven Carlisle, PharmD, BCPS steven.carlisle@phhs.org
Details: Outpatient ID Clinical Pharmacy Specialist

Assistant Professor of Translational Sciences
Location: The University of Texas at Austin College of Pharmacy, San Antonio, Texas
Contact: Christopher Frei, Pharm.D., FCCP, freic@uthscsa.edu, 210-567-8371
Details: Assistant Professor

Pharmacist, Clinical Specialist Infectious Disease
Location: West Covina, CA
Contact: Angela Bernacki
Details: Clinical Specialist ID

Clinical Pharmacy Manager - Infectious Disease
Location: NewYork-Presbyterian Hospital, New York, NY
Contact: Christine Kubin, chk9005@nyp.org
Details: Clinical Pharmacy Manager

Staff Pharmacist, Infectious Disease Specialist
Location: Baptist Hospital East, Louisville, KY
Contact: Lindsey Higginbotham Lindsey.higginbotham@bhsi.com
Details: Staff Pharmacist

Infectious Diseases Medical Science Liaison - South Central
Location: The Medical Affairs Company
Contact: TMAC Career Center http://tmac.hodesiq.com/
Details: ID Medical Science Liaison

Medical Affairs Manager
Location: San Francisco, CA
Company: Theravance
Details: Medical Affairs Manager

Medical Science Liaison - Virology (AL, GA, MS, TN, SC)
Location: Atlanta, Georgia, United States, 30301
Company: Johnson & Jonson
Details: Medical Science Liaison

Jobs continued on next page

Tenure Track Assistant Professor
Location: University of Minnesota
Contact: Michael Kotlyar, PharmD kotly001@umn.edu
Details: Assistant Professor

Senior Clinical Research Scientist
Location: Cubist Pharmaceuticals, Lexington, Massachusetts
Contact/Details: Senior Clinical Research Scientist

Tenured Associate/Full Professor
Location: University of Minnesota
Contact: Pamala Jacobson, PharmD jacob117@umn.edu
Details: Full/Associate Professor

Clinical Scientific Director (Medical Science Liaison)
Location: Cubist Pharmaceuticals/New England Region
Details: Clinical Scientific Dir (Medical Science Liaison) - New England Region

**** All listed job opportunities have more extensive information listed on SIDP's website.***

To add or revise listings please email Stephanie Bulak at sbulak@eami.com.

SIDP
WELCOMES OUR NEWEST MEMBERS!

Active

Amy Hanson
Elizabeth Hesselbacher
Karen Barton
Kristin Otting
Lawrence Pierce
Lucas Schulz
Michele Swihart
Rachel Lovett

Associate

Brett Stubson
Carla Walraven
Julius Li
Lizanne Beigue
Louise-Marie Gillis
Nathan Unger

Trainee-Associate

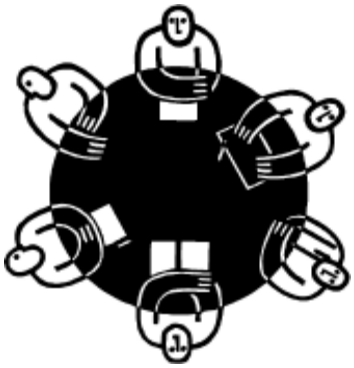
Amit Patel
Brighton Abebe
Christina Caplinger
Christine Pham
Dayla Boldt
Janessa Smith
Majid Almajid

Save the Date!

Friday, September 5th
Madarin Oriental
Washington D.C.

SIDP 2014 Annual Meeting

The 2014 annual meeting will take place in confunction with ICAAC, on Friday, September 5th at the Mandarin Oriental Hotel in Washington D.C. The business meeting and CE programming is planned to begin at noon with a reception to follow at 6:30pm.



SIDP ANNOUNCEMENTS & UPDATES

Board Elections

According to the By Laws of SIDP, only ACTIVE members in good standing may vote in officer elections. Your vote is entirely confidential, however to ensure voting eligibility and that members vote only once, we are asking that you provide your full name. We ensure that your vote will remain confidential.

Please click on the links below to view the candidate's statement.

President-Elect:

John Cleary

Sharon Erdman

Jason Gallagher

Michael Postelnick

Secretary/Treasurer:

Sandy Estrada

Scott McConnell

Marisel Segarra-Newnham

Board member-at-large:

Darryl DePestel

Krista Gens

Vanthida Huang

Rachel Chambers Kenney

Jarrod Kile

Craig Martin

Katie Suda

Click HERE to cast your vote.

The Primary Election closes on Wednesday, May 28 at 5pm PST.

SIDP Elections Committee: Chair: Noreen Chan Tompkins, Vice Chair: Lynne Krop, Board Liasons: Erika Ernst, Scott Bergman, Curtis Collins, Gregory Alan Eschenauer, Lynn Fehrenbacher, Eddie Grace, Kylie Mueller, Jessica Njoku, Patrick J. Scoble, Renata Smith, Velliyur Viswesh, Lynn Wardlow, Suzanne B. Wortman

Stewardship Committee - Update

Enrollment in the SIDP Antimicrobial Stewardship Certificate Program continues to grow at a healthy pace. Current active enrollment as of March 2014 is at 601 participants, which has grown significantly from the 469 participants who were enrolled as of January 2013. The committee continues to work with authors to update the content of the program and is working on establishing procedures to ensure that content remains current and relevant to practice. Committee members continue to review and approve Phase 3 (final projects) for program participants. The program averages 10-20 graduations per month.

A big thank you to our the newsletter's contributors and editors!
Roopali Sharma, Betsy Hirsch, Jim Rhodes, Viki Barr, Trent Towne, P. Brandon Bookstaver

Annual Meetings

(May 2014 - November 2014)

Date / Location	Conference Name
May 29-31 Orlando, FL	17th Annual Making a Difference in Infectious Diseases (MAD-ID) http://www.mad-id.org/
May 31-June 4 Las Vegas, NE	ASHP 2014 Summer Meetings http://www.ashp.org/menu/2014-Summer-Meetings
June 5-6 Kansas City, MO	5th Annual Pediatric Antimicrobial Stewardship Conference https://www.regonline.com/Register/Checkin.aspx?EventID=1333949
June 9-13 Atlanta, Georgia	STD Prevention Conference
June 19 – 22 Washington, DC	1st ASM Conference on Experimental Microbial Evolution
July 20-25 Melbourne, Australia	20th International AIDS Conference http://www.aids2014.org Abstracts accepted throughFebruary 6 (late-breakers through May 15)
July 27-August 1 Vail, Colo	32nd Annual Conference on Pediatric Infectious Diseases
August 26-29 Chicago, Illinois	16th International Symposium on Staphylococci and Staphylococcal Infections (ISSSI)
September 5-9 Washington, DC	ICAAC 2014 http://www.icaac.org/ Abstracts accepted through May 19th, 2014. Late-Breaker Abstract Submission Deadline: Tuesday, July 22
October 8-12 Philadelphia, PA	IDWeek 2014 http://www.idweek.org/ Abstracts accepted through May 6th, 2014. Late breakersthrough July 18.
October 17 Miami, FL	Seventh Annual Symposium on Infection Prevention and Control http://cme.baptisthealth.net/infectionsymposium/pages/index.aspx/
November 2 – 6 New Orleans, Louisiana	The American Society of Tropical Medicine and Hygiene Meeting
November 2-6 Glascow, Scotland	11th International Congress on Drug Therapy in HIV Infection
November 13 – 16 Washington, DC	1st ASM Conference on Polymicrobial Infections

SIDP Member Publications

April 2014 update (includes January - March 2014 citations)

Congratulations to the following SIDP members for recent publications:

Ahmed, Zamzam
Avdic, Edina
Barr, Viktorija
Bauer, Karri
Bearden, David
Bertino, Joseph
Bland, Christopher
Bookstaver, Brandon
Boucher, Bradley
Burke, Stuart
Clay, Patrick
Cleary, John
Crandon, Jared
Darin, Kristin
Danziger, Larry
De Anda, Carisa
DePestel, Daryl
Dilworth, Thomas
Esterly, John
Estes, Lynn
Falcione, Bonnie
Fish, Douglas
Frei, Christopher
Fries, Brittany
Garey, Kevin
Gauthier, Timothy
Goff, Debra
Grabenstein, John
Gross, Alan
Guarascio, Anthony
Gubbins, Paul
Hall, Ronald
Healy, Daniel
Heil, Emily
Hevener, Kirk
Hirsch, Betsy
Holtzman, Christopher
Housman, Seth
Jahng, Maximillian
Jain, Rupali
Jankowski, Christopher
Jung, Rose
Kashuba, Angela
Kays, Michael
King, Travis
Klepser, Michael
Kubiak, David
Kubin, Christine
Kuti, Joseph
Lamp, Kenneth
LaPlante, Kerry
Lewis, James
Liedtke, Michelle
Lodise, Thomas
Lomaestro, Ben
Maples, Holly
Marino Sabo, Elizabeth
Matthias, Kathryn
McConnell, Scott
McGregor, Jessina
McLaughlin, Milena
McNicholl, Ian
Mercier, Renee-Claude
Mehta, Jimish
Morrill, Haley
Mynatt, Ryan
Neuner, Elizabeth
Nevrekar, Sonia
Nicolau, David
Oleksiuk, Louise-Marie
Pai, Manjunath
Piscitelli, Stephen
Pogue, Jason
Postelnick, Michael
Rathbun, R. Chris
Reed, Erica
Rhodes, N. James
Rodvold, Keith
Rose, Warren
Ryan, Keenan
Rybak, Michael
Sabol-Dzintars, Kathryn
Sanders, Jamie
Scarsi, Kimberly
Scheetz, Marc
Schulz, Lucas
Stover, Kayla
Suda, Katie
Swanson, Joseph
Tam, Vincent
Tran, Truc
Walraven, Carla
Werth, Brian
White, Cyle
Wiederhold, Nathan
Wishkirchen, Dora
Wong-Beringer, Annie
Wood, Christopher
Zelenitsky, Sheryl
Zhao, Jing

STEWARDSHIP

Bassetti M, **Nicolau DP**, Calandra T. What's new in antimicrobial use and resistance in critically ill patients? Intensive Care Med. 2014 Mar;40(3):422-6.

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Hawser SP, Badal RE, Bouchillon SK, Hoban DJ, Hackel MA, Biedenbach DJ, **Goff DA**. Susceptibility of Gram-negative aerobic bacilli from intra-abdominal pathogens to antimicrobial agents collected in the United States during 2011. *J Infect*. 2014 Jan;68(1):71-6.

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PK/PD

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CLINICAL RESEARCH

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An Update on the arsenal for multidrug-resistant Acinetobacter infections: POLYMYXIN ANTIBIOTICS.

Authors:

Zahra Kassamali, PharmD, BCPS
(corresponding author)
University of California, Los Angeles Health System
Pharmaceutical Services
Box 957423
Los Angeles, CA 90095
zkassamali@mednet.ucla.edu
Phone: 312-768-8259

Rupali Jain, PharmD, BCPS
Associate Clinical Professor
University of Washington
1959 NE Pacific Street
Box 356015
EA-152
Seattle, WA 98195
phone (206) 598-4416

Key Words:
Polymyxins/pharmacology, Polymyxins/therapeutic use, Acinetobacter infections/drug therapy, Anti-bacterial Agents/administration & dosage, Colistin/administration & dosage, Gram-Negative Bacterial infections/drug therapy

Abstract:
The intrinsic antimicrobial resistance of Acinetobacter baumanii as well as its association with hospital exposure and immunosuppressive states, make selection of appropriate antimicrobial therapy simultaneously more difficult and more important. Recent clinical PK/PD data inform new dosing regimens for polymyxin B and colistimethate sodium (CMS) that incorporate loading doses and higher maintenance doses than previously recommended. These data demonstrate a better PK/PD profile of polymyxin B compared to CMS. Polymyxin B is available as an active drug rather than a prodrug and appears to be relatively unaffected by renal function. This is advantageous both for patients with renal impairment and those with intact renal function, the latter in whom achieving therapeutic serum concentrations of colistin may be difficult, due to rapid clearance of CMS. Clinical data are still lacking for polymyxin B and it remains to be seen whether advantages demonstrated in PK/PD analyses will persist in the larger scale of patient care and safety. In the meantime, in addition to giving higher doses of either colistimethate sodium or polymyxin B, using these drugs in combination with other antibiotics may prevent emerging resistance and preserve the activity of polymyxins against A. baumannii.

Introduction

Acinetobacter baumannii has emerged as a significant nosocomial pathogen worldwide [1]. Acinetobacter infections represented the ninth most common nosocomial pathogen reported to the National Healthcare Safety Network in 2006 – 2007 [2]. Morbidity and mortality associated with these infections is high, with crude mortality rates ranging from about 20 - 60% [3-6]. The intrinsic antimicrobial resistance of A. baumannii as well as its association with hospital and antimicrobial exposure and immunosuppressive states, make selection of appropriate antimicrobial therapy simultaneously more difficult and more important [7].

Since our review of the treatment of A. baumannii in 2004, few new therapies have become available [1]. Tigecycline, a novel tetracycline derivative with antibacterial activity against A. baumannii is a notable exception. However, FDA warnings about increased mortality associated with the drug, have led clinicians to shy from using it except in very limited circumstances [7]. One of the most significant changes in the treatment of treating A. baumannii infections has been the return of polymyxin antibiotics, both polymyxin B and colistin. These antibiotics, originally developed in the 1950s, fell by the wayside due to their toxicities and the availability of multiple other treatment options including a variety of beta-lactams and the fluoroquinolones [9]. Their approval, prior to current FDA new drug application standards, has led to many questions about the appropriate use of both colistin and polymyxin B [10]. Herein, we describe the use of the polymyxins for treatment of A. baumannii infections, discuss their overall pharmacology, and make suggestions for dosing and combination therapy based upon recent clinical data.

Acinetobacter baumannii Complex

Acinetobacter spp. cause a multitude of infections, including ventilator-associated pneumonia, line-associated bloodstream infections, meningitis, catheter-associated urinary tract infections, and skin and soft tissue infections [2]. They account for 8.4% of all ventilator-associated pneumonia isolates, 2.2% of all nosocomially-acquired central-line-associated bloodstream isolates, 1.2% of all catheter-associated urinary tract isolates, , and 0.6% of surgical site infection isolates [2]. Infections due to Acinetobacter baumannii complex represent a significant challenge to patients and healthcare systems given the persistence of the bacterial organism on surfaces and its ability to rapidly develop antibacterial resistance [11].

With respect to use of polymyxins to treat infections due to A. baumannii, an important characteristic of the organism is heteroresistance. Heteroresistance, or the presence of bacteria with mixed susceptibility patterns within a single clinical isolate, is not detectable by standard clinical susceptibility testing methods [12,13]. A. baumannii heteroresistance is particularly concerning for neutropenic patient populations. Without an intact immune system to prevent bacterial regrowth after initial exposure to polymyxins, these patients may be at higher risk of developing and harboring polymyxin-resistant A. baumannii isolates. Clinical strategies, including novel dosing regimens and combination antibiotic therapy, have been proposed as a

solution to prevent emerging resistance in patients treated with polymyxins for A. baumannii infections [13-17].

Pharmacology

Polymyxins are bactericidal drugs that exhibit their antibacterial activity by disrupting bacterial cell membranes, leading to cell lysis [9]. Two commercially available polymyxin antibiotics exist: polymyxin B and colistin (also known as polymyxin E). Colistin is available intravenously as the prodrug, colistimethate sodium (CMS). The availability of colistin as the prodrug CMS and the use of two different dosing terms: milligrams of colistin base activity and millions of international units (MU or IU) of CMS have been the source of significant confusion [18-20]. In this review, we will discuss doses in terms of milligrams of colistin base activity (CBA) with dosing in international units of CMS given in parentheses. Unlike colistin, polymyxin B is available as the active drug. Doses in the package insert are given in terms of international units, however a conversion factor of 10,000 units/mg is often utilized [21,22]. In this review, polymyxin B doses will be described in terms of milligrams with IU dosing given in parentheses, (Table 1).

Table 1: Polymyxin Nomenclature

Active Drug	Pro-drug	Dosing Terms
Colistin (CBA)	Colistimethate sodium (CMS)	1 mg CBA = 30,000 IU CMS
Polymyxin B	N/A	1 mg Polymyxin B = 10,000 IU Polymyxin B

Pharmacokinetics (PK) and Pharmacodynamics (PD)

For treatment of serious infections due to MDR A. baumannii, colistin and polymyxin B are given intravenously. Neither is bioavailable upon oral dosing, although minimal systemic absorption has been demonstrated after CMS is administered via inhalation [23,24]. Both polymyxin B and colistin are highly protein bound [16,25]. However, they have relatively low volumes of distribution: 0.19 L/kg, 0.17 L/kg, and 0.4 L/kg for CMS, colistin, and polymyxin B respectively [17,26]. Each has a propensity to accumulate in renal tissue, which likely contributes to renal toxicity [27,28]. The penetration of colistin into the cerebral spinal fluid (CSF) after intravenous dosing of CMS is only 5% of the total colistin serum concentration [29]. Higher concentrations may be achieved using intraventricular administration [30]. The penetration of polymyxin B into CSF is not well described. However, intraventricular administration of polymyxin B has been safely accomplished [31].

Non-renal pathways are the major route of elimination for both colistin and polymyxin B [25,27]. The prodrug, CMS, is eliminated renally. As result, CMS requires dose adjustment in renal dysfunction while polymyxin B does not [16,17,32,33]. In patients with unimpaired renal function, the high rate of renal CMS elimination raises concerns for achieving target serum concentrations [16,34]. By contrast, polymyxin B serum concentrations are not significantly altered by renal function, whether impaired or intact [17,33]. Metabolic pathways of drug elimination have not been described in the literature and neither drug has demonstrated significant interactions with other drugs and chemicals via enzymatic inhibition or induction.

The PK/PD parameter for both drugs involves maximizing the ratio of drug exposure, as measured by area under the curve (AUC) concentrations to the bacterial minimum inhibitory concentration, (MIC) [16,17,35]. Target AUC:MIC values for colistin against A. baumannii have been established in mouse thigh and lung models and range from 17 – 95 [16,35]. Although established with colistin, this information has been extrapolated for the PK/PD target of polymyxin B as well [17]. These data can be used to inform patient-specific dosing regimens.

In a large pharmacokinetic study, Garonzik et al. provided dosing equations to achieve target steady state colistin concentrations [16]. Based on their population PK analysis, steady state serum concentrations of 2.5 mg/L correlated to an AUC of 60 mg*h/L [16]. The authors concluded CMS dosing regimens achieving this serum concentration would be sufficient to treat an infection due to A. baumannii with an MIC < 1 mcg/mL. Conversely, treatment of an infection due to A. baumannii with an MIC = 1 mcg/mL would require a doubling of the dosage, raising concerns for tolerability and toxicity [16].

In 2013, Sandri et al. conducted a population pharmacokinetic analysis of 24 patients treated with polymyxin B [17]. Based upon these data, the authors utilized Monte Carlo analysis, a simulation of a large virtual population with varying pharmacokinetic parameters, to evaluate various dosing regimens and their ability to achieve a target fAUC:MIC of 40 [17]. fAUC quantifies

the non-protein bound concentration of polymyxin B, approximately 40% of the total concentration, and the presumed active form of the drug [17]. AUC values varied 3-fold among the virtual subjects modeled to receive the same dose [17]. However, the authors concluded that a total daily dose of 3 mg/kg/day (30,000 IU/kg/day) would be sufficient to achieve the target fAUC:MIC in subjects with infection due to A.baumannii with an MIC = 1 mcg/mL [17]. Again, concerns were raised for the ability to design a tolerable regimen to overcome infections due to A. baumannii with an MIC > 1 mcg/mL [17].

The susceptibility breakpoint for A. baumannii to colistin or polymyxin B is 2 mcg/mL, as established by the Clinical Laboratory Standards Institute (CLSI) [36]. The standard error of the test, allows for MIC variance of 1 doubling dilution [36]. Therefore a reported MIC of 1 mcg/mL may actually be anywhere between 0.5 – 2 mcg/mL. For clinicians wishing to implement PK/PD targets in their practice, MIC variation must be considered [10]. Achieving the PK/PD target is highly dependent upon organism MIC, given its place in the denominator of the ratio, AUC:MIC. Susceptibility testing assays contribute additional variation to the MIC depending on both the method and materials used [10,37,38]. Since the correlation of these PK/PD targets to clinical outcomes has not yet been determined, risks must be carefully assessed for each individual patient before significantly increasing a dose based on an MIC exceeding 1 mcg/mL [16,17].

Clinical Use

Dosing recommendations derived from PK/PD data support the use of a loading dose in order to more rapidly achieve target serum concentrations [16,17,34]. Additionally, doses predicted to achieve target AUC:MIC values are higher than those listed in the package inserts for both drugs [16,17,22,39]. Given the recent publications outlining new dosing regimens, clinical data describing them remain limited. Most information evaluating polymyxin B and CMS for treatment of A. baumannii was collected and/or published prior to the availability of these alternate dosing regimens. The following discussion will review outcomes associated with the use of CMS and polymyxin B for treatment of MDR A. baumannii infections, bearing in mind the limitations of the doses utilized.

Monotherapy

Three clinical studies, two of which were prospective, evaluated CMS compared to imipenem or ampicillin-sulbactam for the treatment of ventilator-associated pneumonia (VAP) due to MDR A. baumannii. A. baumannii infections treated with CMS were resistant to all other routinely tested antibiotics including penicillins, cephalosporins, carbapenems, aztreonam, fluoroquinolones, aminoglycosides, and tetracyclines [5,40,41]. Rates of clinical success ranged from 57 – 75%, whereas in-hospital mortality was 30.3 – 61.9% [5,40,41]. These mortality rates were consistent with previously published rates in patients with VAP due to drug-resistant Gram-negative bacilli [42,43]. Subjects treated with CMS had similar outcomes as those treated with comparator antibiotics [5,40,41]. Each of the three trials was small; the two prospective studies evaluated 28 and 35 subjects whereas the retrospective study evaluated 60 subjects. These small numbers and heterogeneous populations likely contribute to the wide variation demonstrated among the outcomes evaluated.

CMS doses utilized in each of the studies varied from fixed doses of 200 – 300 mg/day (6 – 9 MU/day) to weight-based doses of 2.5 – 3 mg/kg/day (15,000 – 75,000 IU/kg/day) without the use of a loading dose. [5,40,41]. An additional clinical study evaluated clinical outcomes according to the CMS dosing regimen proposed by pharmacokinetic data [32]. However, infectious syndromes other than VAP were included [32]. Dalfino et al. incorporated loading doses and higher daily doses, not necessarily as CMS monotherapy, and demonstrated lower mortality and higher cure rates, approximately 25% and 82% respectively [32]. Due to differences in patient populations and study designs, conclusions regarding outcomes by doses administered cannot be reliably drawn. Other data have demonstrated greater treatment success with higher CMS doses, but these may be confounded by baseline differences in renal function as patients with renal injury or failure would have received lower doses [44].

Data evaluating polymyxin B as monotherapy for treatment of A. baumannii are limited. However there are data describing use of polymyxin B for treatment of infections due to other pathogens [45]. One single-center, retrospective study evaluated the use of polymyxin B as monotherapy for treatment of infections due to carbapenem-resistant K. pneumoniae (CRKP) [45]. Dosing varied over the 4 years data were collected. Initially subjects received 1.5 – 2.5 mg/kg/day (15,000 – 25,000 IU/kg/day) in divided doses. After two years, loading doses of 2.5 mg/kg (25,000 IU/kg) were implemented. Across all 4 years, doses were adjusted for renal dysfunction [45]. Among 40 subjects, 73% improved or resolved their infection. Thirty-day mortality was only 18%, however 12 of the 40 subjects were treated for a urinary tract infection. Upon univariate regression analysis, factors associated with clinical failure included septic shock, pneumonia, admission to the ICU, and baseline renal dysfunction [45]. After multivariate analysis, only baseline renal dysfunction remained an independent risk factor [45]. As we will discuss further, this may be related to a problem of under-dosing as recent data suggest that polymyxin B does not require adjustment for renal dysfunction [17,33].

Bacterial persistence was an issue described in data discussing CMS and polymyxin B monotherapy [5,40,45]. In 2 of the 3 CMS VAP studies, failure to eradicate A. baumannii was demonstrated in 30% of the subjects evaluated for this secondary outcome [5,40]. Repeat susceptibility testing was not reported; therefore it is unknown whether drug resistance emerged. Interestingly, persistence of A. baumannii was not always associated with clinical failure [5,40]. In the CMS trial reported by Dalfino et al., failure to clear bacterial cultures was statistically significantly associated with clinical failure among 17 subjects with bloodstream infections but not among subjects with VAP. [32]. Among subjects with VAP, the rate of bacterial clearance was only 40%; although, all 10 patients responded clinically. No emerging resistance was detected among subjects with persistent cultures [32]. Dubravskaya et al. found 19 subjects of 40 treated with polymyxin B monotherapy had repeat CRKP cultures after completion of their initial antibiotic treatment. Emerging resistance was detected in 6 subjects, 3 during their first course of therapy and 3 during subsequent infection [45]. Despite high rates of treatment success, persistence of bacterial growth and emerging resistance raises concern for long-term efficacy of polymyxin monotherapy.

Combination Therapy

Clinical, microbiological, and pharmacokinetic data for both polymyxin B and CMS suggest important benefits for use of this class of antibiotics in combination with other antimicrobial therapies [13,15,16,25,46]. The most robust clinical antimicrobial combination therapy data for MDR A. baumannii infections have evaluated CMS and rifampin [47-52]. Collectively, these data describe outcomes primarily for ventilator-associated and hospital-acquired pneumonia but also include some patients with other infection syndromes including bacteremia and intra-abdominal infections [47-52]. Comparative studies found no statistically significant improvements in clinical outcomes or mortality when CMS was combined with rifampin or given alone for the treatment of MDR A. baumannii infections [47,48]. However, combination therapy with CMS and rifampin was associated with greater and more rapid bacterial eradication in two prospectively designed trials [47,48].

The improvement in bacterial eradication seen in these clinical trials is consistent with animal and in vitro data demonstrating a bactericidal benefit of combination treatment [53,54]. The lack of a difference identified for clinical outcomes and mortality between treatment arms does not preclude use of combination therapy. It is possible that the benefit of combination therapy was not detected in a group of severely ill patients with a high propensity for mortality based on co-morbidities and circumstances leading to infection with MDR A. baumannii. Enrollment in the study published by Aydemir et al. achieved only half of the targeted enrollment, thus it was likely underpowered [47]. CMS doses employed by Durante-Mangioni et al. were substantially lower than doses that have subsequently been recommended based on PK/PD data [48,16]. Given minimal toxicity found upon the addition of rifampin to CMS and increased rates of bacterial eradication, there appears to be a benefit associated with combination therapy.

Additional clinical data describe combination therapy with CMS and other therapies, in particular the carbapenems [55-57]. These data are retrospective in nature and have produced signals of improved clinical outcomes for treatment of MDR A. baumannii infections treated with CMS in combination with either meropenem or imipenem [55-57]. Two multi-center, randomized controlled trials are currently enrolling patients to evaluate CMS monotherapy compared to CMS and carbapenem combination therapy for the treatment of infections due to MDR gram negative bacteria [58,59]. Until these data are collected and evaluated, the best combination treatment evidence available for A. baumannii eradication supports therapy with rifampin and CMS. Clinical circumstances, institutional resistance rates, and individual patient characteristics, i.e. concomitant infections, co-morbidities, allergies, drug-drug-interactions, renal and hepatic function, should be carefully considered when designing a combination therapy regimen.

Combination therapy data for polymyxin B are even more lacking than for CMS [21,60,61]. A 2014 observational study evaluated 104 subjects with carbapenem-resistant Gram-negative bacterial infections [60]. Subjects received polymyxin B with a loading dose of 2.5 mg/kg (25,000 IU/kg) most commonly in combination with a carbapenem, or a carbapenem plus rifampin [62]. Among 34 subjects with A. baumannii infections, 44.1% improved or resolved their signs and symptoms, 46.8% demonstrated bacterial eradication, and 50% survived [62]. With respect to combination therapy, no statistically significant differences were identified; microbiological and clinical success were more common in the subjects who received combination therapy compared to the small group of subjects who received polymyxin B monotherapy [62]. Another single-center, retrospective study described clinical use and outcomes among 25 patients who received polymyxin B either intravenously or inhaled for respiratory tract infections due to MDR gram-negative bacilli [21]. All patients received polymyxin B in combination with another antibiotic, most commonly a carbapenem. Intravenous polymyxin B was initiated with a loading dose of 2.5 – 3 mg/kg (25,000 – 30,000 IU/kg) followed by 1.0 – 2.5 mg/kg/day (10,000 – 25,000 IU/kg/day) given in varying frequency based upon renal function. The most common inhaled dose was 2.5 mg/kg/day (25,000 IU/kg/day) in four divided doses [21]. Although the data were not comparative, it was noted that bacterial eradication was associated with decreased mortality [21]. Based on similar pharmacology between colistin and polymyxin B, and in spite of minimal data evaluating combination therapy with polymyxin B, the use of polymyxin B in combination with other antimicrobial agents is a reasonable clinical approach to treating infections due to MDR A. baumannii.

Inhaled Therapy

Prospective pharmacokinetic data demonstrated undetectable colistin concentrations in the bronchoalveolar lavage (BAL) fluid of critically ill patients following intravenous administration of CMS [63]. Inhaled antimicrobial therapy is a strategy used to increase drug exposure at the site of infection among patients with bronchitis and/or pneumonia. The median peak epithelial lining fluid concentration following delivery of CMS by inhalation was 6.7 mcg/mL in a study of 20 mechanically ventilated patients [64]. Concentrations of this magnitude would be expected to eradicate infection due to colistin-susceptible A. baumannii [64]. Although there are multiple observational studies evaluating the effect of inhaled CMS upon clinical outcomes, to date, there are no prospective case-controlled data comparing outcomes in patients with and without inhaled CMS. Use of inhaled CMS has been associated with greater bacterial eradication from the lungs; however this has not consistently translated to differences in clinical outcomes [65]. Data regarding the use of inhaled CMS are contradictory, with some studies demonstrating benefit [66], and others, a lack of benefit [67]. This may be due to heterogeneity of patient populations and their infections, as well as the drug delivery systems themselves. The delivery of drug particle sizes varies by the type of nebulizer used which can affect the dose of inhaled CMS a patient receives [64].

Inhaled polymyxin B has been evaluated in one observational study of 19 subjects with pneumonia or tracheobronchitis primarily due to P. aeruginosa [68]. Subjects received 50 mg (500,000 IU) of inhaled polymyxin B twice daily for an average duration of 14 days, often in combination with intravenous antibiotics [68]. While clinical improvement or cure occurred in all but one patient, in-hospital mortality was documented in almost half of the patients evaluated. Additionally, 4 experienced cough or bronchospasm related to the inhaled therapy, which abated after decreasing the dose of polymyxin B [68]. Overall, the data supporting inhaled polymyxins are equivocal as they lead to greater bacterial eradication but not always better clinical outcomes [65]. There are more data and overall experience with inhaled CMS compared to polymyxin B. Given

high frequency of bronchospasm or cough among the small number of subjects evaluated for inhaled polymyxin B, the use of CMS is more prudent than polymyxin B. Despite questionable clinical efficacy of inhaled CMS, the toxicity reported in both prospective and retrospective studies is rather minimal [65,66,69]. However a 2007 FDA Medwatch alert reported on the investigation of a patient death following administration of inhaled colistin which had been pre-mixed by the pharmacy prior to nebulization [70]. The alert concluded that pre-mixing and storing the product in aqueous solution more than 24 hours leads to a greater rate of conversion of CMS to colistin, and may result in toxicity to lung tissue [70]. Thus, in MDR A. baumannii pulmonary infections, this therapy may be considered as adjunctive treatment to intravenous antibiotic therapy. Daily doses of approximately 75 - 133 mg of CBA (approximately 1.5 - 4 MU CMS) given in 1 – 3 divided doses have been evaluated [44,65,69].

Dosing and Dosing Strategies

Dosing recommendations for polymyxin B and colistin have been updated significantly in the past 3 years due to the relatively recent availability of assays to detect concentrations of both active and pro-drugs in serum and other biological sites [71-73]. We have selected to review this information proceeding the discussion of polymyxin B and CMS clinically because with the exception of one study by Dalfino et al., these dosing recommendations have not yet been validated with clinical data [32].

Loading Doses

In the absence of a loading dose, both polymyxin B and colistin serum concentrations may take 2 to 3 days to achieve steady state [17,34]. Given that delaying time to appropriate antibiotic therapy is associated with greater mortality, this provides a strong rationale for initiating therapy with a loading dose [74]. Clinical outcomes data comparing CMS dosing with and without initial loading doses are not available. However, the PK/PD data supporting this strategy have been robust and toxicities associated with colistin do not appear to increase with use of a loading dose [16,17,32,62]. It should be cautioned that safety data for polymyxin B are limited, especially for single doses exceeding 3 mg/kg (30,000 IU/kg) or 200 mg (2,000,000 IU) of polymyxin B per day [17,75].

Dosing Weight

The CMS package insert recommends use of ideal body weight as a dosing weight in obese patients, though data are limited with respect to dosing in obesity [39]. Gauthier et al. demonstrated that neither total daily doses nor cumulative doses of CMS were associated with incidence of nephrotoxicity in overweight and obese patients [76]. However, the total daily doses utilized were less than those suggested by 2011 clinical PK analyses [16,76]. In the absence of compelling data demonstrating which definition of body weight to use, it is judicious to use ideal body weight at this time.

Polymyxin B should be dosed using total body weight in most cases [17,33]. Data regarding dosing of polymyxin B in obesity appears to be represented in the literature by one 250 kg man with a reported body mass index of 77.2, and renal disease, dependent upon continuous renal replacement therapy (CRRT) [17,33]. The patient received a total daily dose of 2 mg/kg (20,000 IU/kg) and was found to have similar total drug exposure, as measured by polymyxin B AUC, compared to a 51 kg woman also dependent upon CRRT [17,32]. This suggested that for polymyxin B, dosages should be based upon actual and not ideal body weight. However, caution should be exercised when selecting doses for obese patients as drug clearance may not scale directly to body size [77]. Thus, using the total body weight to calculate a dose could result in overdose [77]. Since there are minimal data to guide polymyxin dosing among morbidly obese patients, clinicians may consider selecting doses on the lower end of the polymyxin B dosing range and/or using an adjusted body weight [17,33,77].

Dose Adjustments for Renal Dysfunction

Although renal clearance of colistin is minimal, the prodrug, CMS, is primarily cleared via the kidneys [16]. Due to the renal dependence of CMS, the drug requires dose-adjustment for renal dysfunction [16]. Based on pharmacokinetic data published by Garonzik et al., even for patients with renal impairment, the initial dose of CMS should be a load (Table 2). To account for renal dysfunction, the dosing recommendations include decreasing the dose and/or extending the dosing interval, (Table 2) [17,32].

For patients dependent upon renal replacement therapy, dosing recommendations for CMS are based upon achieving a serum colistin concentration of 1 mg/L [16,71]. For patients dependent on continuous renal replacement therapy (CRRT), the regimen of 200 mg of CBA (6 MU CMS), divided q 8 hours, is supported by the greatest amount of data (in a total of 9 patients) [16,72,78]. For intermittent hemodialysis (IHD), the doses suggested are much lower, ranging from 30 – 70 mg of CBA (0.9 – 2.0 MU CMS) daily. Variation in dosing recommendations for IHD is related in part to the degree of residual renal function remaining. This alters CMS clearance, particularly on non-dialysis days [16]. A session of hemodialysis reduces serum concentrations of CMS and colistin substantially. This warrants use of a supplemental CMS dose: 30 – 50% of the daily maintenance dose, following hemodialysis [16]. Dosing equations published by Garonzik et al. utilize residual renal function as a factor to determine total daily dose [16]. In the absence of any residual renal function, their PK analyses predict a total daily dose requirement of 30 mg of CBA (0.9 MU of CMS) on non-dialysis days and 50 mg of CBA (1.5 MU of CMS) on dialysis days to achieve a steady state concentration of 1 mg/L [16]. Overall, data describing clinical efficacy and safety outcomes associated with CMS dosing among patients dependent on renal replacement therapy remain limited.

Polymyxin B is not eliminated renally [17,25,33]. Only 1 - 4% of a polymyxin B dose is excreted unchanged into the urine [17,25]. Therefore, even for subjects reliant upon renal replacement therapy, a dose adjustment of polymyxin B is not required, (Table 2) [17]. Although polymyxin B is not eliminated by the kidneys, there is still significant renal exposure to the drug [17]. About 90% of the drug filtered by the glomerulus is reabsorbed by the renal tubules [17]. Therefore, patients with higher creatinine clearance have the greatest renal tubular exposure to polymyxin B which may lead to greater risk of kidney injury compared to those with lower filtration rates [17].

Table 2: **Dosing and Dose Adjustments for CMS and Polymyxin B According to Renal Function**

	Loading Dose	Maintenance Doses				
Renal Function ClCr (mL/min)		≥50	> 20 – 50	≤20	IHD[1,2]	CRRT[1,2]
CMS	5 mg/kg CBA (9 MU CMS) x1	2.5 mg/kg CBA (4.5 MU CMS) q 12 hours	2.5 mg/kg CBA (4.5 MU CMS) q 24 hours	2.5 mg/kg CBA (4.5 MU CMS) q 48 hours	30 mg CBA (0.9 MU CMS) on non-IHD days, 50 mg CBA (1.5 MU CMS) on IHD days, after HD	67 mg CBA (2 MU CMS) q 8 hours
Polymyxin B	2.5 mg/kg (25,000 IU/kg) x1	1.5 mg/kg (15,000 IU/kg) q 12 hours				

Dosing based on recommendations from Garonzik et al., Dalfino et al., and Sandri et al. [16,17,32]. See text for discussion of dosing weight.
CBA: colistin base activity, ClCr: Creatinine clearance, CMS: colistimethate sodium, CRRT: continuous renal replacement therapy, IHD: intermittent hemodialysis
[1] For anuric patients, dosing targeted to achieve a steady state serum concentration of 1 mg/L. Higher doses can be considered in patients for whom a higher target study state serum concentration is desired and/or patients with residual renal function despite dialysis-dependence.
[2] Dose listed as total daily dose, not mg/kg

Conclusions

Infections due to *A. baumannii* continue to challenge patients, practitioners, and healthcare systems. Given the lack of new antibacterial agents, many clinicians have returned to the polymyxins. The optimal use of this class is imperative in order to preserve their effectiveness in the face of antibacterial resistance. Based upon PK/PD information, dosing strategies including loading doses, should be implemented as a means to maximize either colistin or polymyxin B exposure without delay [16,17]. Combination treatment may also preserve the utility of polymyxin antibiotics especially given heteroresistance patterns of *A. baumannii*. The selection of an agent to use in combination with either CMS or polymyxin B remains a patient-specific decision in the absence of strong clinical data supporting one agent over another. The clinical decision should include an assessment of the site of infection, susceptibility of the isolate, drug-drug interactions, and adverse effects.

Polymyxin B has a better PK/PD profile compared to CMS, given its availability as an active drug rather than a prodrug [25]. Doses of polymyxin B appear to be relatively unaffected by renal function, which may prove a huge advantage in critically ill patients with temporary or permanent organ dysfunction [17,33]. Polymyxin B may also be useful among patients with intact renal function, for whom achieving therapeutic serum concentrations of colistin may be difficult, due to rapid clearance of CMS [16]. However, clinical data are still lacking for polymyxin B and it remains to be seen whether advantages demonstrated in PK/PD analyses will persist in the larger scale of patient care and safety. Fortunately, both polymyxin B and CMS are under active investigation. Thus, more information about how to optimize their use and whether one is superior to the other will be forthcoming in the near future.

Acknowledgements: The authors thank Larry H. Danziger for reviewing this manuscript

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SOCIETY OF INFECTIOUS DISEASES PHARMACISTS
MEMBERSHIP APPLICATION

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Last Name _____ First Name _____ Middle Initial _____ Sex: M/F _____

Company/Organization _____

Mailing Address _____ Department _____

City _____ State or Province _____ Zip/Postal Code _____ Country _____

Telephone _____ Fax _____

Business Email Address _____ Personal Email Address _____

DEGREE(S) EARNED: ☐ B.S. (Pharmacy) ☐ M.S. ☐ Pharm.D. ☐ Ph.D. ☐ Other _____

TRAINING EXPERIENCE: Pharmacy Practice Residency Advanced Practice Residency Infectious Diseases Residency

Infectious Diseases Fellowship Informal Training Other _____

My primary place of employment is (check one):
☐ Hospital Setting ☐ Private Medical Group Setting ☐ Managed Care
☐ Industry ☐ Academic Setting ☐ Governmental Organization ☐ Other _____

I am applying for *(check only one)*:

☐ **Active Member** - Any pharmacist who has substantial professional activities in the area of infectious diseases pharmacotherapy or research may participate as a voting, active member of The Society. Prospective members must have been practicing or performing research in infectious diseases pharmacotherapy for at least two years after receipt of the terminal academic degree. Active member applicants must submit 2 letters of reference from fellow health care professionals attesting to substantial professional activities in the area of infectious disease pharmacotherapy or research and a current curriculum vitae.

☐ **Associate Member** - Pharmacist or non-pharmacist not meeting the requirements for the Active membership, but with an interest in the area of infectious disease pharmacotherapy, may participate as a non-voting member of The Society. Associate member applicants must submit 1 letter of reference from a fellow health care professional attesting to his/her interest in the area of infectious disease pharmacotherapy or research along with a current curriculum vitae.

☐ **Trainee-Associate Member** - Pharmacist in either a residency or fellowship program with emphasis on infectious disease pharmacotherapy, and not more than two years past the receipt of the terminal degree, or student in an accredited school of pharmacy pursuing a degree in pharmacy, may participate as a non-voting member of The Society. Those individuals more than two years past the terminal degree should apply for active or associate status, whichever is appropriate. Trainee-Associate member applicants must provide a letter from their program director and student applicants must provide a letter from a professor. All applicants must also provide a current curriculum vitae.

Are you a current member applying for a membership upgrade? **Yes** ☐ **No** ☐

Membership Dues Structure (U.S. Funds):
☐ **Active and Associate Members:** $100 for one year or three year membership for $270
☐ **Trainee-Associate Members:** $25 per year. (No multiple year rate is available.)

Payment Information:

Check enclosed ☐

Charge my: ☐ Visa ☐ MC ☐ Amex ☐ Discover Amount authorized $_____

Account number_____ CVV (back of card)_____ Exp. date_____

Cardholder's name_____ Signature of cardholder_____

Cardholder's billing address_____

City_____ State _____ Zip _____

All dues are in U.S. Funds. Send a check, money order or you may charge your dues to Mastercard, Visa, American Express, Discover or Diner's Club.
Include card number, name on card, CVV (back of card) and expiration date. If you use a credit card, SIDP's management company, "EAMI", will charge your credit card for your SIDP dues.

Application/dues fees are non-refundable. If you are denied membership in the active category, your dues will be applied to associate member status. Thank you.

Please mail this completed application, appropriate information and dues payment to:
The Society of Infectious Diseases Pharmacists
823 Congress Ave., Ste. 230
Austin, TX 78701