

October 12, 2016

Andrew Slavitt  
Acting Administrator  
Centers for Medicare & Medicaid Services  
Department of Health and Human Services  
Attention: CMS-1461-P  
P.O. Box 8013  
Baltimore, MD 21244-8013

Re: Sepsis National Hospital Inpatient Quality Measure (SEP-1)

Dear Mr. Slavitt,

The Infectious Diseases Society of America (IDSA) in collaboration with the American College of Emergency Physicians (ACEP), the Society of Critical Care Medicine (SCCM), and the Society of Hospital Medicine (SHM) would like to collectively share our concern with the Severe Sepsis and Septic Shock: Management Bundle (SEP-1) performance measure and the unintended consequences it may have on the appropriate use of antibiotics.

IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases.

ACEP represents over 34,000 emergency physicians dedicated to the emergent care of patients who may suffer from a wide array of conditions ranging from chest pain to spinal disorders.

SCCM represents more than 16,000 critical care physicians internationally who are committed to the treatment of critically ill patients who require intensive care.

SHM represents nearly 15,000 hospitalists whose primary professional focus is the general medical care of hospitalized patients.

According to the Healthcare Cost and Utilization Project (H-CUP) Statistical Brief #204, sepsis was the most expensive condition treated across all payers and the second most common reason for hospitalization in 2013.<sup>i</sup> Given the costs as well as the high mortality rate (182,242 sepsis deaths in 2014), a focused effort is needed to improve sepsis outcomes. Increasing the difficulty to optimally treat septic patients, antibiotic-resistant infections have substantially burdened the health and economics of the U.S. health care system and population<sup>ii</sup> in addition to causing 2 million illnesses and approximately 23,000 deaths each year in the United States.<sup>iii</sup>

Understanding the need to address the sepsis issue, the Center for Medicare and Medicaid Services (CMS) adopted the SEP-1 performance measure to the Hospital Inpatient Quality Reporting (IQR) Program in July 2015, with the performance period starting in October 2016. The undersigned specialty societies agree with the need for SEP-1, which requires timely administration of appropriate antibiotics

to patients with sepsis or septic shock. However, we strongly believe that all the listed antibiotics in the antibiotic tables for SEP-1 (Table 5.0: Monotherapy Antibiotics, Sepsis, Combination Antibiotic Therapy Table, Table 5.1: Antibiotic Generic/Trade Name Crosswalk, Sepsis) are not appropriate and we believe the use of antibiotics as called for in the SEP-1 measure are not in alignment with prudent antimicrobial stewardship.

## **Concerns with SEP-1**

In August 2015, ACEP, SCCM, and IDSA expressed concern with the SEP-1 performance measure in [a letter](#) to CMS.<sup>iv</sup> The letter specifically brought attention to the unintended consequences of requiring the administration of specific listed broad-spectrum antibiotics to severe sepsis patients who present with a known infection that responds better to an antibiotic or antibiotics not in the tables. Addressing those concerns, in July 2016 CMS made amendments to SEP-1's "Broad Spectrum or Other Antibiotic Administration Selection" data element to include the following language,

*"If an IV antibiotic from Table 5.0 or an appropriate combination of IV antibiotics from Table 5.1 is not started or given within the 3 hours following presentation of severe sepsis, but there is a lab report or physician/APN/PA documentation indicating the causative organism and susceptibility is known (see exception for C. difficile) and an IV antibiotic identified as appropriate to treat the causative organism is given within 3 hours following presentation of severe sepsis, choose Value "1" v"*

We appreciate the action CMS has taken to allow for a process for physicians to exercise clinical judgement to optimally treat septic patients. We also do recognize the difficult situation CMS must address to decrease the high mortality rate and costs associated with sepsis. There is a delicate balance between utilizing clinical quality measures to standardize care according to best practices, allowing physicians to provide patient care that applies their clinical expertise, and addressing the unique clinical situation that is presented.

While this exception is necessary and does not penalize hospitals and subsequently physicians for administering an antibiotic not listed on the SEP-1 antibiotic tables, further effort is needed to promote the practice of antibiotic stewardship to combat the larger issue of antibiotic resistance and unintended consequences including adverse drug events and increased risk for C. difficile infections. This need has been highlighted by the National Action Plan for Combating Antibiotic-Resistant Bacteria developed by the White House in March 2015<sup>vi</sup> as well as the proposed rule for the Medicare and Medicaid Hospitals Conditions of Participation published in June 2016.<sup>vii</sup>

## **Modification of Antibiotic Tables for SEP-1 Workgroup Process and Results**

Recognizing the need to promote the judicious use of antibiotics in the treatment of sepsis, IDSA convened a multi-stakeholder workgroup in May 2016 to address the aforementioned concerns. The Modification of Antibiotic Tables for SEP-1 Workgroup (MATS WG) was composed of one representative from ACEP, two from SCCM, one from SHM, and two from IDSA with the goal to strengthen patient safety by promoting the optimal use of antibiotics. The specific objectives of the MATS WG was to

evaluate and revise as necessary the antibiotic tables specified for SEP-1 to enable the appropriate empiric treatment of sepsis.

**Table 1: Composition of MATS WG**

Organizations	Physician Representatives
The American College of Emergency Physicians (ACEP)	Jessica Whittle, MD, PhD, FACEP University of Tennessee College of Medicine Chattanooga
The Society of Critical Care Medicine (SCCM)	Mitchell Levy, MD, MCCM Rhode Island Hospital
	Craig Coopersmith, MD, FCCM Emory University
The Society of Hospital Medicine (SHM)	Caleb Hale, MD, SFHM Beth Israel Deaconess Medical Center
The Infectious Diseases Society of America (IDSA)	Ed Septimus, MD, FIDSA HCA Healthcare Systems
	Neil Fishman, MD, FIDSA University of Pennsylvania Health System

A total of 12 respondents completed the survey. For Table 5.0: Monotherapy Antibiotics, a total of 14 antibiotics were reviewed. Of the 14 monotherapy antibiotics, 9 received majority approval by the respondents, 3 antibiotics were not approved (ampicillin/sulbactam, levofloxacin, moxifloxacin), and 2 antibiotics (ertapenem, ticarcillin/clavulanate) received an equal amount of votes for approval and disapproval. The survey respondents cited a common concern of large amounts of antibiotic resistance as to why ampicillin/sulbactam, levofloxacin, and moxifloxacin were not approved. *E. coli* resistance to ampicillin/sulbactam has been observed in numerous studies<sup>viii,ix,x,xi</sup>. Levofloxacin has been shown to be efficacious against many pathogens, namely pneumonia caused by the *Haemophilus* species<sup>xii</sup>, however levofloxacin resistance have been observed in *H. influenzae*<sup>xiii,xiv</sup> as well as high levels of resistance in *P. aeruginosa* and *E. coli*<sup>xv</sup>. Similarly, moxifloxacin has been shown to have very high rates of resistance in *C. difficile* isolates.<sup>xvi</sup> As for the antibiotics that resulted in a draw, the MATS WG was polled again to reach consensus on only ertapenem and not ticarcillin/clavulanate (Timentin), as ticarcillin/clavulanate was discontinued due to safety issues<sup>xvii</sup>. Ertapenem was ultimately approved by majority of respondents for inclusion on Table 5.0. Furthermore, respondents were asked to provide suggestions for monotherapy antibiotics not listed in Table 5.0. The MATS WG agreed to include 2 antibiotics (ceftazidime avibactam, cefolozane tazobactam) that were proposed to be included in the revised Table 5.0.

**Table 2: Results of Monotherapy Antibiotics Review by MATS WG**

Results	Antibiotic Selection Options (generic names)	
<b>Approved</b>	Doripenem Cefepime Imipenem/Cilastatin Meropenem Cefotaxime	Ceftazidime Ceftriaxone Ceftaroline fosamil Piperacillin/tazobactam
<b>Not Approved</b>	Ampicillin/sulbactam Moxifloxacin Levofloxacin	
<b>Draw</b>	Ertapenem Ticarcillin/clavulanate	

The Combination Antibiotic Therapy Table allows for a total of 21 antibiotic class combinations. Of the total combinations, 10 were approved by the majority of respondents. The antibiotic class combinations not approved for the empiric treatment of sepsis consisted of any combination with macrolides or ciprofloxacin as well as the specific combinations of aztreonam with cephalosporins and aminoglycosides with clindamycin IV. Macrolide antibiotics, predominately administered as the first line of treatment for community-acquired respiratory tract infections caused by *M. pneumoniae*, have been observed to have high rates of resistance in *M. pneumoniae* in Asia and moderate levels of resistance in Europe and US.<sup>xviii</sup> As well, resistance to macrolides in *S. pneumoniae* has been steadily increasing since the 1990's.<sup>xix</sup> With the efficacy of available antibiotics diminishing and the dearth of development of new antibiotics, restricting the use of effective antibiotics with relatively low resistance rates is imperative to preserve an efficacious antibiotic pipeline. Furthermore, the macrolide antibiotic telithromycin (Ketek), specified in Table 5.1 for SEP-1, has been discontinued due to business reasons.<sup>xx</sup> Ciprofloxacin has also seen an increase in clinical ineffectiveness, particularly in nosocomial gram-negative bacteremia.<sup>xxi</sup> Additionally, as part of the larger antibiotic class of fluoroquinolones, ciprofloxacin resistance has remained high among MRSA, *P. aeruginosa*, *E. coli*, anaerobes, and pathogens found in intensive care units.<sup>xxii</sup> In alignment with the combinations not approved by the workgroup, concerns with increasing resistance and adequate coverage of pathogens were cited for reasons why the combinations of aztreonam<sup>xxiii</sup> with cephalosporins<sup>xxiv</sup> and aminoglycosides<sup>xxv</sup> with clindamycin IV<sup>xxvi</sup> were not approved.

**Table 3: Results of Combination Antibiotic Therapy Review by MATS WG**

Results	Antibiotic Class Combination Options
Approved	Aminoglycosides + Cephalosporins OR Daptomycin OR Glycopeptides OR Linezolid OR Penicillins
	Aztreonam + Daptomycin OR Glycopeptides OR Linezolid OR Penicillins OR Clindamycin IV
Not Approved	Macrolides Ciprofloxacin Aztreonam + Cephalosporins Aminoglycosides + Clindamycin IV

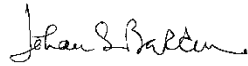
**Modification of Antibiotic Tables for SEP-1 Workgroup Recommendations**

Resulting from the work the MATS WG, we respectfully provide our recommendations for Table 5.0: Monotherapy Antibiotics in **Table 4**, the Combination Antibiotic Therapy Table in **Table 5**, and Table 5.1 Antibiotic Generic/ Trade Name Crosswalk in **Table 6**.

Revisiting the amendments CMS has made to the SEP-1 measure specifications, we believe the addition of cefotetan to the Table 5.1 Antibiotic Generic/Trade Name Crosswalk is not appropriate. Cefotetan is mainly administered as a surgical prophylactic and has resulted in high rates of surgical site infections<sup>xxvii</sup> as well as IDSA recommending cefotetan not be used to treat community-acquired intra-abdominal infections in adults due to increasing resistance<sup>xxviii</sup>. **We respectfully recommend that CMS remove cefotetan from Table 5.1 due to the above-mentioned rationale.**

We appreciate the effort CMS has made to address the serious issue of sepsis and hope that consideration will be given to our proposed resolution. We welcome further discussion with CMS and other stakeholders on this matter related to the SEP-1 measure. If you have any questions, please contact Thomas Kim, Program Officer, Quality Improvement, at 703-638-1502 or [tkim@idsociety.org](mailto:tkim@idsociety.org).

Sincerely,



Johan S. Bakken, MD, PhD, FIDSA  
President, Infectious Diseases Society of America



Jay Kaplan, MD, FACEP  
President, American College of Emergency Physicians



Todd Dorman, MD, FCCM  
President, Society of Critical Care Medicine



Brian Harte, MD, SFHM  
President, Society of Hospital Medicine

Cc: Kate Goodrich, MD, MHS - Director, Quality Measurement and Value-based Incentives Group, Center for Clinical Standards & Quality, Centers for Medicare & Medicaid Services

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**Table 4: MATS WG Recommendation for SEP-1, Table 5.0: Monotherapy Antibiotics, Sepsis**

Antibiotic Selection Options (includes trade & generic name)	Generic Name Crosswalk
Doribax	Doripenem
Doripenem	Doripenem
Ertapenem	Ertapenem
Invanz	Ertapenem
Imipenem/Cilastatin	Imipenem/Cilastatin
Primaxin	Imipenem/Cilastatin
Meropenem	Meropenem
Merrem	Meropenem
Cefotaxime	Cefotaxime
Claforan	Cefotaxime
Ceftazidime avibactam	Ceftazidime Avibactam
Avycaz	Ceftazidime avibactam
Ceftazidime	Ceftazidime
Fortaz	Ceftazidime
Ceftolozane tazobactam	Ceftolozane tazobactam
Zerbaxa	Ceftolozane tazobactam
Ceftriaxone	Ceftriaxone
Rocephin	Ceftriaxone
Cefepime	Cefepime
Maxipime	Cefepime
Ceftaroline fosamil	Ceftaroline fosamil
Teflaro	Ceftaroline fosamil
Piperacillin/tazobactam	Piperacillin/tazobactam
Zosyn	Piperacillin/tazobactam

**Table 5: MATS WG Recommendation for SEP-1, Combination Antibiotic Therapy Table**

Column A		Column B
Aminoglycosides	+	Cephalosporins OR Daptomycin OR Glycopeptides OR Linezolid OR Penicillins
OR		
Column A		Column B
Aztreonam	+	Daptomycin OR Glycopeptides OR Linezolid OR Penicillins OR Clindamycin IV

**Table 6: MATS WG Recommendation for SEP-1, Table 5.1: Antibiotic Generic/Trade Name Crosswalk, Sepsis**

Antibiotic Selection Options (includes trade & generic name)	Generic Name Crosswalk
<b>Aminoglycosides</b>	
Amikacin	Amikacin
Garamycin	Gentamicin
Gentamicin	Gentamicin
Kanamycin	Kanamycin
Kantrex	Kanamycin
Nebcin	Tobramycin
Tobramycin	Tobramycin



<b>Aztreonam</b>	
Azactam	Aztreonam
Aztreonam	Aztreonam
<b>Cephalosporins</b>	
Ancef	Cefazolin
Cefzolin	Cefazolin
Cefoxitin	Cefoxitin
Ceftin	Cefuroxime
Cefuroxime	Cefuroxime
Mefoxin	Cefoxitin
<b>Clindamycin IV</b>	
Cleocin	Clindamycin
Clindamycin	Clindamycin
<b>Daptomycin</b>	
Cubicin	Daptomycin
Daptomycin	Daptomycin
<b>Glycopeptides</b>	
Targocid	Teicoplanin
Teicoplanin	Teicoplanin
Telavancin	Telavancin
Vancocin	Vancomycin
Vancomycin	Vancomycin
Vibativ	Telavancin
<b>Linezolid</b>	
Linezolid	Linezolid
Zyvox	Linezolid
<b>Penicillins</b>	

Ampicillin	Ampicillin
Nafcillin	Nafcillin
Oxacillin	Oxacillin
Penicillin G	Penicillin G

<sup>i</sup> Torio C (AHRQ), Moore B (Truven Health Analytics). National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2013. HCUP Statistical Brief #204. May 2016. Agency for Healthcare Research and Quality, Rockville, MD. <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb204-Most-Expensive-Hospital-Conditions.pdf>.

<sup>ii</sup> Ventola CL. The Antibiotic Resistance Crisis. P.T. 2015 Apr; 40(4): 277-283.

<sup>iii</sup> CDC. Antibiotic resistance threats in the United States, 2013. Atlanta, GA: US Department of Health and Human Services, CDC; 2013. Available at <http://www.cdc.gov/drugresistance/threat-report-2013>.

<sup>iv</sup> IDSA, ACEP, SCCM. Re: National Hospital Inpatient Quality Measures: Sepsis Bundle Project (SEP) Performance Measure. Aug 2015. Available: [http://www.idsociety.org/uploadedFiles/IDSA/Policy\\_and\\_Advocacy/Current\\_Topics\\_and\\_Issues/Access\\_and\\_Reimbursement/2015/IDSA\\_SCCM\\_ACEP%20SEP%20Letter%20to%20CMS%20AUG2015.pdf](http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Access_and_Reimbursement/2015/IDSA_SCCM_ACEP%20SEP%20Letter%20to%20CMS%20AUG2015.pdf)

<sup>v</sup> The Joint Commission, The Center for Medicare and Medicaid Services. Specifications Manual for National Hospital Inpatient Quality Measures v.5.2: Alphabetical Data Dictionary: Broad Spectrum or Other Antibiotic Selection. Jul 2016.

<sup>vi</sup> The White House. National action plan for combating antibiotic-resistant bacteria, 2015. Available at: [https://www.whitehouse.gov/sites/default/files/docs/national\\_action\\_plan\\_for\\_combating\\_antibiotic-resistant\\_bacteria.pdf](https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf).

<sup>vii</sup> CMS. Medicare and Medicaid Programs; Hospital and Critical Access Hospital (CAH) Changes To Promote Innovation, Flexibility, and Improvement in Patient Care. Federal Register 2016; 81: 39448-39480. Available at: <https://www.gpo.gov/fdsys/pkg/FR-2016-06-16/pdf/2016-13925.pdf>

<sup>viii</sup> Kaye KS, et al. Risk factors for recovery of ampicillin-sulbactam-resistant Escherichia coli in hospitalized patients. Antimicrob Agents Chemother. 2000 Apr; 44(4):1004-9.

<sup>ix</sup> Oliver A, et al. Ampicillin-sulbactam and amoxicillin-clavulanate susceptibility testing of Escherichia coli isolates with different beta-lactam resistance phenotypes. Antimicrob Agents Chemother. 1999 Apr; 43(4):862-7.

<sup>x</sup> Mendonça N, et al. Spread of extended-spectrum beta-lactamase CTX-M-producing escherichia coli clinical isolates in community and nosocomial environments in Portugal. Antimicrob Agents Chemother. 2007 Jun; 51(6):1946-55.

<sup>xi</sup> Thomson KS, et al. Beta-lactamase production in members of the family Enterobacteriaceae and resistance to beta-lactam-enzyme inhibitor combinations. Antimicrob Agents Chemother. 1990 Apr; 34(4):622-7.

<sup>xii</sup> Yayan J. et al. No development of ciprofloxacin resistance in the Haemophilus species associated with pneumonia over a 10-year study. BMC Infect Dis. 2015 Nov 13; 15:514.

<sup>xiii</sup> Kuo SC, Chen PC, Shiau YR, Wang HY, Lai JF 1st, Huang W, et al. Levofloxacin-resistant haemophilus influenzae, Taiwan, 2004–2010. Emerg Infect Dis. 2014;20:1386–90.

<sup>xiv</sup> Chang CM, Lauderdale TL, Lee HC, Lee NY, Wu CJ, Chen PL, et al. Colonisation of fluoroquinolone-resistant Haemophilus influenzae among nursing home residents in southern Taiwan. J Hosp Infect. 2010;75:304–8.

<sup>xv</sup> Yayan J, Ghebremedhin B, Rasche K. Antibiotic Resistance of Pseudomonas aeruginosa in Pneumonia at a Single University Hospital Center in Germany over a 10-Year Period. PLoS One. 2015 Oct 2;10(10).

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- <sup>xvi</sup> Snyderman DR, et al. U.S.-Based National Sentinel Surveillance Study for the Epidemiology of Clostridium difficile-Associated Diarrheal Isolates and Their Susceptibility to Fidaxomicin. *Antimicrob Agents Chemother*. 2015 Oct;59(10):6437-43.
- <sup>xvii</sup> Glaxosmithkline. Safety Advisory. Feb 2015. Available:  
<http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM433688.pdf>
- <sup>xviii</sup> Pereyre S, et al. Mycoplasma pneumoniae: Current Knowledge on Macrolide Resistance and Treatment. *Front Microbiol*. 2016; 7:974.
- <sup>xix</sup> Jenkins SG, Farrell DJ. Increase in pneumococcus macrolide resistance, United States. *Emerg Infect Dis*. 2009 Aug. Available from <http://wwwnc.cdc.gov/eid/article/15/8/08-1187>
- <sup>xx</sup> FDA Drug Shortages. Accessed: Aug 2016. Available:  
[http://www.accessdata.fda.gov/scripts/drugshortages/dsp\\_ActiveIngredientDetails.cfm?AI=Telithromycin%20\(Ketek\)%20Tablets&st=d](http://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Telithromycin%20(Ketek)%20Tablets&st=d)
- <sup>xxi</sup> Sligl WI, et al. Nosocomial Gram-negative bacteremia in intensive care: epidemiology, antimicrobial susceptibilities, and outcomes. *Int J Infect Dis*. 2015 Aug; 37: 129-34.
- <sup>xxii</sup> Dalhoff A. Global Fluoroquinolone Resistance Epidemiology and Implications for Clinical Use. *Interdisciplinary Perspectives on Infectious Diseases*. Vol 2012; 37 pages, 2012.
- <sup>xxiii</sup> Gasnik LB, et al. Risk factors for and impact of infection or colonization with aztreonam-resistant Pseudomonas aeruginosa. *Infect Control Hosp Epidemiol*. 2007 Oct; 28:1175-80.
- <sup>xxiv</sup> Huh K. et al. Risk factors and treatment outcomes of bloodstream infection caused by extended-spectrum cephalosporin-resistant Enterobacter species in adults with cancer. *Diagn Microbiol Infect Dis*. 2014 Feb; 78(2):172-7.
- <sup>xxv</sup> Labby KJ, Garneau-Tsodikova S. Strategies to overcome the action of aminoglycoside-modifying enzymes for treating resistant bacterial infections. *Future Med Chem*. 2013 Jul; 5(11):1285-309.
- <sup>xxvi</sup> Cadena J, et al. Clindamycin-resistant methicillin-resistant Staphylococcus aureus: epidemiology and molecular characteristics and associated clinical factors. *Diagn Microbiol Infect Dis*. 2012 Sep; 74(1):16-21.
- <sup>xxvii</sup> Wilson SE, et al. Comparative costs of ertapenem and cefotetan as prophylaxis for elective colorectal surgery. *Surg Infect*. 2008; 9: 349-56.
- <sup>xxviii</sup> Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010;11:79-109.