Nightmare bacteria and the worldwide threat to carbapenems

FEATURE ARTICLES

3 Introduction to this issue
Bonnie Marshall (APUA News Staff)

4 Carbapenemases: a real threat
Dr. Moises Morejon Garcia, MSc (Hospital Universitario Manuel Fajardo, Havana, Cuba)

7 U.S. CDC is sounding the alarm on nightmare bacteria
Arjun Srinivasan, MD (U.S. CDC, Division of Healthcare Quality Promotion, Atlanta, GA)

10 Therapeutic approaches to carbapenem-producing Enterobacteriaceae: a brief update
Gabriel Levy Hara, MD (Hospital Durand, Buenos Aires, Argentina)

FOLLOW-UP: C. difficile

13 The epidemiology of community-acquired Clostridium difficile infection: a population-based study
Sahil Khanna, MBBS, MS (Mayo Clinic, Rochester, MN)

APUA FIELD REPORTS & CHAPTER UPDATES

15 Impact of ESBLs and CREs—the Nigerian experience

17 ESBL-producing Enterobacteriaceae in Bulgaria

19 APUA-Kenya’s antimicrobial stewardship program

20 Acinetobacter baumannii epidemiology and resistance in north Lebanon

18 Upcoming events

21 State & national responses to CRE & ESBL alarms

22 APUA headquarters in action: 2013 Leadership Award and Directorship transition

23 APUA Learning Lab

24 Policy updates

25 News & publications of note

A light micrograph of the genus Klebsiella. These non-motile, rod-shaped gram-negative bacteria live normally in the human intestinal tract and commonly cause opportunistic infections of the intestinal and urinary tracts, lungs, and wounds. Highly prone to developing antibiotic resistance, they are the most common carriers of ESBL genes in healthcare facilities and are the source of the KPC-type carbapenemases that have spread globally.

Source: Med. Mic. Sciences Cardiff Uni, Wellcome Images
Chief Executives
Stuart B. Levy, President
Thomas F. O’Brien, Vice President
Kathleen T. Young, Executive Director

Board of Directors
Stuart B. Levy, Chairman
Sherwood Gorbach
Gordon W. Grundy
Bonnie Marshall
Mark Nance
Thomas F. O’Brien
Arnold G. Reinhold
Dennis Signorovitch
Philip D. Walson
Mary Wilson

Editorial Staff
Stuart B. Levy, Editor
Bonnie Marshall, Associate Editor
Michelle Haan, Assistant Editor
Thu Do, Contributor
Christopher Logan, Contributor

Advisory Board
Jacques F. Acar, France
Werner Arber, Switzerland
Fernando Baquero, Spain
Michael I. Bennish, USA
Otto Cars, Sweden
Patrice Courvalin, France
Jose Ramirez Cruz, Guatemala
Julian Davies, Canada
Abdoulaye Djimde, Mali
Paul Farmer, Haiti
Walter Gilbert, USA
Herman Goossens, Belgium
Sherwood I. Gorbach, USA
Ian M. Gould, Scotland
George Jacoby, USA
Sam Kariuki, Kenya
Ellen L. Koenig, Dominican Republic
Calvin M. Kunin, USA
Jacobo Kupersztch, USA

Advisory Board (cont.)
Stephen A. Lerner, USA
Jay A. Levy, USA
Donald E. Low, Canada
Scott McEwen, Canada
Jos. W.M. van der Meer, The Netherlands
Richard P. Novick, USA
Iruka Okeke, USA & Nigeria
Maria Eugenia Pinto, Chile
Vidal Rodriguez-Lemoine, Venezuela
Jose Ignacio Santos, Mexico
Mervyn Shapira, Israel
K. B. Sharma, India
Atif M. Shibli, Saudi Arabia
E. John Thriftall, United Kingdom
Alexander Tomasz, USA
Thelma e. Tupasi, Philippines
Anne K. Vidaver, USA
Fu Wang, China
Thomas E. Wellems, USA
Bernd Wiedemann, Germany

Supporting Chapters:
APUA—Abu Dhabi
APUA—South Korea
Australian Society for Antimicrobials
(APUA-Australia)
British Society for Antimicrobial Chemotherapy
(APUA-UK)

APUA gratefully acknowledges unrestricted grants from corporate sponsors:

Leadership Level ($20,000+)
Clorox Healthcare
Bayer Healthcare Pharmaceuticals
Optimer Pharmaceuticals
Alere Inc., bioMérieux

Partner Level ($10,000+)
Alcon Laboratories
GlaxoSmithKline

Supporter Level ($2,500+)
Cubist Pharmaceuticals

Disclaimer
APUA accepts no legal responsibility for the content of any submitted articles, nor for the violation of any copyright laws by any person contributing to this newsletter. The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by APUA in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The APUA Newsletter (ISSN 154-1424) © 2013 APUA
Since 1983, the APUA Newsletter has been a continuous source of non-commercial information disseminated without charge to healthcare practitioners, researchers, and policy-makers worldwide. The Newsletter carries up-to-date scientific and clinical information on prudent antibiotic use, antibiotic access and effectiveness, and management of antibiotic resistance. The publication is translated into three languages and distributed to over 7,000 affiliated individuals in more than 100 countries. The material provided by APUA is designed for educational purposes only and should not be used or taken as medical advice. We encourage distribution with appropriate attribution to APUA. See previous editions of the Newsletter on the APUA website.

*APUA welcomes letters to the Editor. Please send us your thoughts and questions. Names will be published but not addresses. All letters may be edited for style and length.

Phone: 617-636-0966 | Fax: 617-636-0458 | Email: apua@tufts.edu | Website: www.apua.org
The beta-lactam enzymes play a long and complex role in the evolution of antibiotic resistance mechanisms. These enzymes effectively inactivate the beta-lactam family of antibiotics by hydrolyzing the four-atom beta-lactam ring that is common to these agents.

The first beta-lactamase, called “penicillinase”, was discovered in 1940 in *E. coli*, not long after the discovery of penicillin. With over 750 variants now reported, the beta-lactamases comprise the most diversified of the resistance mechanisms, and to complicate matters further, are variably categorized. Functionally, they have been classified into groups (Groups 1, 2, 3, 4) according to their activity, i.e., which beta-lactam drugs they can hydrolyze and their inhibition by clavulanic acid. They have also been classified molecularly (Ambler Classes A-D), based on their nucleotide and amino acid sequences and other compounds. In this system, mechanisms for effective hydrolysis are dependent either on the amino acid serine (Classes A, C, D) or on the metal zinc (class B), hence the name, metallo-beta lactamase (MBL). Among nosocomial pathogens, Classes A, B, and D are of greatest clinical importance.

The early beta-lactamases were chromosomally mediated and non-transferable. However, the newer, extended (or expanded) spectrum beta-lactamases (ESBLs) are frequently plasmid-encoded and first appeared in the mid-1980s. These enzymes hydrolyze the extended-spectrum cephalosporin antibiotics (such as cefotaxime, ceftriaxone, ceftazidime), and also aztreonam, but not the carbapenem cephalosporins. With increasing cephalosporin use, the ESBLs underwent sequential mutations, raising the MICs (minimal inhibitory concentrations) to these drugs more than 100-fold (Fig. 2). Because transferable plasmids often specify resistance to other antibiotic classes (e.g., aminoglycosides), multidrug resistance has ensued and therapeutic options have become increasingly limited. For serious infections caused by ESBL-producing strains, the carbapenem family of antibiotics (imipenem, meropenem, ertapenem, doripenem) have become the agents of choice and, sometimes, the only remaining one. However, in 1993, the first carbapenemase-producing strain (*Enterobacter cloacae*) was described in Paris. This was followed by a large variety of carbapenemase-resistant *Enterobacteriaceae*, or “CRE”—generating the latest wave of “superbugs.” High-level carbapenem-resistance consists essentially of three types: the KPCs (*Klebsiella pneumoniae* carbapenemases), the MBLs (metallo-beta lactamase types), and the OXAs (oxacillinase types). The spread of these carbapenemases may now constitute the edge of two concomitant epidemics: one within community-acquired *E. coli* infections, and a second within nosocomial *Klebsiella pneumoniae*—the most common ESBL carrier found in healthcare facilities for the past 30 years.

To escalate the problem further, the ESBLs have become a diagnostic challenge. The transferable genes are very difficult to differentiate from those based on the chromosome, and some appear susceptible to cephalosporins, but still result in high failure rates. A convincing case
Carbapenemases: A real threat

Dr. Moises Morejon Garcia, MSc; APUA-Cuba President
Hospital Universitario Manuel Fajardo, Havana, Cuba

Translated from Spanish

Although bacterial resistance is a natural evolutionary phenomenon, the selective pressure exerted by antibiotic use in the past 70 years has greatly accelerated this process. In their evolution, bacteria have developed multiple mechanisms of resistance—principally inactivating enzymes, mutations in target sites and efflux pumps. The development and emergence of inactivating enzymes began with the discovery and use of the beta-lactams antibiotics—first penicillin in the 1940s and subsequently, the cephalosporins in the 1960s. Over time, these beta-lactam-inactivating enzymes expanded their spectrum of activity—from penicillinases and cephalosporinases, to extended-spectrum beta-lactamases (ESBLs) and most recently, to the metallo-beta-lactamases (MBLs). These latter enzymes, capable of hydrolyzing the carbapenems imipenem, meropenem, ertapenem, and doripenem are virtually incapacitating the last remaining treatments for multiresistant gram-negative bacilli. The first reports of carbapenemase in the 1980s, and their subsequent spread across the globe, have raised concern, and coincide with a decade in which no new antimicrobial against gram-negatives is anticipated.

In the 1980s, Japan reported isolation of the first carbapenemase from *Aeromonas hydrophila.* This was followed by reports of the Seoul imipenemase (SME-1) from *Serratia marcescens* in London (1982), and imipenemases IMI-1 in California (1984) and NMC-A in France (1990), both from *Enterobacter cloacae.*

A report of the first *Klebsiella pneumoniae* carbapenemase (KPC) in 1996 at a hospital in North Carolina raised concerns, but outbreaks in 2001 in New York and New Jersey hospitals created major alarm. These strains then spread across 27 U.S. states to many Latin American countries, including Argentina, Bolivia, Colombia, Venezuela, Uruguay, Brazil, Puerto Rico and abroad (China, Israel, and France). 

In the 2000s, carbapenemase activity appeared in Southeast Asia, Hong Kong and Singapore, while in Europe, the first variant, IMP-2, appeared in a strain of *Acinetobacter baumannii.* Meanwhile, reports of IMP increased in the U.S., Canada, and Brazil.

A second family of carbapenemases, the Verona integron-encoded metallo-lactamases (blaVIM-1), were isolated simultaneously in 1999 from strains of *Pseudomonas aeruginosa* and *Acinetobacter spp* in Italy. Subsequently, a third metallo-beta-lactamase family, SPM-1, was isolated from *Pseudomonas aeruginosa* in Brazil. In Cuba, several reports of carbapenemase-producing strains have sparked increased vigilance.

As the carbapenem antibiotics have been the primary therapy against serious infections from multiresistant gram-negative organisms, the emergence and increasing prevalence of the carbapenemases jeopardize the effectiveness of this family of antibiotics. According to the SENTRY global surveillance report, rates in Latin America are higher than those in U.S. and Europe.

In 2008, the isolation of a new metallo-beta-lactamase, called New Delhi metallo (NDM-1), raised global alarm due to its isolation from Swedish and English patients who had previously travelled to India and Pakistan. A surveillance study between 2008 and 2010 in 29 European countries reported 77 cases of the NDM-1 enzyme in 13 of the countries, predominantly in isolates of *Klebsiella pneumoniae* (54%). Subsequently, NDM-1 was found in Japan, Australia, Canada and the USA.

In November 2011, NDM-1 was first isolated in Latin America—from a strain of *Klebsiella pneumoniae.* The Guatemalan isolate prompted the Pan American Health Organization (PAHO) to issue an alert for surveillance of these healthcare associated pathogens that seriously impact morbidity and mortality.

The carbapenemases fall into two groups: the serine beta-lactamases (serine-based) and the metallo-beta-lactamases (zinc-based) (Table 1). The serine-based enzymes (enzymes of Ambler class A or D) have less hydrolytic activity than the...
metallo-enzymes, are not hydrolyzed by aztreonam, and can be inhibited by beta-lactamase inhibitors.13

The metallo-beta-lactamases belong to Ambler class B of (Group 3 in the Bush classification). These acquired carbapenemases are the most clinically significant as they are capable of hydrolyzing all beta-lactam antibiotics, with the exception of aztreonam, and are not susceptible to beta-lactamase inhibitors.

Both metallo- and serine-based enzymes are found primarily in Enterobacteriaceae and the non-fermenting bacilli (Pseudomonas aeruginosa, Acinetobacter baumannii). These create a therapeutic conundrum, as the antibiotic of choice against these multidrug-resistant strains (piperacillin/tazobactam, 3rd and 4th generation cephalosporins, fluoroquinolones and aminoglycosides) has not yet been determined. Intravenous (disodium) fosfomycin has proven useful against KPC strains. Other possible options are tigecycline, colistin and aztreonam, either alone, or more often in combination.14-18

The increasing prevalence and global spread of these enzymes, coupled with their impacts on treatment outcomes, obligate countries to undertake surveillance monitoring. In 2009, the Clinical and Laboratory Standard Institute (CLSI) recommended the modified Hodge test (MHT) for detection of carbapenemase—a method that permits detection, but does not discriminate between serine- and metallo-beta-lactamases (Fig 1).19

Recommendations for identifying metallo-beta-lactamases utilize chelating agents such as ethylenediaminetetra-acetic acid (EDTA) and 2-mercapto-propionic acid (2-MPA). However, there is no consensus on the best substrate or the best inhibitor of these enzymes. Thus, there are two options: the IMP disk with EDTA, and the epsilometric MBL detection assay (Etest MBL)—using strips IMIK/IMI + EDTA—a less complex, but more costly method that cannot be used in the carbapenemase-producing strains of the oxacillinase (OXA) type, as it can give false positives (often found in A. baumannii).20-22

It is worrisome that the genes encoding these enzymes are carried on conjugative plasmids that possess considerable potential for nosocomial spread to other pathogens. The overuse of carbapenems is an important factor in the generation and selection of carbapenemase-producing organisms. The proper use of these agents will prolong their future at a critical time when no new antimicrobials that target gram-negatives are anticipated.

References


Carbapenemases—a real threat • The APUA Newsletter Vol. 31. No. 2 • © 2013 APUA • 5


**Recommended Viewing**


**INTRODUCTION, continued from page 3**

... can be made for the surveillance of ESBL activity. Many ESBL resistances are a combination of sequential mutations. Because the second and third mutations may result in very rapid rises in MIC values, it is essential to detect the initial mutation early in the process. Current clinical surveillance breakpoints are set too high to detect these and thus will miss the first signal of an impending resistance crisis.

The prevalence of carbapenemases is difficult to assess because they very so widely from country to country (e.g., 3-5% in France and >80% in India for ESBL-positive E. coli) and because the possible “reservoir countries” have no surveillance systems for detecting them.

This issue of the APUA Newsletter presents some of the serious present-day challenges posed by the ESBLs and by the newer carbapenemases in particular. The article by Garcia overviews the emerging threat posed by the global spread of carbapenemases, while that of CDC expert Srinivasan outlines the seriousness of the problem in the US and government interventions, including a “prevention toolkit” and recommendations for providers and patients. Levy Hara discusses the intricacies of CRE detection, as well as antimicrobial treatment options. The articles by Ogbuli and by Markovska/Keulyan present perspectives from sub-Saharan Africa (Nigeria) and from Bulgaria, respectively.

**References**


Sounding the alarm on nightmare bacteria

By Arjun Srinivasan, MD
Associate Director for Healthcare Associated Infection Prevention Programs, U.S. CDC, Division of Healthcare Quality Promotion

The Centers for Disease Control and Prevention (CDC) and the nation’s healthcare providers are now battling what may be one of the most pressing patient safety threats of our time—carbapenem-resistant Enterobacteriaceae (CRE). In its March 2013 issue of Vital Signs, CDC sounded the alarm on the spread of CRE—“nightmare bacteria”—in U.S. inpatient medical facilities, stating that action is needed now to halt the spread of these deadly bacteria. CDC is asking for rapid action from healthcare leaders to ensure that CRE prevention measures are aggressively implemented in your facility and by those around you.

Enterobacteriaceae are a family of more than 70 different bacteria including Klebsiella pneumoniae and E. coli that normally live in the digestive system. Over time, some of these bacteria have become resistant to a group of antibiotics known as carbapenems, often referred to as last-resort antibiotics. During the last decade, CDC has tracked one type of CRE from a single health care facility to health care facilities in at least 42 states. In some medical facilities, these bacteria already pose a routine threat to patients.

Here are other important facts to know about CRE:

• About 4% of US short-stay hospitals had at least one patient with a serious CRE infection during the first half of 2012. About 18% of long-term acute care hospitals had one. This totals almost 200 facilities.
• The most common type of CRE is also rising rapidly—there has been a seven-fold increase in its presence during the last 10 years.
• Up to half of patients who get CRE bloodstream infections will die.

CRE often spread between patients on the hands of health care personnel. In addition, CRE bacteria can transfer their resistance to other bacteria within their family. This type of spread can create additional untreatable infections. Currently, almost all CRE infections occur in people receiving significant medical care in hospitals, long-term acute care facilities, or nursing homes.

The Vital Signs report describes that although CRE bacteria are not yet common nationally, the percentage of Enterobacteriaceae that are carbapenem-resistant has increased fourfold in the past decade. One type of CRE, a resistant form of Klebsiella pneumoniae, has shown a sevenfold increase in the last decade. In the U.S., northeastern states report the most cases of CRE. During just the first half of 2012, almost 200 hospitals and long-term acute care facilities treated at least one patient infected with these bacteria.

In the U.S., CRE infections are almost never seen in healthy people. However,
CRE’s ability to spread among people, coupled with their ability to transfer resistance to other bacteria, raises the worry that potentially untreatable infections could appear in otherwise healthy people.

So how do we stop the rise of these deadly, resistant CRE germs? Halting the rise of CRE will take a combination of infection control measures and improved antibiotic use. CRE have shown a propensity to spread quickly in healthcare facilities and hence aggressive measures to find cases and apply appropriate infection control measures are essential. But infection control is only half the battle—we also have to focus on antibiotic use. One study demonstrated that exposure to a carbapenem increased a patient’s risk of developing CRE by more than 15-fold. Reducing unnecessary use of antibiotics like carbapenems could help slow the emergence of these deadly bacteria. In 2012, CDC released a concise, practical CRE prevention toolkit with recommendations for healthcare and public health for controlling CRE transmission in hospitals, long-term acute care facilities and nursing homes.

Key recommendations include:
- enforcing use of infection control precautions (standard and contact precautions)
- grouping patients with CRE together
- dedicating rooms, staff, and equipment to the care of patients with CRE whenever possible
- having facilities alert each other when patients with CRE transfer back and forth
CDC encourages all healthcare providers to:

- Know if patients with CRE are hospitalized at your facility, and stay aware of CRE infection rates. Ask if your patients have received medical care somewhere else, including another country.
- Follow infection control recommendations with every patient, using contact precautions for patients with CRE. Whenever possible, dedicate rooms, equipment, and staff to CRE patients.
- Prescribe antibiotics wisely. Use culture results to modify prescriptions if needed.
- Remove temporary medical devices as soon as possible.

CDC also encourages patients to:

- Tell your doctor if you have been hospitalized in another facility or country.
- Take antibiotics only as prescribed.
- Insist that everyone wash their hands before touching you.

If rapid action is not taken today, we will miss our window of opportunity, and CRE could become widespread across the country. Let’s act now to protect patients from healthcare-associated infections, including CRE.

For additional information on CRE, click here.
Carbapenems are one of few available last-resort therapeutics for the treatment of serious infections caused by the *Enterobacteriaceae* and by gram-negative non-fermenting rods (GNB). Regrettably, in recent years, the prevalence of carbapenemase-producing *Enterobacteriaceae* (CPE) has increased rapidly in most parts of the world, leaving the medical profession—and their patients—with limited, if any, therapeutic options.

**Classification of carbapenemases**

These enzymes are encoded by *bla* genes carried on plasmids and/or integrons that could easily disseminate among different gram-negative species. Classes A, B, and D are the most important carbapenemases.

**Class A**

Within the diversity of Class A enzymes, the KPC-types (*Klebsiella pneumoniae* carbapenemases) are the most frequently identified among clinical isolates. While often present in *Klebsiella pneumoniae*, KPC can also be found in other *Enterobacteriaceae*, as well as the non-fermenting GNB. They are generally broadly active against all β-lactam antibiotics, despite the fact that organisms containing them may test susceptible to many carbapenems (with the exception of ertapenem) by standard antimicrobial susceptibility tests (ASTs).

**Class B**

Metallo-beta-lactamases (MBLs) are mostly VIM- and IMP-types. However, the most recent to appear, the NDM-type, is currently the most dangerous, both because of the high-level of carbapenem resistance typically exhibited among *Enterobacteriaceae* harboring this enzyme (e.g., MICs for imipenem and meropenem are ≥32 mg/L), and because of its rapid worldwide dissemination.

**Class D**

These enzymes are usually OXA-48-like producers. Their recognition can be difficult because they exhibit no resistance to broad-spectrum cephalosporins and only decreased susceptibility to carbapenems. In such a case, the microbiologist must be aware that *Enterobacteriaceae* (mainly *E. coli* producing OXA-48-like enzymes only, and not co-possessing ESBLs) demonstrate low MIC values for imipenem and meropenem (e.g., 0.25-1 mg/L) and exhibit susceptibility to the extended-spectrum cephalosporins.

**Detection of carbapenemase-producers**

As noted above, the detection of CPE can be difficult because their MIC values do not always reflect resistance. This is a concern, both in terms of early detection and adoption of infection control measures, as well as for early prescription of effective antibiotic therapy. CPE can be suspected based on antimicrobial susceptibility test (AST) results obtained by diffusion methods or by automated systems by paying close attention to the MICs or inhibition diameters for carbapenems. Reference methods, such as broth microdilution and agar dilution, are preferred, since these are more sensitive than disk diffusion, Etest, and automated methods. Susceptibility to ertapenem can be used for the initial screening of carbapenemase production. When possible, more appropriate phenotypic (e.g., modified Hodge test) and molecular methods (e.g., PCR-based or microarray) should be utilized for confirming the presence of resistance enzymes.

**Antimicrobial treatment options**

Optimal treatment for CPE infections is not well established, as most published reports have evaluated only a few patients, retrospectively. Nonetheless, rapidly growing evidence suggests that combined therapy can significantly reduce mortality in severe infections. Considering the different susceptibilities to potentially effective drugs, it is essential to choose an antibiotic based on the AST results for each and every specific clinical situation. Patients who are colonized only, and who demonstrate no clinical infection, should not be treated, and current practices for prevention of dissemination of CPE (e.g., isolation, hand hygiene, etc) should be strictly observed.
The following drugs are potentially useful for CPE treatment:

**Colistin**

Colistin is frequently the only agent to achieve adequate serum levels for treatment of CPE bloodstream infections (BSIs). Globally, the sensitivity of GNB to colistin varies from 70% to 100%. Regrettably, in some countries and in certain city hospitals, resistance is increasing due to the clonal spread of strains. The emergence of multi drug-resistant (MDR) and extreme drug-resistant (XDR) pathogens has led to a significant increase in utilization of colistin—a formerly uncommon drug. While our knowledge of the PK/PD issues of colistin has improved, it is not yet fully established.

To avoid confusion related to different formulations, it should be noted that 100 mg of colistin sulfate base is equivalent to 240 mg of colistin methanesulfonate (CMS) and to 3 million units (MU) of CMS (the non-active pro-drug of colistin). Current dosing schemes (commonly, 3 MU of CMS every 8h) reach only suboptimal concentrations—i.e., below the MIC breakpoint of 2 mg/liter—at least during the critical first 2 to 3 days of therapy. These levels can greatly increase mortality in critically ill patients, as well as promote selection of resistant strains. In one study, a 20-fold difference in the AUC\textsubscript{0-24}* between patients was observed. Creatinine clearance was an important covariate in the population PK model applied. Recent studies that a loading dose of 6 to 9 MU, followed by maintenance doses of 4.5 to 6 MU every 12h—always adjusting to renal function—could be more effective than previously prescribed regimens of 3 MU every 8h, without an increase of nephrotoxicity. In different studies, nephrotoxicity varied from 10%-15% and, in most cases, was transient and probably related to dosage and duration of treatment. A recent survey of the use of colistin showed that barely 21.2% of institutions worldwide are currently using loading doses.

“Patients who are colonized only, and who demonstrate no clinical infection, should not be treated, and current practices for prevention of dissemination of CPE (isolation, hand hygiene, etc.) should be strictly observed.”

**Tigecycline**

The clinical use of this glycyclcycline, a bacteriostatic agent, is limited for several reasons. First, a scarcity of controlled studies demonstrate its efficacy in the treatment of infections due to MDR and XDR bacteria. Secondly, the PK/PD profile of tigecycline suggests that it is not appropriate for treatment—at least as monotherapy—of serious disease. Its protein binding is 71 - 89%, and with a standard dosing regimen of 50 mg bid, the peak serum concentrations range from 0.6 - 0.9 mg/l. In contrast, the MICs for the majority of KPC-producing *K. pneumoniae* isolates range between 1 to 2 mg/L. Higher doses are badly tolerated due to gastrointestinal toxicity (e.g., nausea and vomiting). Finally, there is a concern regarding the development of resistance via upregulation of cellular efflux pumps during therapy. However, as discussed below, there is some good evidence for the efficacy of tigecycline in combination with colistin and carbapenems in the treatment of severely ill patients.

**Aminoglycosides**

Resistance to this class is increasing among CPE. In the regrettably few infections produced by susceptible strains, these drugs have been efficacious options as part of combined therapeutic regimens.

**Fosfomycin**

Like colistin, this older drug has been revitalized for the treatment of some MDR and XDR GNB, and displays *in vitro* activity against many CPE, including colistin-resistant strains. Some reports suggest that fosfomycin should always be used in high doses (e.g., 4 grams, 4X/day in a normal renal functioning patient) and in combination regimens (see below).

**Combination therapy**

Recently published evidence supports the use of combination therapy in patients with CPE infections. Tzouvelekis *et. al.* performed a systematic search to evaluate the efficacy of different treatment approaches. Among 34 small studies, a total of 298 patients were identified: 244 with blood stream infections (BSIs), and 32 with pneumonia. One hundred and forty three patients received monotherapy (only one drug was active *in vitro* against the infecting organism); 99 received combination therapy (at least two drugs active *in vitro*), and the remaining 56 received inappropriate therapy (no drug active *in vitro*). Combination therapy was superior to monotherapy, and those patients treated with carbapenems as part of the regimen had the lowest failure rate (8.3%). In contrast, treatment with tigecycline or colistin as single active agents resulted in failure rates (35.7% and 47.2%, respectively) comparable to that observed for patients improperly treated (45%). Combinations...
of carbapenem plus colistin (5.5% of failures) or carbapenem plus an aminoglycoside (6.2%) exhibited better outcomes than when these drugs were used alone or as part of other combinations. Finally, combinations of tigecycline (24% of failures), colistin (32%), and aminoglycosides (33.3%) in regimens not including a carbapenem, exhibited higher failure rates.

A recently published multicenter retrospective cohort study of 125 patients with BSIs caused by KPC- K. pneumoniae also showed higher mortality rates in patients treated with monotherapy (54.3% vs. 34.1% with combined drug therapy; P = 0.02). Combination therapy with tigecycline, colistin, and meropenem was independently associated with survival (OR: 0.11; 95% CI: .02-.69; P = 0.01). With MIC values of ≤4 mg/l for meropenem, inclusion of this drug in a combined regimen led to a survival rate of 86.6%, and with even higher MIC values, the survival rate was 75%.7

Carbapenems display time-dependent bactericidal killing when free drug concentrations remain above the MIC for 40–50% of the time between doses. The probability of attaining 50% T>MIC* target for an isolate with a MIC of 4 mg/l is 69% for the traditional dosing regimen (e.g., 30 min infusion of 1g every 8 hours for meropenem) and increases to 100% for the high-dose/prolonged infusion regimen (e.g., 3 hour infusion of 2g every 8 hours for meropenem). Even for an MIC of 8 mg/l, the high-dose/prolonged-infusion carries a high probability (85%) of bactericidal activity.8

In the February 2013 issue of the Journal of Chemotherapy, an International Working Group** published some pivotal recommendations for the detection, treatment and prevention of CPE.9 For all the above reasons, the recommendations of this Working Group support the use of carbapenem, provided that:

- the carbapenem MIC for the infecting organism is >4 mg/l (and possibly up to 8 mg/l)
- a high-dose, prolonged-infusion regimen is administered (e.g. 2g meropenem every 8h, or 1g imipenem every 6-8h)
- they are used in combination with another active compound, preferably colistin or an aminoglycoside.

Considering the deficit of new drugs on the near horizon, our most immediate option for preventing more deaths from CPE will be the enforcement of infection control practices combined with diligent antimicrobial stewardship.

*(Time above MIC) = the percentage of a dosage interval in which the serum level exceeds the minimal inhibitory concentration.
**This group included representatives from the Argentinian Society of Infectious Diseases (SADI), the International Society of Chemotherapy (ISC), the Pan American Association of Infectious Diseases (API), the Pan American Health Organization/World Health Organization (PAHO/WHO), the Infection Control African Network (ICAN), Mediterranean Society of Chemotherapy (MSC) and the Federation of European Societies for Chemotherapy and for Infections (FESCI). This article briefly summarizes the key points of their recommendations.

References


Community-acquired *C. difficile* infection—old bug, new insights

Sahil Khanna, MBBS, MS
Mayo Clinic, Rochester, Minnesota

---

In a population-based study from Olmsted County, Minnesota between 1991-2005, 41% of all CDI cases were community-acquired, 50% were hospital-acquired, and 9% were nursing home-acquired. In accordance with the existing literature, the majority of cases (53%) occurred in the elderly (age ≥65 years). The overall age- and sex-adjusted incidence of CDI was 25.2 per 100,000 person-years and there was a significant increase in both hospital-acquired (19.3-fold) and community-acquired (5.3-fold) cases over the study period.

In this study, patients with community-acquired CDI were younger, had fewer co-morbid conditions, were less likely to have an underlying malignancy, and were less likely to develop severe disease. Interestingly, of all CDI patients, 13% had no documented antibiotic exposure in the preceding 90 days. Compared to hospital-acquired CDI patients, those with community-acquired CDI were significantly less likely to be exposed to antibiotics (94% vs. 78%) or gastric acid suppression medications (47% vs. 22%).

CDI cases were predominantly female (75.3%); one-fifth had severe CDI; 20% had treatment failure and a significant proportion required hospitalization for CDI. Community-acquired CDI patients who required hospitalization were significantly older (median age difference 20 years), had more comorbid conditions and were more likely to have severe CDI.

Within the pediatric population of Olmsted County (1991-2009), the majority of cases (75%) were community-acquired. The overall age and sex-adjusted CDI incidence was 13.8 per 100,000 persons, which increased 12.5-fold over the study period. The incidence of community-acquired CDI was 10.3 per 100,000 persons and increased 10.5-fold over the study period. Of all community-acquired cases, 85.5% had an outpatient or an emergency-department visit in the three months prior to onset of CDI. Severe, severe-complicated, and recurrent CDI occurred in 9%, 3%, and 20% respectively.

---

*Clostridium difficile* infection (CDI) is the most common hospital-acquired infection and the most common cause of infection diarrhea in the hospital—with ~500,000 - 1,000,000 infections and ~14,000 deaths annually in the United States. While the traditional risk factors for CDI include increasing age, antibiotic exposure and hospitalization, recent data have shown that CDI is also present in the community—in patients who may lack these traditional risk factors.

According to guidelines from the Infectious Diseases Society of America, CDI is defined as “hospital-acquired” if symptom onset occurs more than 48 hours after admission to, or less than 4 weeks after discharge from, a health care facility. CDI is considered “community-acquired” if symptom onset occurs in the community or within 48 hours of admission to a hospital, provided that symptom onset was more than 12 weeks after the last discharge from a hospital. CDI is defined as “indeterminate” if symptom onset occurs between 4 and 12 weeks following a hospital dismissal.

Community-acquired CDI is probably an under-diagnosed and under-recognized sub-group of patients—likely due to a lack of awareness of the existence of CDI outside the healthcare setting. Studies have shown that the proportion of community-acquired CDI ranges from 27 - 41% in adults and up to 75% in pediatric patients. CA-CDI has been described in populations previously considered to be at low risk, including peri-partum women, children and young adults. Many of these patients lack traditional risk factors for CDI, such as antibiotic exposure or recent hospitalization.
There were fewer treatment failures in those treated with vancomycin compared to metronidazole.\textsuperscript{7}

The lack of traditional risk factors in a subset of patients with community-acquired CDI suggests alternate novel risk factors for CDI and newer modes of transmission in the community. Studies have suggested that up to 94\% of patients may have had health-care exposure predisposing them to CDI.\textsuperscript{8} Potential risk factors for community-acquired CDI include contaminated food consumption, and personal contact (person-to-person, environment-to-person, and potentially animal-to-person). \textit{C. difficile} strains have been identified in retail meat and meat products, including beef, chicken and pork. Similarities have been reported in animal feed isolates with those reported to cause CDI in humans.\textsuperscript{9, 10}

Person-to-person spread is important both within and outside hospitals. Recently published guidelines have suggested that visitors to hospital rooms harboring CDI patients should practice the same isolation precautions as healthcare personnel.\textsuperscript{11} Additionally, there is a potential for increased exposure to colonized or infected persons in the community, such as health care workers, and studies have shown that family members of patients with recent infection have a higher risk of CDI.\textsuperscript{12} Infants and children may be asymptomatically colonized with \textit{C. difficile}, and exposure to a colonized infant may be a risk factor for recurrent CDI in mothers in the post-natal period. Environmental contamination has been found in daycare centers, and up to one-third of households and half of water and swimming pool samples may be contaminated with \textit{C. difficile}.\textsuperscript{12} In these settings, strict hand hygiene precautions with soap and water (not alcohol-based hand rubs) is the cornerstone to the prevention of CDI.\textsuperscript{3, 11}

As the incidence of community-acquired CDI increases, CDI should be considered in all outpatients with acute diarrhea, even in the absence of traditional risk factors such as hospitalization or antibiotic exposure.\textsuperscript{4}

“\textbf{As the incidence of community-acquired CDI increases, CDI should be considered in all outpatients with acute diarrhea, even in the absence of traditional risk factors such as hospitalization or antibiotic exposure.}”

As a higher risk for CDI. Additionally, community-acquired CDI may have serious consequences. Given the additional risks and costs associated with hospitalization, physicians should be aware of risk factors (increasing age, comorbid conditions and disease severity) that predict the need for hospitalization. Patients with community-acquired CDI should be managed aggressively, with close clinical follow-up to prevent adverse outcomes.\textsuperscript{6}

\begin{flushleft}
\textbf{References}
\end{flushleft}


Impact of ESBLs and CREs—the Nigerian Experience

David Olusoga Ogbolu, PhD, FMLSCN
Ladoke Akintola University of Technology, Ogbomosho, Nigeria

The distribution and epidemiology of extended-spectrum beta-lactamases (ESBLs) in various pathogens have been intensively studied in developed countries, but data are extremely limited from sub-Saharan Africa, including Nigeria. Antibiotic use in Nigeria is unregulated; there are no regional or national surveillance data on bacterial resistance to antibiotics, and only a few localized institutional studies have reported the prevalence or level of antibiotic resistance, particularly to β-lactams. In Nigeria, extended-spectrum cephalosporins and fluoroquinolones are widely used as broad-spectrum antibiotics and remain the drugs of choice to treat infections caused by various gram-negative pathogens. Gram-negative bacteria cause a significant number of infections in Nigerian hospitals and represent the majority of both wound and urinary isolates, which form the largest group of clinical specimens received in microbiology laboratories.

A diversity of ESBL enzymes have evolved and been detected in gram-negative pathogens over the last 30 years, with the CTX-M group becoming the dominant ESBL identified worldwide. In Nigeria, Aibinu et al. reported 20% carriage of ESBLs in Enterobacter species in the capital, Lagos—a rate similar to that found in gram-negatives from four teaching hospitals of the southwest region. The predominant ESBL genotype detected is CTX-M-15. CTX-M-3 was also reported in 2011 with TEM, SHV and OXA variants. Plasmidic or chromosomal ampC genes (ACT-1, DHA-1 and CMY-2) have also been identified, co-existing with ESBL genes such as CTX-M-15, TEM-1, SHV-1 and OXA-1. Additionally, other plasmid-mediated β-lactamases (VEB-1, OXA-10) have been found in Providencia species, although they are believed to be less common. It remains to be seen whether they are of clinical significance in other genera of Enterobacteriaceae.

Plasmids believed to be responsible for the dissemination of ESBLs are largely members of the IncF replicon/incompatibility group and parallels the pattern observed worldwide for CTX-M-15-carrying plasmids, as well as the spread of plasmid-mediated ampC genes (blaCMY and blaDHA). Nigerian ampC strains demonstrate low-level resistance to third-generation cephalosporins, but are associated with high-level resistance to quinolones. The blaCTX-M genes are associated with plasmids that also carry other resistance genes: the tet(A) gene, aminoglycoside resistance genes (aac(3)II and aac(6’)-Ib-cr), and PMQR (plasmid-mediated quinolone resistance qnr genes, aac(6’)-Ib-cr), and the efflux pump gene, qepA. Carbapenems have recently been introduced to patient management in Nigeria, but are rarely used by physicians, due largely to high cost. We previously (in 2009) found extremely high levels of resistance to all antibiotics tested and the presence of numerous mobile genetic elements carrying resistance to β-lactams. While the focus of the study was on ESBL resistance, we did identify potential carbapenem resistance, indicating a reservoir of carbapenem-resistant strains. Most recently, we have found high-level carbapenemase production in gram-negative clinical isolates, with carriage of various known carbapenemases and potential for variants of existing carbapenemases or unknown carbapenemase (submitted). It is surprising that such a number of highly carbapenem-resistant isolates were observed, of which more than half were carbapenemase-producers and pan-drug resistant.

ESBLs have been detected not only in clinical isolates, but also in commensal bacteria from humans and animals in Nigeria and in isolates from products of the food chain and sewage, demonstrating a variety of sources and reservoirs for these re-
sistance determinants. In humans, carriage of ESBL genes in fecal isolates of commensal *E. coli* and *Klebsiella* species in out-patients revealed carriage of *bla*\(_{CTX-M-15}\), *bla*\(_{CTX-M-2}\), *bla*\(_{OXA-1}\), *bla*\(_{TEM-1}\) and *bla*\(_{SHV-1}\), including non-chromosomal AmpC enzymes. These *bla*\(_{ampc}\) genes were found in isolates carrying other ESBL genes, as commonly reported in bacterial pathogens.\(^{13}\) Similarly, ampicillin-resistant commensal *E. coli* isolated from healthy chickens and pigs have been found to harbour *bla*\(_{TEM}\) and *bla*\(_{CTX-M-15}\) genes.\(^{14}\) These ESBL-producing bacteria can enter the human food chain through the consumption of meat or by direct contact, colonizing the human gut.

In conclusion, there is a diversity of beta-lactamases and high-level resistance to many antimicrobials, including cephalosporins and carbapenems among *Enterobacteriaceae* in Nigeria. This has led to increased and widespread use of reserved antibiotics such as carbapenems, with consequent ineffectiveness and escalation to pan-drug resistance. The uncontrolled use of antibiotics in Nigeria is likely to have contributed largely to this situation. In an era of frequent global travel, the selection of highly resistant isolates in countries such as Nigeria, where beta-lactamases are not routinely identified, may elicit a reservoir of resistant strains with high mobility for export to other countries.

References


ESBL-producing Enterobacteriaceae in Bulgaria – a short overview

Rumyana Markovska, APUA-Bulgaria
Medical University—Sofia, Bulgaria

Emma Keuleyan, APUA-Bulgaria
Medical Institute—Ministry of the Interior

Since the first report of an ESBL-producing microorganism in Bulgaria in 1992, the national data tracking system (BulSTAR) has recorded increases from 1 - 5.7% for ESBL-producing Escherichia coli and from 5 - 22.5% for ESBL-producing Klebsiella pneumoniae (2001-2010). These rates are lower than those for Bulgaria in the European Antimicrobial Resistance Surveillance System (EARSS) which reported increases from 7 - 22.9% in E. coli (mostly from bacteremia resistant to oxyimino-cephalosporins; 2001-2011) and from 50 - 81% (also invasive isolates; 2005-2011) in K. pneumoniae. Early studies among different enterobacteria between 1994 and 1999 at the National Cancer Centre reported ESBL production at 4.4% and detected enzymes of the SHV and TEM families.

The APUA-funded small grants program project on Antimicrobial Resistance Surveillance (1999–2000) confirmed an emerging problem. Beta-lactamases TEM-3, SHV-5, SHV-12 were detected among nosocomial strains of K. pneumoniae isolated in 1999 in Military Medical Academy. The wide investigation of 451 different enterobacteria (K. pneumoniae, E. coli, Enterobacter spp., Serratia marcescens, Citrobacter freundii, K. oxytoca, Salmonella enterica serotype Corvallis 1) conducted between 1997 and 2003 has shown a similar distribution. Until 2000, only SHV- and TEM- ESBLs were detected, with TEM-139 being reported for the first time globally. It was limited mainly to one city (Pleven) and one species (K. pneumoniae). SHV enzymes detected included SHV-2, -5, and -12. They were found in all centers through the entire investigation period. The first CTX-M enzyme found in Bulgaria was CTX-M-15, isolated in 2001 (shortly after its first report in India). CTX-M-3 was also detected for the first time in Bulgaria in 2002. CTX-M frequency subsequently increased to 65% by the end of the investigation period. A novel CTX-M enzyme, CTX-M-71, was first detected in Bulgaria in 2003.

The increased rates of ESBL-producing isolates in Bulgaria are most probably due to the distribution of a few specific clones or plasmids. Various studies have found a few primary clones: K. pneumoniae with SHV-12 or CTX-M-3; E. coli with CTX-M-15; and S. marcescens with CTX-M-3. Further investigation demonstrated country-wide dissemination of a highly resistant B2 O25b-ST131 CTX-M-1- producing E. coli clone in Bulgaria, representing 68% of all ESBL-producing E. coli isolates. Almost all O25b-ST131 E. coli produced CTX-M-15 (96%). The important role of horizontal transfer of plasmids, carrying blaESBL, predominantly blaCTX-M-3, has been shown as well.

In conclusion, the wide spread of ESBLs in Bulgaria is extremely worrying and suggests a need for more prudent antibiotic prescription, (e.g. limitation of 3rd generation cephalosporins) and stricter infection control. It is becoming obvious that the problem of ESBL-producing Enterobacteriaceae cannot be resolved without the intervention of strict government controls and the external assistance of international societies/communities.

References:


For instance, a surgical site infection study in one of the local district hospitals was successfully completed recently. Interventions done through continuous medical education on rational use of antibiotics for surgical prophylaxis showed a decrease in antibiotic consumption and eventual rational use of antibiotics through the development of an antibiotic use policy within the hospital. Currently, this study is being replicated in two other hospitals by members of the working group, with the aim of rationalizing antibiotic use in surgical procedures. In addition, the working group is in the process of developing an exciting 5-day training course on AMR and rational antibiotic use targeting both human and veterinary medicine practitioners from different regions in the country who will then serve as “AMR champions” countrywide.

In the course of its activities, the working group has learned a number of lessons, including the following:

- Global problems are best tackled through national action
- Both underuse and overuse of antibiotics co-exist. Underuse of antibiotics leads to childhood deaths from common infectious diseases, while overuse is propagated mostly by hospitals and through self-treatment.
- The need for antibiotics can be reduced through coverage by childhood immunization programs (e.g. Hib and the newly introduced pneumococcal vaccines) and improved hospital infection control.
- Inappropriate antibiotic use can be reduced through the following three ways: reducing provider and self-prescribing for coughs and colds; reducing use for watery diarrhea; and reducing use in food animals.
**Acinetobacter baumannii** epidemiology and resistance in north Lebanon

Ziad Daoud, PhD, APUA-Lebanon Chapter Leader
University of Balamand; CHN Hospital, Deir El-Balamand, Al-Kurah, North Lebanon

**Objective**
This study aimed to determine the relatedness of *Acinetobacter baumannii* strains collected from the north of Lebanon and to identify their mechanism(s) of resistance to imipenem. *Acinetobacter baumannii* causes opportunistic nosocomial infections, mainly in intensive care units. In addition to its natural resistance, acquired resistance to many antibiotics can occur. As a result, carbapenems have become the drug of choice in treating such resistant strains. Unfortunately, resistance to imipenem has been reported in several countries since 1990.

**Methods**
A total of 149 non-duplicate strains of *A. baumannii* (identified by API 20NE) were isolated and analyzed between 2006 and 2012 from different types of infections in hospitalized patients. Their profile of resistance was determined using the Kirby-Bauer disk diffusion method, in which the diameters of inhibition were measured and used for Quantitative Antibiogram Typing. Typing was also performed using ST typing by multiplex PCR and PFGE. For the detection of the mechanisms of resistance, phenotypic methods were used: DDST IMP-EDTA for MBL detection, 200mM NaCl for OXA detection, 200mg/l cloxacillin and PBA for AmpC detection, and noital carbonyl-cyanide m-chloro phenylhydrazone as efflux inhibitor. In addition, PCR was used to detect the genes of resistance and SDS-PAGE was performed to study the protein profiles of resistant versus susceptible strains.

**Results**
Forty-five percent of the isolates were collected from the Intensive Care Unit and 58% of the specimens were from the sputum. Colistin was associated with the highest susceptibility (98.57%), followed by imipenem (85.94%). PFGE and Quantitative Antibiotic Testing both revealed the presence of 2 clusters. Phenotypic tests for MBL and AmpC production were negative. The 4 strains of *A. baumannii* (2 each from 2011 and 2012) selected for SDS-PAGE analysis revealed no difference in the OMP profile. An efflux pump for imipenem was not detected in any isolate (all CCCP negative); however, all 8 strains isolated in 2011 and 2012 revealed positive results for the oxacillinase phenotype test. The PCR performed for *bla*\(_{OXA-23}\)-like and *bla*\(_{OXA-24}\)-like genes gave negative results, while all 8 strains gave positive results for *bla*\(_{OXA-51}\) and *bla*\(_{OXA-58}\) genes.

**Conclusion**
Determining the mechanism of resistance to imipenem in *A. baumannii* and the number of circulating epidemic strains helps to understand how the resistance is spreading and emphasizes the need for having infection control and antimicrobial stewardship programs in hospitals.
State and national responses to CRE & ESBL alarms

**U.S. CDC to publish comprehensive report on antibiotic-resistant bacteria**

The U.S. CDC is releasing a full scientific report on antibiotic resistant organisms on September 16th, 2013. The report is the first of its kind, covering 18 specific organisms and the problems they each pose as they increasingly become resistant to available antibiotics.

**CDC Vital Signs: Making health care safe—“Stop infections from lethal CRE germs now”**

The CDC recently published a Vital Signs article on the increasing prevalence of difficult-to-treat carbapenem-resistant Enterobacteriaceae (CRE) infections among patients in medical facilities. The fact sheet is geared towards health providers and the public, and it describes in detail the growing problem of CRE infections, which are resistant to all or most antibiotics. Infections with CRE are increasing, and have now been reported in hospitals in 42 US states. The incidence of CREs can be reduced using comprehensive prevention programs, and the US CDC provides guidelines that hospitals can follow.

For a more comprehensive discussion of the Vital Signs publication, see our feature article, “Sounding the alarm on nightmare bacteria,” by CDC expert Dr. Arjun Srinivasan.

**Colorado initiates statewide CRE surveillance**

In 2011, the Colorado Department of Public Health and Environment (CDPHE) began a major effort to better understand the extent of carbapenem-resistant Enterobacteriaceae (CRE) in Colorado. They began by administering an online survey to laboratories to gather data on CRE detection methods and statewide prevalence. CDPHE then formed a working group of infection control experts, physicians, pharmacists, and public health officials to determine the next best steps and to facilitate the process of making CRE a reportable condition in the state.

After managing a CRE outbreak in August of 2012, the state of Colorado successfully made CRE infection a reportable condition by November of the same year. This has led to major improvements in CRE surveillance and outbreak detection, which, in addition to educational support for health care providers, now enables outbreaks to be rapidly detected and contained.

**Oregon’s statewide network to contain CRE**

After conducting a needs assessment survey of acute-care hospitals, laboratories, and long-term care facilities in Oregon, the Oregon Health Authority (OHA) decided to develop a comprehensive approach to combat the rising threat of CRE. OHA created the Drug-Resistant Organism Prevention and Coordinated Regional Epidemiology (DROP-CRE) Network to establish statewide approaches for the prevention and control of multi-drug resistant organisms, including CRE. The DROP-CRE Network is currently: developing a statewide database for resistant organisms; conducting rapid identification of CRE; promoting CRE education; tracking CRE across the spectrum of care; and providing real-time outbreak assistance to Oregon facilities reporting cases of CRE. The success of these initial goals has led to a focus on active CRE response methods and network expansion to other states.

**New UK study to assess impact of ESBL-positive E. coli**

The UK government announced last month that it is launching a new study on increasingly prevalent extended-spectrum beta-lactamase (ESBL)-positive E. coli. E. coli is the most common bacterial pathogen in the world, and it is estimated that as many as 80% of urinary tract infections are caused by E. coli. Certain strains of E. coli can produce ESBL enzymes that destroy commonly used β-lactam antibiotics. The study will establish the most significant reservoirs of ESBL E. coli by looking at sewage, raw meat, and farm slurry to assess the potential risks they pose to human health.
APUA 2013 Leadership and Chapter Award Recipients

APUA is pleased to award Dr. Keith Klugman, Director for Pneumonia at the Gates Foundation, the 2013 Leadership Award. Keith has served on numerous committees as an expert in antimicrobial resistance, including those for the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC). He has published more than 450 scientific papers on the subjects of pneumonia, meningitis, antimicrobial resistance, and vaccines for bacterial pathogens.

The annual APUA Leadership Award recognizes an individual or organization demonstrating extraordinary leadership in promoting the prudent use of antibiotics in order to contain antibiotic resistance.

APUA is also pleased to announce APUA-Cuba as the winner of the 2013 Chapter Award. APUA-Cuba has over 1,000 members in 60 different medical specialties. Chapter leader Dr. Moisés Morejón (Manual Fajardo Hospital) and his colleagues have held multiple symposia on antimicrobial resistance and the need for new antibiotics.

The annual APUA Chapter Award recognizes one of 66 international chapters affiliated with the organization for its members’ dedication to the APUA mission of ensuring access to effective treatment and promoting appropriate antibiotic use to contain drug resistance.

The 2013 winners will be celebrated a special event at ID Week, October 2—6 in San Francisco, CA.

Directorship Transition at APUA

Effective October 15, Ms. Kathleen Young will be transitioning from her position as APUA Executive Director to a role as program consultant. According to Dr. Stuart B. Levy, APUA President, “Through Kathy’s commitment and initiative, APUA has played a major role in driving the drug resistance issue to the top of the national and international health agenda.” During her 15 year tenure, APUA expanded its affiliated international chapter network to over 66 countries and extended its mission to increase access to effective antibiotics in resource-poor countries.

Ms. Young introduced important research projects to document antibiotic resistance problems and then forged public and private partnerships to build consensus on interventions. Among the projects she initiated were:

- the first international antibiotic resistance surveillance meeting involving over fifteen major surveillance systems (1997)
- the first peer-reviewed study providing evidence and detailed recommendations to limit antibiotics in food animal production (FAAIR report 2002)
- the first multi-university network investigating resistance in commensal organisms for early warning signs for resistance in pathogens (2002-2007)
- the first report to document global antimicrobial resistance trends in the major pathogens (GAARD report 2005)
- the first detailed African country situation analysis of antibiotic use and resistance (2008), and
- an updated peer-reviewed estimate of the U.S. cost of antibiotic resistance in over ten years, now widely cited in policy debates (2009)

Ms. Young notes: “Fortunately, we are now seeing active investments in antibiotic stewardship and infection control and new treatment and diagnostics coming online. With the continued commitment of APUA’s board and advisors and dedicated staff in place, APUA will continue to play a leadership role in ensuring access to effective antimicrobials for generations to come.” With a background in biochemistry and corporate organizational development, Dr. Barbara Lapinskas, PhD (Barbara.lapinskas@tufts.edu), will continue as APUA’s Administrative Director. Jane Kramer, JD, is serving as APUA’s Program Development Director with experience as Director of Communications for several global pharmaceutical companies supporting programs to increase access to medicines.

APUA cautions against use of antibiotics to treat malnutrition

On June 20, a letter crafted by the APUA Nutrition Group was
APUA invites its chapter organizations and any interested readers to submit commentary on their opinions and observations regarding the use of antibiotics to treat malnourished children in their countries.

APUA compiled expert opinion from its Scientific Advisory Board, including co-authors Iruka Okeke, Jose Ramiro Cruz, and Gerald Keusch, in order to formulate an editorial in response to the suggested implementation of routine antibiotics for severe malnutrition. APUA supports further research because the potential broad-scale expansion of antibiotic use could prompt widespread antibiotic misuse and resistance in the community. Instead, researchers should focus on immediate expansion of validated interventions, including breast-feeding, the use of probiotics, and increased access to traditional RUTFs and clean water. These strategies will be more effective in reducing malnutrition in the long run.

As part of an ongoing partnership, APUA and Alere Diagnostics held the first of three live webinars on July 2nd. Dr. Philip Carling, Professor of Clinical Medicine at Boston University School of Medicine, hosted the webinar on the impact of antimicrobial stewardship in healthcare settings. With over 500 attendees, the webinar discussed the elements of successful antimicrobial stewardship, how to analyze and measure antibacterial use in hospitals, and the importance of rapid diagnostics to ensure appropriate antimicrobial use.

The full webinar recording and slides can be accessed here.
German parliament proposes strict measures to cut antibiotic use

Germany’s Parliament, The Bundestag, has made major revisions to its policies on the use of medications for livestock. The Ministry for Food, Agriculture and Consumer Protection announced in March that the use of antibiotics in food animal production needs to be significantly reduced, and ideally, strictly limited to therapeutic purposes. The policy will give regional authorities greater power over the exchange of information between regions thanks to a new national database of antibiotic use on farms. Authorities, as well as farmers, will be able to compare the frequency of antibiotic therapy between farms across the country. Farmers and veterinarians will bear the responsibility of monitoring the frequency of medication and enacting measures to reduce antibiotic use if appropriate.

FY14 Global Health Appropriations

In the last week of July, the House Appropriations Committee approved its FY 2014 State/Foreign Operations spending bill, allocating $40.6 billion in discretionary funding—a 19% decrease from FY 2013. While eliminating spending for certain international organizations, the House bill does provide generous funding to various key global health programs, including $6 billion to the President’s Emergency Plan For AIDS Relief, and hundreds of millions of dollars each to tuberculosis, malaria, maternal and child health, and nutrition programs. Meanwhile, the Senate Appropriations Committee passed its FY 2014 bill which sets overall spending at $50.5 billion and provides much more for foreign assistance than the House. It appears most likely that committee staff on both sides of the Capitol will have to work to bridge the major gaps between the two bills.

India poised for National Antibiotics Policy

The Union Health Ministry of India is considering a new National Antibiotics Policy to restrain the overuse of antibiotics and reduce an already alarming rate of resistance. A policy was drawn up in 2011 following the release of Timothy Walsh’s article in The Lancet which detailed the emergence of a new enzyme—that made bacteria resistant to all antibiotics. The policy was ultimately scrapped, but as antibiotic resistance has only increased, policy makers are re-examining options to limit antibiotic use. The Chennai Declaration, an August 2012 event that convened specialists to form a plan for tackling antimicrobial resistance in India, is believed to have rekindled Indian stakeholders’ calls for change.

FDA requires veterinary oversight for livestock antibiotics

The U.S. Food and Drug Administration (FDA) is implementing a new strategy to encourage more appropriate and prudent use of antibiotics in food animal production. The strategy intends to curb antibiotic overuse and misuse by identifying certain antibiotics that will now require veterinary oversight via the Veterinary Feed Directive (VFD). The FDA will also help drug companies voluntarily re-label antibiotic products to remove feed efficiency and growth promotion claims. Labels will instead emphasize antibiotic use for the prevention, control, and treatment of bacterial diseases. Michelle Arnold, a veterinarian from the University of Kentucky College of Agriculture, Food, and Environment, approved of the FDA’s program, stating that “veterinarians are uniquely qualified to determine which specific disease-causing organisms are likely to be present and to determine appropriately timed administration of medication relative to the disease.”

In July, APUA, along with multiple other national health organizations, signed a letter submitted to the FDA and the US Department of Agriculture (USDA) commenting on their proposed changes to the VFD. While the changes would keep certain over-the-counter drugs under closer supervision by veterinarians, they would alter the definition of the veterinary client patient relationship (VCPR) in a way that allows a veterinarian’s practice to issue a VFD without requiring a visit to each facility. The letter states support for the FDA and USDA to retain the current, stricter VCPR definition. The letter also recommends that language be included to define a limit of 21 days for the duration of use of an antibiotic in a herd, pen or barn.
Triclosan alters stream bacteria—leads to resistance

Evidence continues to mount regarding the toxic nature of triclosan, an antibacterial incorporated into a host of commercial products, including soap, toothpaste, fabrics, deodorants, cosmetics, toys, and plastics. Antibacterial chemicals such as triclosan enter waterways mostly via household wastewater and combined sewer overflows. Triclosan has been accumulating in the environment, causing growing concern over potential ecologic effects. In a recent study of both field surveys and artificial stream experiments, researchers noted marked declines in diversity among sediment bacteria, shifts in community composition (notably, increases in cyanobacteria), and a marked die-off of algae. In artificial stream experiments, the proportion of triclosan-resistant bacteria reached a maximum of 14% over the course of the 5-week study. This is the first report of evidence for a link between triclosan exposure and bacterial resistance in environmentally relevant field conditions.

Ocean mud yields new antibiotic effective against anthrax

Researchers from the University of California, San Diego along with biopharmaceutical company Trius Thera upeutics, recently discovered a novel antibiotic compound that exists in the mud along the coast of Santa Barbara, CA. The new antibacterial, derived from a species of Streptomyces and named “anthracimycin,” has been successful at destroying anthrax and bears potential for treatment of other gram-positive pathogens such as Staphylococcus aureus (MRSA), enterococci and streptococci. A chlorinated derivative also demonstrates activity against some gram-negative bacteria.

CDDEP showcases new ResistanceMap

The Center for Disease Dynamics, Economics & Policy (CDDEP) has created a fascinating and useful array of interactive tools called ResistanceMap that explore antibiotic use and bacterial resistance in North America and Europe (Fig. 1). The maps allow comparison of antibiotic use and resistance across different geographic areas over time.

Synthetic stool will enable treatment of stubborn C. difficile infections

Researchers are now creating synthetic feces using “Robogut,” a mechanical device that mimics the conditions of the human colon. The synthetic stool, which consists of 33 different types of bacteria, will be used to treat patients infected with Clostridium difficile, the bacterium that causes serious bouts of diarrhea and is increasingly resistant to antibiotic treatment. A recent report in Microbiome found that the synthetic stool successfully cured the infections in two study patients, who had previously failed standard antibiotic therapy.

Study quantifies antibiotic resistance on Chinese swine farms

Recent research published in the Proceedings of the National Academy of Sciences quantifies for the first time the amount of bacterial resistance on swine farms in China. The study found 149 unique resistance genes at just three large swine farms in China. Quantified, scientific evidence of such high resistance levels increases cause for alarm over the growing international issue of antibiotic resistance. China uses four times more antibiotics for veterinary purposes than the United States.
News and publications of note

A novel community addresses antibiotic resistance

Martha E. Lentz
Founder and President of The Harmony Institute

Within the scope of the natural environment is antibiotic resistance, an area the Institute refers to as the “invisible” environment and believes is of critical importance to human interaction and health. To inform Harmony residents of the impending crisis of antibiotic resistance and the overuse of antibacterial products, the Institute included language in the Residential Properties document and regularly educates residents through science advisories in its quarterly newsletter. The Institute also presents a youth education program entitled “Good Germ, Bad Germ” in an effort to instill in children the reality that bacteria are alive and the vast majority of them are their friends.

A major Florida university has recently committed to pursuing longitudinal studies within the town of Harmony and the Institute is proposing that antibacterial resistance be one of two initiating studies.

Updates in C. difficile management

In a recent Medscape article, Dr. John G. Bartlett discussed five important developments on the topic of preventing and treating C. difficile infections (CDI):

1. A new U.S. CDC study found that 75% of patients admitted to a hospital or nursing home were already colonized with C. difficile at the time of admission. This knowledge has important ramifications for infection control practices.

2. Fidaxomicin is now the second drug approved by the U.S. FDA for the treatment of CDI. While relatively costly, it has global cure rates superior to those of vancomycin.

3. Doctors in the Netherlands have trained a beagle to detect CDI based on the odor of p-cresol, the phenolic compound that is thought to be associated with C. difficile. The beagle’s performance in the trial was near perfect.

4. Surgeons at the University of Pittsburgh have reported a new surgical approach, called “diverting loop ileostomy with colonic vancomycin lavage,” which has lower mortality rates than the standard colectomy procedure.

5. Stool transplants for patients with multiple relapses of CDI are becoming more widely accepted, thanks to more research and relaxed FDA requirements.
About us

Antibiotics are humanity’s key defense against disease-causing microbes. The growing prevalence of antibiotic resistance threatens a future where these drugs can no longer cure infections and killer epidemics run rampant. The Alliance for the Prudent Use of Antibiotics (APUA) has been the leading global non-governmental organization fighting to preserve the effectiveness of antimicrobial drugs since 1981. With affiliated chapters in more than 66 countries, including 33 in the developing world, we conduct research, education and advocacy programs to control antibiotic resistance and ensure access to effective antibiotics for current and future generations.

Our global network of infectious disease experts supports country-based activities to control and monitor antibiotic resistance tailored to local needs and customs. The APUA network facilitates the exchange of objective, up-to-date scientific and clinical information among scientists, health care providers, consumers and policy makers worldwide.

The APUA Clinical Newsletter has been published continuously three times per year since 1983.
Tel: 617-636-0966 • Email: apua@tufts.edu • Web: www.apua.org