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In her blog (12/14/2015; You can’t buy antibiotics over the counter, can, you? [Yes, you can]), journalist Maryn McKenna offers positive proof to skeptics by purchasing the above 1.6-lb bag of chlortetracycline online with nothing more than a credit card. Nearly 99% of antibiotics used for agriculture are sold without prescription and 62% are considered medically important to human disease treatment. For updates on the topic of antibiotic use in animals, see APUA news items here and here.
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*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 | Email: apua@tufts.edu | Website: www.apua.org

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Antibiotic-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE) and multi-drug resistant *Acinetobacter* are increasing in prevalence worldwide, resulting in infections that are difficult and expensive to treat. Sievert et al.¹ describes antimicrobial resistance patterns for hospital-associated infections (HAIs) reported to the National Healthcare Safety Network (NHSN) during 2009-2010. They found *S. aureus* was the primary pathogen causing overall HAIs, with MRSA being the most common multi-drug resistant organism (MDRO).¹

Humans are natural reservoirs for *Staphylococcus aureus* (*S. aureus*). Twenty to fifty percent of healthy adults are colonized with *S. aureus* (10-20% are persistent carriers, and approximately 30% are intermittent carriers).² Colonization rates are highest among diabetics, intravenous (IV) drug users, patients on hemodialysis or continuous peritoneal dialysis, and those having dermatologic conditions (eczema and psoriasis) and human immunodeficiency virus (HIV). Nasal colonization with *S. aureus* is the single most important determinant of subsequent *S. aureus* infection. However, colonization—whether presented on admission or hospital-acquired—increases risk of HAIs.³⁻⁵

**Infection control measures to reduce *S. aureus* HAIs**

In recent years, the infection control community has taken two different approaches, vertical and horizontal (*Table 1*), towards preventing HAIs. Vertical approaches, like decolonization of patients, are an essential practice in reducing MDRO (like MRSA) transmission in hospitals. The two most common decolonization methods are: 1) chlorhexidine gluconate (CHG) bathing and 2) intranasal therapies (mupirocin and povidone-iodine).

**CHG bathing**

Cleansing with CHG has been shown to decrease the bioburden of microorganisms on the patient, the environment, and

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**Table 1. Approaches towards reduction of infection risk**

<table>
<thead>
<tr>
<th><strong>Vertical approaches reduce risk of infections due to specific pathogens:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Active surveillance testing to identify asymptomatic carriers</td>
</tr>
<tr>
<td>• Contact precautions for patients colonized or infected with specific organisms</td>
</tr>
<tr>
<td>• Optimal decolonization of patients colonized or infected with specific organisms (i.e., CHG bathing, mupirocin, povidone-iodine)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Horizontal approaches reduce risk of a broad range of infections and are not pathogen specific:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Standard precautions (i.e., hand hygiene)</td>
</tr>
<tr>
<td>• Universal use of gloves or gloves and gowns</td>
</tr>
<tr>
<td>• Universal-optimal decolonization (i.e. CHG bathing, mupirocin, povidone-iodine)</td>
</tr>
<tr>
<td>• Antimicrobial stewardship</td>
</tr>
<tr>
<td>• Environmental cleaning and disinfection</td>
</tr>
</tbody>
</table>

Source: modified from Septimus 2015⁶
the hands of healthcare personnel.\(^8\) Daily bathing of intensive care unit (ICU) patients with chlorhexidine has been associated with decreased central line-associated blood stream infections (CLABSIs) and decreased acquisition of healthcare pathogens.\(^7\) CHG is also commonly used for preoperative bathing to reduce the risk of surgical site infections (SSIs). Lipke et al\(^9\) showed the effectiveness of reducing SSIs by bundling multiple risk reduction strategies, i.e., preadmission showers with CHG, and nasal decolonization for MRSA with mupirocin. As a result, overall SSIs were reduced by 63%, and SSIs caused by MRSA decreased 78%. The facility experienced savings of over $200,000.

**Nasal decolonization with mupirocin**

For intranasal decolonization, mupirocin (an antibiotic) is commonly applied to the anterior nares two times per day for five days. The reported effectiveness of mupirocin is comparable among methicillin-susceptible \(S.\) \( aureus\) (MSSA) carriers and MRSA carriers. Recently, Ammerlaan et al\(^10\) reviewed 23 clinical trials, including 12 that looked at topically applied antibiotics only. They concluded short-term nasal application of mupirocin is the most effective treatment for eradicating MRSA carriage, with an estimated success rate of 90% at one week post treatment and approximately 60% after a longer follow-up.\(^10\) Mody et al\(^11\) published a double-blind randomized study looking at the efficacy of intranasal mupirocin versus placebo in reducing colonization and preventing infections in two long-term care centers. Twice-daily treatment was given for two weeks with follow-up to 6 months; after treatment, mupirocin eradicated colonization in 93% of residents compared to only 15% in the placebo group \((p = .001)\). At 90 days after

<table>
<thead>
<tr>
<th>Table 2. Mupirocin resistance</th>
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<tbody>
<tr>
<td><strong>Context</strong></td>
</tr>
<tr>
<td><strong>Community Decolonization</strong></td>
</tr>
<tr>
<td>New Zealand</td>
</tr>
<tr>
<td>Western Australia</td>
</tr>
<tr>
<td>(Notification data)</td>
</tr>
<tr>
<td>U.S.– military CA-MRSA</td>
</tr>
<tr>
<td><strong>Targeted Decolonization in Hospitals</strong></td>
</tr>
<tr>
<td>Kuwait - burn unit</td>
</tr>
<tr>
<td>Brazil - hospital</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>U.S. (Illinois) - 3 hospitals</td>
</tr>
<tr>
<td>Hemodialysis patients (serial)</td>
</tr>
<tr>
<td><strong>Universal Decolonization</strong></td>
</tr>
<tr>
<td>29 ICUs (13 U.S. hospitals)</td>
</tr>
<tr>
<td><strong>Surgical Prophylaxis</strong></td>
</tr>
<tr>
<td>2,000 patients (U.S. hospital)</td>
</tr>
<tr>
<td>6 hospital units (U.K. hospital)</td>
</tr>
<tr>
<td>20,000 patients (multi-country)</td>
</tr>
</tbody>
</table>

* >512µg/mL (minimum inhibitory concentration range); Source: Patel JB et al. CID 2009: 935-41
** administered over-the-counter rather than by prescription
† 2/20 vs 11/64

**References for this table:**
1 Upton et al. JAC 2003; 51: 613-17.
3 Ellis MV et al. AACT 2007; 51: 3591-98
7 Boelaert JR et al. Neph Dial Trans 1989; 4: 278-81
8 Lolans K et al. IDWeek 2014.
10 Fawley WN et al. J. Hosp Infect 2006; 62: 327-32

Source: Huang S. 2015

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treatment, 61% of residents in the mupirocin group remained decolonized. The authors concluded that mupirocin was effective in decolonizing persistent carriers in long-term care and showed a trend towards reduction of infections.¹¹

Mupirocin has emerged as the topical agent of choice for elimination of S. aureus nasal carriage. However, there is growing evidence of increasing mupirocin resistance to S. aureus and treatment failures, especially with widespread use over long periods of time.¹²,¹³ To illustrate how mupirocin resistance has increased, Table 2 provides a summary of mupirocin resistance in several clinical studies, across different regions and decolonization strategies.¹⁴

**Nasal decolonization with povidone-iodine: an antibiotic alternative**

Due to the increasing demands for antimicrobial stewardship and the need to prevent further spread of resistance across the globe, there is renewed interest in evaluating newer agents and alternative methods for intranasal decolonization.

Povidone-iodine (PI) is an excellent alternative for intranasal decolonization because it has a broad activity against gram-positive and gram-negative bacteria. Hill et al.¹⁵ evaluated the in vitro activity of 5% povidone-iodine as a possible alternative to mupirocin for the elimination of nasal carriage of S. aureus. The results suggested povidone iodine may have a role in the prevention of colonization and infection due to MRSA, including mupirocin-resistant strains. Phillips et al.¹⁶ conducted a prospective, open label trial of twice daily application of nasal mupirocin ointment for 5 days before surgery and compared it to two applications of a 5% PI solution in each nostril within 2 hours of surgical incision in patients undergoing arthroplasty or spine fusion surgery. Both groups also received a bath with 2% CHG-impregnated cloths the night before and the morning of surgery. In the analysis, S. aureus deep SSI developed in 5 of 763 surgical procedures in the mupirocin group and in 0 of 776 surgical procedures in the PI group (P=.03).¹⁶ Bebko et al.¹⁷ recently published a preoperative decontamination protocol to reduce SSIs in orthopedic patients undergoing elective hardware implantations.

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- Clinically proven to be non-irritating²

* "Risk" refers to the growing evidence of resistance of S. aureus and MRSA to mupirocin. "Complexity" refers to the 5-day, twice-daily application protocol of mupirocin.
1. Clorox Study #0550-005 (in vitro study); 2. Clorox Study #2015-002/2015-003
The study demonstrates that preoperative MRSA decontamination with CHG washcloths and oral rinse, plus intranasal povidone-iodine, decreased the SSI rate by more than 50% among patients undergoing elective orthopedic surgery with hardware implantation.

To date, studies have not shown development of resistance to PI antiseptic. Antiseptics work quickly, are dose-independent, and continue working long after they are applied, making it difficult for bacteria to build resistance. Moreover, the cost of using a skin antiseptic is less than the cost of the screening test for S. aureus. Consequently, hospitals have less expensive alternatives for decolonizing patients that can complement the benefit of preserving antibiotic efficacy.

References:


7. Supple L, et al. Chlorhexidine only works if applied correctly: use of a simple colorimetric assay to provide monitoring and feedback on effectiveness of chlorhexidine application. Infect. Control Hosp Epidemiol. 2015; 36 (9): 1095-1097


The Importance of Surface Disinfection in an Antibiotic-Resistant World

Sarah C. Bell-West, Ph.D., Senior Scientist, Clorox Healthcare

Resistance to antimicrobial agents, especially antibiotics, is a major public health concern throughout the world. In the United States alone, The Centers for Disease Control and Prevention (CDC) estimates that antibiotic-resistant bacteria cause two million illnesses and approximately 23,000 deaths each year.¹ Multimodal infection prevention approaches coupled with antimicrobial stewardship efforts are essential for the prevention of infections caused by antibiotic resistant organisms. A recent CDC report estimated that if improved infection control practices and antibiotic stewardship efforts were adopted nationally, 619,000 infections and 37,000 deaths could be prevented over five years.²

Given the growing problem of antibiotic resistance, environmental cleaning and disinfection can play an important role in helping to prevent the spread of antibiotic-resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae (CRE) in addition to other deadly pathogens associated with antibiotic usage, including Clostridium difficile. Additionally, the infection control community is asking questions about the relationship between disinfectant use and antibiotic resistance. This article will focus on the role of surface disinfection in reducing transmission of antibiotic-resistant bacteria and the relationship between antibiotic resistance and the susceptibility of bacteria to surface disinfectants.

Does surface disinfection help to reduce transmission of antibiotic resistant bacteria?

Compliant cleaning and disinfection of environmental surfaces and medical equipment is a critical first line of defense against all pathogens in the healthcare environment, and especially those that are resistant to antibiotics. There is a growing body of evidence to demonstrate the effectiveness of environmental cleaning and disinfection as part of multimodal strategies to reduce pathogen transmission, prevent healthcare associated infections (HAIs), and improve patient outcomes.³ For example, researchers in Canada recently demonstrated that compliant daily cleaning and disinfection of high-touch surfaces in patient rooms (>80% cleaning compliance) was associated with a significant reduction in infections caused by MRSA, VRE, and Clostridium difficile in their hospital.⁴

However, studies have also demonstrated that often times fewer than 50% of hospital room surfaces are adequately cleaned and disinfected, potentially putting patients at increased risk for acquiring an HAI.⁵ This was documented in a recently-published review and meta-analysis of six studies highlighting that a patient in a room that previously housed a patient colonized or infected with a pathogenic bacteria, which included MRSA, VRE, or Clostridium difficile, was twice as likely to be infected with the same pathogen.⁶

Antibiotic-resistant bacteria are not always the most...
common or deadly, underscoring the need for infection prevention strategies to focus on all HAI-causing pathogens, regardless of their antibiotic susceptibility. This was highlighted by a recent study in infant populations showing methicillin susceptible *Staphylococcus aureus* (MSSA) infections were more common and more deadly than those caused by MRSA.⁷

**Does the use of surface disinfectants contribute to an increased risk for antimicrobial resistance?**

The topic of whether there is a relationship between the use of surface disinfectants in the home and in healthcare settings and the development and selection of antibiotic resistant organisms is heavily debated within the field of infection control.⁸ Antibiotics and surface disinfectants differ in both their mode and speed of action (Table 1). Antibiotics often work through a specific site of action, and bacteria can adapt to overcome the action of the drug over time. Surface disinfectants often have multiple, non-specific target sites across different classes of microorganisms. For example, oxidative disinfectants like sodium hypochlorite and hydrogen peroxide quickly and indiscriminately react with proteins, nucleic acids and other biomolecules, leading to oxidative cell destruction. This activity makes it challenging for pathogens to develop mechanisms to survive exposure to these surface disinfectants.

<table>
<thead>
<tr>
<th>Table 1: Comparison of antibiotics and disinfectants:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic</strong></td>
</tr>
<tr>
<td>Designed for: Humans</td>
</tr>
<tr>
<td>Target site on bacteria: Specific molecular site</td>
</tr>
<tr>
<td>Activity: Specific</td>
</tr>
<tr>
<td>Concentration, frequency: Variable</td>
</tr>
<tr>
<td>Dosage: Multiple</td>
</tr>
<tr>
<td>Timescale of action: Days, weeks or longer</td>
</tr>
<tr>
<td><strong>Surface Disinfectant</strong></td>
</tr>
<tr>
<td>Designed for: Inanimate objects</td>
</tr>
<tr>
<td>Target site on bacteria: Multiple sites</td>
</tr>
<tr>
<td>Activity: Broad-spectrum</td>
</tr>
<tr>
<td>Concentration, frequency: High concentrations</td>
</tr>
<tr>
<td>Dosage: Single Application</td>
</tr>
<tr>
<td>Timescale of action: Minutes</td>
</tr>
</tbody>
</table>

There is emerging research that suggests that the use of quaternary ammonium-based antimicrobial compounds may lead to decreased susceptibility in bacteria and cross-resistance to antibiotics.⁹ Studies have demonstrated that exposure of bacteria to sublethal concentrations of quaternary ammonium compounds in laboratory settings, which mimics disinfectant misuse over long time periods, can trigger resistance mechanisms.¹⁰ There is also evidence to support the position that the use of disinfectants does not contribute to antibiotic resistance, and some have cited studies demonstrating that both antibiotic resistant and antibiotic susceptible bacteria are still susceptible to surface disinfectants under normal usage conditions.¹¹,¹² For example, Campos and colleagues in Brazil recently reported that there was no significant difference in the susceptibility of clinical isolates MRSA and MSSA to various disinfection chemistries.¹³

While there is evidence to support both viewpoints, additional research is required to understand the relationship between sustained usage of antiseptics and disinfectants in clinical settings and the corresponding changes in antimicrobial susceptibility of clinical isolates over time.

**Where do we go from here?**

A multi-faceted approach utilizing both infection control and
antimicrobial stewardship strategies is needed to reduce the infection burden attributed to antimicrobial resistant organisms. Killing pathogenic bacteria, viruses and fungi on surfaces before they infect a host can reduce the number of difficult-to-treat infections caused by antibiotic resistant organisms and reduce the risk of the development of antibiotic resistance.

Combining the key principles of antimicrobial stewardship\textsuperscript{14} to include proper selection and usage of surface disinfectants,\textsuperscript{15} the following steps are recommended:

1. Educate all staff, including clinical and environmental services team members, about the burden of drug-resistant infections in your facility.
2. Communicate internally when drug-resistant infections in patients are identified and externally when patient with a drug-resistant infection are transferred to another facility.
3. Protect patients from drug-resistant infections by implementing best practices in infection control.
4. Reinforce the importance of compliant cleaning and disinfection of medical equipment as well as hard and soft environmental surfaces to reduce pathogen contamination of surfaces prevent pathogen transmission.
5. Follow relevant guidelines and precautions at every patient encounter.
6. Prescribe antibiotics wisely.
7. Remove temporary medical devices such as catheters and ventilators as soon as they are no longer needed.

\textbf{References}

Antimicrobial Stewardship and Novel Strategies for the Management of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in the Acute Care Setting

Glenn R. Oettinger, Jr., PharmD, BCPS, Emergency Medicine Pharmacy Specialist, Clinical Assistant Professor, Thomas Jefferson University and Hospital

Charles V. Pollack, Jr., MA, MD, FACEP, FAAEM, FAHA, FESC, Associate Provost and Professor of Emergency Medicine,

Establishing a Sense of Urgency

Overcrowding of hospitals and emergency departments presents many challenges to health systems, operationally and financially. Acute bacterial skin and skin structure infections (ABSSSI) are common diagnoses that contribute to stress on those systems. The most commonly used antimicrobial agent for patients with ABSSSI, vancomycin, is resource intensive. It involves weight-based loading and maintenance dosing, which often escape the attention of overstretched staff. The requirement for pharmacokinetic monitoring presents additional responsibility for prescribers, nurses, and pharmacists.

High utilizers and poor compliance can also play a factor in health systems meeting their patient care goals. Patients often leave the hospital against medical advice amid a twice-daily vancomycin regimen. This poses obstacles for care since treatment will be interrupted or discontinued by the patient opening the possibility for failing to return for scheduled visits, antibiotic resistance because of partial treatment, and increased expenditures for both patient and system. A more streamlined, safe, reliable, and less cumbersome strategy for ABSSSI requiring parenteral therapy would be welcomed.

What is ABSSSI?

The FDA defines ABSSSI to include cellulitis/erysipelas, wound infection, and major cutaneous abscess with a minimum lesion surface area of 75 cm² (Fig. 1). Operationally, ABSSSIs usually require parenteral antimicrobial therapy. Diabetic foot ulcers, chronic wounds, and burn wound infections are excluded. Bacterial pathogens that commonly cause ABSSSI include Streptococcus pyogenes and Staphylococcus aureus, including MRSA (Fig 2). Less commonly identified bacteria include other Streptococcus species, Enterococcus faecalis, and Gram-negative bacteria.²-³

Treatment Setting

While the majority of patients presenting with skin and skin structure infections are suitable for outpatient treatment with oral antimicrobials, patients with ABSSSI requiring parenteral therapy may also be appropriate for outpatient or truncated inpatient treatment. Effective outpatient management can reduce hospital resource consumption and cost while improving patient outcomes and satisfaction.

Microbiological Considerations

Since the majority of cases of ABSSSI do not yield positive wound or blood cultures, empiric coverage for the most common pathogens is very important. In current emergency medicine practice, it is prudent to assume the ABSSSI is caused by MRSA, and to treat accordingly. Empiric Gram negative coverage is not indicated in most cases of ABSSSI.²-³
Understanding that, the choice of empiric antibiotics in this population has not always been ideal. In a 2004 study of emergency department (ED) practice, when the medical community had not yet identified MRSA as a common cause of ABSSSI, 59% of patients were found to have infection caused by MRSA and only 57% received an empiric antibiotic that matched ultimate susceptibility testing.\(^4\)

Prevalence of MRSA in the community has shifted dramatically in the two decades since. One study from the early 1990’s found no MRSA among those patients presenting with cutaneous abscesses associated with intravenous drug use.\(^5\) Unfortunately, this is no longer the situation and it appears to be worsening. The rise in MRSA infections among patients with ABSSSI is illustrated by another study from a single Los Angeles ED. It found that from 2001-2005, the prevalence of MRSA increased from 29% to 64%.\(^6\) Furthermore, MRSA was identified as the most common cause of ABSSSI among a geographically diverse network of EDs across the US collecting isolates in the early 2000s.\(^4\) This shift in microbial prevalence is also supported by the SENTRY Antimicrobial Surveillance Program that analyzed causes and types of SSTI from 1998 to 2004, finding that *S. aureus* was found in 44.6% of isolates in N. America, of which 35.9% were methicillin resistant.\(^7\)

The SOLO randomized trials evaluated the safety and efficacy of a single dose of 1200 mg of oritavancin, compared to a regimen of intravenous vancomycin twice daily for 7 to 10 days, in adults with ABSSSI (Table 1).\(^8\) Oritavancin was non-inferior to vancomycin in terms of clinical and microbiologic outcomes, but more importantly, the incidence of adverse events was similar between treatment groups that were hospitalized, as well as those treated outpatient.

Utilizing a single-dose antibiotic for ABSSSI comes at a price that should be compared to the cost of unnecessary hospital admissions. Currently, only one antibiotic is available for single-dose treatment of ABSSSI. However, it is anticipated that dalbavancin, a long-acting glycopeptide like oritavancin, will also receive approval for single-dose therapy in 2016. Dalbavancin is currently approved for the treatment of ABSSSI using a two-dose strategy; 1000 mg IV followed by a second dose of 500 mg IV one week later.

### Process Changes

In addition to these aspects of managing ABSSSI, important process changes should be considered to facilitate successful outpatient treatment and appropriate follow-up.

<table>
<thead>
<tr>
<th>Incidence of Adverse Events in SOLO(^9)</th>
<th>Outpatient</th>
<th>Hospitalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>70.2%</td>
<td>63.6%</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>72.7%</td>
<td>60.5%</td>
</tr>
</tbody>
</table>

The SOLO randomized trials evaluated the safety and efficacy of a single dose of 1200 mg of oritavancin, compared to a regimen of intravenous vancomycin twice daily for 7 to 10 days, in adults with ABSSSI (Table 1).\(^8\)

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<tbody>
<tr>
<td>In addition to these aspects of managing ABSSSI, important process changes should be considered to facilitate successful outpatient treatment and appropriate follow-up.</td>
</tr>
</tbody>
</table>
These include drug payment, logistics, and confirmation of treatment success. Payment through a commercial insurer or company-sponsored patient assistance program can be verified with the help of case managers. This can be accomplished using traditional in-house methods or by utilizing a company-sponsored portal, which can also facilitate vial replacement programs to support the treatment of uninsured patients. Once drug access is secured, the next step is clinical and logistical coordination with an observation unit, infusion center, or home infusion service. Finally, arranging follow up with the ED or a general practitioner is necessary to conduct a routine wound check and confirm treatment success.

Establishing a clear process that emphasizes communication with each linked entity will optimize the success and safety of this contemporary approach to treating ABSSSI. Operationalizing a well-coordinated program utilizing a single-dose strategy requires planning and staff education. Nonetheless, outpatient single-dose therapy may improve adherence to treatment, decrease the need for hospitalization, and ultimately decrease overall resource consumption.¹⁰

A clinical review published in 2014 offers guidelines for the management and care transitions for patients in the emergency department and hospital with ABSSSI.¹¹

References:


The Alliance for the Prudent Use of Antibiotics is pleased to honor Kevin Outterson, J.D., LL.M., professor at the Boston University School of Law and Boston University School of Public Health, as the recipient of our 2015 Leadership Award.

Professor Outterson, the N. Pike Scholar in Health and Disability Law and co-director of BU’s health law program, is the author of groundbreaking models to address the economic challenge of developing new antibiotics. Together with his scholarship and testimony before the United States Congress, he elevates the issues of antimicrobial resistance to a new level, catalyzing access to effective treatment of bacterial infections for all.

"We recognize Professor Outterson as a thought leader in the worldwide effort to contain antibiotic resistance," said APUA President Stuart B. Levy. "His intellectual commitment to the economic realities of developing new drugs that affect the global aspects and consequences of antibacterial resistance alter our thinking about answers to these complex problems."

Professor Outterson recently co-edited a special supplement to the Journal of Law, Medicine & Ethics that is devoted entirely to the problem of antibiotic resistance and the need for an integrated global solution. His other publications on the topic can be viewed here. On Jan 30, Prof. Outterson will be chairing the American Journal of Law Symposium, Global Infectious Diseases: New Challenges and Solutions.

APUA President Levy and board member Gorbach honored with Dean’s medal

On November 5, 2015, Dean of Tufts University Medical School, Harris Berman bestowed the Dean’s Medal for exemplary faculty service to three Tufts Medical School faculty, which included APUA president Stuart Levy and board member Sherwood S. Gorbach, along with Tufts Professor Emeritus Te-Wen Chang. All were celebrated for forging groundbreaking careers in the field of infectious disease.

In a gala event attended by approximately 200 peers, friends and students, Dr. Levy was honored for his outstanding contributions to the field of antibiotic resistance research, which focuses on the mechanism and control of resistance in both bacterial and mammalian cells. Dean Berman, a former APUA board member himself, also noted Levy’s leadership as a health policy advocate and his founding of the Alliance for APUA Headquarters News • The APUA Newsletter Vol. 33 No. 3 • © 2016 APUA • 13
the Prudent Use of Antibiotics in 1981.

A revered educator, researcher and mentor, Sherwood Gorbach, was feted for his work with enterotoxigenic *E. coli* as a cause of diarrhea, particularly in the developing world. His collective research received the IDSA’s Alexander Fleming Award for Lifetime Achievement in 2007.

**ROAR-funded project leads to new publication**

In the early 2000s, APUA’s Reservoirs of Antibiotic Resistance (ROAR) project—initially supported by the NIH—issued several competitive grants for the support of novel projects that could capture the role of commensal bacteria in the emergence and proliferation of antibiotic resistance in human and animal pathogens. One of these projects (Population Phylogenetic Framework of Antibiotic Resistance Emergence in Commensal *Escherichia coli* Isolates), led by Erik Denamur of the Institut Pasteur, proposed to examine a collection of commensal *E. coli* isolates exposed to varying levels of antibiotic selective pressure (animals in tropical rainforests versus mammals in high-intensity agricultural settings). In a recent publication that stemmed from this initial support (*Emergence of antimicrobial-resistant *Escherichia coli* of animal origin spreading in humans*), author David Skurnik and his team have studied 403 *Escherichia* strains isolated from animals and humans having variable contact with each other. Using multilocus sequence typing, the authors demonstrated a decrease in diversity among strains from animals that had increased contact with humans. Strains bearing increased antimicrobial resistance also showed declining diversity. Of particular note, the authors found a unique *E. coli* clonal complex of animal origin that could mobilize and spread antibiotic resistance.

**APUA supports two initiatives**

In a letter signed by several stakeholders, including APUA, the petitioners request USDA Acting Commissioner Stephen Ostroff to “work expeditiously with USDA and CDC to create a system for collecting as much quantitative data on the use of antibiotics in food animals as possible.” To correct existing deficits in data collection, the letter urges that data should be quantitative, comprehensive, ongoing (to facilitate trends analysis) and mandatory. The letter criticizes proposed data collection efforts as falling short of these criteria and recommends collection of data from feed mills that incorporate antibiotics to feed as an additional means of capturing species-specific data.

In a letter to President Barack Obama, over 30 stakeholder organizations in medicine, public health, industry and patient advocacy have expressed deep concern over the alarming antibiotic resistance problem and lack of effective therapies. The letter urges quick action to finalize and release the report of the CARB Economic Incentives Working Group (EIWG)* which had been convened to analyze economic incentives for antibiotic development, develop other innovative diagnostics and treatments, and slow resistance emergence. The letter requests an update and projected release date so that stakeholders can review recommendations and provide feedback.

*The CARB EIWG was generated from the National Action Plan for Combating Antibiotic-Resistant Bacteria in March 2015.*

**CHAPTER UPDATE: APUA – Australia**

APUA-Australia reports the following activities:


✧ Upcoming conferences: Antimicrobials 2016 (http://www.antimicrobials2016.com) and the 16th Asia Pacific Congress of Clinical Microbiology and Infection (http://www.apccmi2016.org/) (hosted by the Australian Society for Antimicrobials).

Submitted by Prof Geoffrey Coombs, Australian Society for Antimicrobials (ASA) Vice President
that can test for multiple pathogens simultaneously with a quick turnaround time. Alternative approaches include a focus on identifying specific infection types or agents that will likely require antibiotic treatment. While a number of companies have stepped up to the plate, and point-of-care-diagnostic tests are emerging steadily, the cost of bringing these devices to market has impeded their uptake. It costs an estimated $55 million to develop a novel diagnostic and an additional $50 million to market and sell it. To spur innovation in this area, the UK and US have offered prize and grant monies worth $36 million to rapidly diagnose resistant pathogens.


Misunderstanding of antimicrobial resistance is widespread

Following on the heels of a Wellcome Trust report (Exploring the consumer perspective on antimicrobial resistance) that revealed poor comprehension of the antibiotic resistance issue among the British population, the WHO has released results of a 12-country survey (Barbados, China, Egypt, India, Indonesia, Mexico, Nigeria, the Russian Federation, Serbia, South Africa, Sudan and Viet Nam) of 10,000 people on their knowledge and attitudes. (Antibiotic resistance: Multi-country public awareness survey). While 64% of those surveyed know that antibiotic resistance is an issue that could impact them, the same proportion (64%) still believed that antibiotics were useful against colds and flu. 32% believed in stopping antibiotics when they felt better, rather than taking the full prescription. It is still wrongly believed by many that the human body grows immune to antibiotics, rather than that the bacteria themselves become resistant. Likewise the societal impacts of antibiotic use are poorly understood. According to WHO’s Keiji Fukuda, the findings “point to the urgent need to improve understanding around antibiotic resistance.”

For a very clear presentation of the problem of antibiotic resistance, see the TED talk “What do we do when antibiotics don’t work anymore?” by Maryn McKenna, winner of Resistance in the News

MCR-1 superbug emerging globally

Following the routine surveillance of antibiotic resistance in farm animals, Chinese scientists have reported a “major increase in resistance against colistin” in a strain of E. coli. Because this toxic drug is used sparingly as a “last resort” antibiotic for treatment of highly resistant superbugs, the finding of significant resistance is alarming. Jian-Hua Liu and colleagues found a mutated, plasmid-based gene, mcr-1, in 20% of pigs and chickens tested and in 15% of raw meat samples from four Chinese provinces. 1.2% of 1,322 hospitalized patients infected with E. coli and Klebsiella pneumoniae also carried the gene. The findings, reported in The Lancet, describe the emergence of the first polymyxin resistance gene that can readily move between E. coli and Klebsiella, creating an alarm that mirrors which followed the emergence of the NDM-1 gene in India. These “extremely worrying results” says Liu, suggest that “the progression from extensive drug resistance to pandrug resistance is inevitable.” Scientists have now called for urgent restrictions on the use of the polymyxin class of antibiotics that are widely employed in food-animal husbandry, and also for worldwide surveillance. Since the November Lancet report, mcr-1 has been reported in at least 10 countries, including Denmark, Germany, France, the UK and most recently, Canada.

Global demand for colistin (a polymyxin antibiotic) reached 26.3 million pounds in 2015, with peak consumption occurring in China, Germany, Spain and Italy.

New rapid diagnostics emerge, but at considerable cost

With rapidly escalating antimicrobial resistance, the demand for new diagnostics that will differentiate between bacterial infections, which require antibiotics, and viral infections that don’t has never been greater. Currently an estimated two-thirds of antibiotic prescriptions are deemed unnecessary. State-of-the-art, rapid diagnostics, which can reduce the demand for antibiotics are as, or more important than developing new drugs, according to economist Jim O’Neill. In high demand are tools that can test for multiple pathogens simultaneously with a quick turnaround time. Alternative approaches include a focus on identifying specific infection types or agents that will likely require antibiotic treatment. While a number of companies have stepped up to the plate, and point-of-care-diagnostic tests are emerging steadily, the cost of bringing these devices to market has impeded their uptake. It costs an estimated $55 million to develop a novel diagnostic and an additional $50 million to market and sell it. To spur innovation in this area, the UK and US have offered prize and grant monies worth $36 million to rapidly diagnose resistant pathogens.


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Microbiome diversity affected by a single course of antibiotics

Netherlands researcher Egija Zaura and colleagues have reported findings of a double-blind study which tracked the fecal and oral flora of 66 healthy adults following consumption of one of four antibiotics: ciprofloxacin, clindamycin, amoxicillin or minocycline. 16S rRNA gene amplicon sequencing was performed at baseline, one, two, four and 12 months post consumption, and metagenomics shotgun sequencing was used to track the emergence of antibiotic resistance.

While oral bacteria showed signs of recovery within a few weeks, the diversity of fecal flora was disrupted for up to four months in those taking clindamycin, and up to 12 months in those taking ciprofloxacin. Particularly affected were butyrate-producing species, which are influential in inhibiting inflammation, cancer formation, and gut stress. Although amoxicillin consumption did not significantly affect microbiome diversity, it showed the largest accumulation of antibiotic resistance genes.

Zaura hypothesizes that the differences between oral and gut flora may be due to length of antibiotic exposure or to the intrinsic resilience of the oral flora towards stress. She concluded that “…antibiotics should only be used when really, really necessary.”

CDC reports rise of “phantom menace”

A particularly worrisome strain of CRE (carbapenemase-resistant Enterobacteriaceae), dubbed the “phantom menace” by concerned scientists in 2012, is emerging and spreading...
across the U.S. according to a Dec. 2015 report by the Centers for Disease Control. The OXA-48-like carbapenemase is a variant of the original OXA48 first reported in Turkey in 2001. The enzyme cleaves carbapenem, a last resort antibiotic for serious multidrug resistant infections. However, unlike other members of the CRE family, which are often resistant to most antibiotics, this variant tends to escape standard detection methods in most clinical laboratories. Because OXA-48-like producers do not exhibit resistance to broad-spectrum cephalosporins, or only decreased susceptibility to carbapenems, their recognition and detection can be challenging. Importantly, they carry their carbapenemase-cleaving genes on a highly mobile plasmid that can easily and rapidly disseminate.

The U.S. cases involved infections primarily with Klebsiella and E. coli in patients with a history of healthcare outside the U.S., although some clusters suggest local transmission. The CDC has released a map of the 43 confirmed cases which emerged in 19 states between 2010 and 2014 — described by CDC director Tom Frieden as “just the tip of the iceberg.” Improved screening and detection methods were instituted in January 2015 in attempts to control further dissemination.

**FDA reports rising trend in sales of food-animal antibiotics**

Following the FDA’s 2013 release of voluntary guidelines to phase out growth promotional antibiotic use in food animals by 2016, the agency has now reported (2014 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals) that U.S. antibiotic sales for animals have risen steadily over the last 6 years. Sales reached 33.8 million pounds in 2014—an increase of 4% over the previous year—and 22% over the first report in 2009. Twenty-one million pounds, or 62% of the total, are deemed “medically important” to human disease treatment. Representative Louise Slaughter (Dem-NY) called this disappointing trend in the wrong direction “disgraceful, since it came after the FDA issued voluntary guidance they claimed would actually reduce the use of antibiotics in agriculture.”

Antibiotic Resistance News continued on p.18
Internet antibiotic sales remain commonplace

While over-the-counter sales of antibiotics are illegal in most countries, the unregulated sale of antibiotics over the internet is still a common problem according to a November 2015 report commissioned by the UK government (Safe, secure and controlled: managing the supply chain of antimicrobials). Commission chair and economist Jim O’Neill called on government, regulators and internet companies to crack down on a practice that is fueling the rise of deadly superbug strains and to address the problem of falsified and poor quality products. In Southern and Eastern Europe, estimated rates of non-prescription antimicrobial use are between 20% and 30% of total consumption. These rates equal or exceed those in low and middle income countries such as India, Mexico and Indonesia.

In the U.S., a 2012 FDA report (Table 6), shows that almost 99% of food-animal antibiotics were sold over-the-counter without oversight, indicating that purchase is controlled by the farmer. This policy is scheduled to change by the end of 2016 when the FDA’s new Veterinary Feed Directive is fully implemented.

Drug companies counter that sales do not necessarily translate into usage, and that actual antibiotic resistance trends in pathogens, animals and meat as tracked by the FDA have been “largely encouraging.”

U.S. federal budget allocates $774M for combating antibiotic resistance

The recently approved 2016 Congressional budget has nearly doubled funds for fighting the resistance problem. Major recipients are the Centers for Disease Control (CDC—$160M), the National Institutes for Health (NIH—$100M) and the Biomedical advanced Research and Development Authority (BARDA -$96M).

Antibiotic Resistance News continued on p.19
SHEA releases recommendations aimed at avoiding antibiotic overuse in hospitals

In October, 2015, the Society for Healthcare Epidemiology (SHEA) released a list of five stewardship practices that can assist conversations about antibiotic use between doctors and their patients. The effort joined other leading healthcare organizations in supporting ABIM Foundation’s Choosing Wisely® campaign. The five avoidance practices (see box) are specifically aimed at reducing hospital overuse of antibiotics. According to Richard J Baron, President and CEO of ABIM Foundation, “SHEA’s Choosing Wisely® list will help frontline medical staff across the country engage their patients in a dialogue about what care is best for them, and what we can do to reduce waste and overuse in our health care system.”

SHEA guidelines for antibiotic use in the hospital

1. Don’t continue antibiotics beyond 72 hours in hospitalized patients unless the patient has clear evidence of infection
2. Avoid invasive devices (including central venous catheters, endotracheal tubes and urinary catheters) and, if required, use no longer than necessary. Device use poses a major risk for infections.
3. Don’t perform urinalysis, urine culture, blood culture or C. difficile testing unless patients have signs or symptoms of infection. Tests can be falsely positive leading to over-diagnosis and overtreatment.
5. Don’t continue surgical prophylactic antibiotics after the patient has left the operating room.

Oettinger and Pollack References cont. from p12:


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 around the globe, 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.

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Tel: 617-636-0966 • Email: apua@tufts.edu • Web: www.apua.org