Spring 2017
Volume 35, No. 1

APUA NEWSLETTER

PUBLISHED CONTINUOUSLY SINCE 1983 BY THE ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS

Antimicrobial Stewardship in Practice and in Theory

FEATURE ARTICLES

3 Antimicrobial Stewardship Begins at the Door: Promoting Prudent Antimicrobial Use in the Emergency Department

Kenneth Klinker, PharmD and Veena Venugopalan, PharmD, BCPS, University of Florida College of Pharmacy, Gainesville, FL

7 Post Antibiotic Era is Business as Usual

Jack A. Heinemann and Brigitta Kurenbach, School of Biological Sciences, University of Canterbury, Christchurch, New Zealand

10 The Hygiene Hypothesis Misnomer and its Potential Impact on Strategies to Tackle the Global Problem of Antibiotic Resistance

Elizabeth Scott PhD, Department of Public Health, Simmons College, Boston, MA and Sally F. Bloomfield PhD, London School of Hygiene and Tropical Medicine, London, UK

APUA AND OTHER ANTIMICROBIAL RESISTANCE NEWS

13 APUA in Action

14 Upcoming Events

15 APUA Chapter News

16 Antibiotic Resistance in the News

19 Publications of Interest

21 About Us

Northeastern University School of Pharmacy students and friends sign in for the "*Run from Resistance*" 5K road race to support the missions of the *Alliance for the Prudent Use of Antibiotics*. See full story on page 13.

APUA

"Preserving the Power of Antibiotics"®

The APUA Newsletter (ISSN 1524-1424) © 2017 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 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 | Email: apua@tufts.edu | Website: www.apua.org

Antimicrobial Stewardship Begins at the Door: Promoting Prudent Antimicrobial Use in the Emergency Department

Kenneth Klinker, PharmD and
Veena Venugopalan, PharmD, BCPS
University of Florida College of Pharmacy,
Gainesville, FL

Numerous antimicrobial stewardship programs across the US have established a track record of success in reducing antimicrobial consumption, curtailing bacterial resistance, decreasing hospital length of stay, and antimicrobial costs.[1-3] This being said, it is widely accepted that there are still areas within the acute care setting with need for greater antimicrobial stewardship oversight. The high patient turn-over rate, quick pace of practice, and shift-based work model, which increases the number of providers, all present unique challenges to the integration of antimicrobial stewardship initiatives in the emergency department (ED).[4] Despite these barriers, the ED presents tremendous opportunity for antimicrobial steward-ship as it is the gateway for most hospital admissions. Some examples of ASP strategies successfully implemented in the ED are presented in Table 1.

"...the ED presents tremendous opportunity for antimicrobial stewardship as it is the gateway for most hospital admissions."

ED providers often serve as the primary decision-maker determining whether antimicrobial therapy is started for patients requiring inpatient or outpatient management. In view of their role in establishing appropriate care, adherence to antimicrobial policies is paramount. Further, a majority of antimicrobial dollars spent in the US occurs within outpatient settings, which includes services provided by the ED.[5] These services are responsible for 154 million outpatient prescriptions annually.[6] Unfortunately, approximately 30% are considered unnecessary, especially for the management of respiratory conditions.[6] Beyond increasing the risk for the selection of multidrug-resistant organisms, patients may also experience adverse sequelae. An estimated 142,000 ED visits occur annually due to adverse events from antibiotics.[7] Compounding the problem is an unwillingness to change course of therapy once initiated within the ED. ED physicians are highly respected clinicians; therefore, they play a vital role in establishing empiric therapy, which is continued by the primary providers.[8] In combination, these data highlight the importance of integrating stewardship initiatives into ED workflow to maximize outcomes and minimize adverse events.

Initial steps for establishing ASP initiatives in the ED involve identifying a clinician champion and a dedicated clinical pharmacist. Together, these members collaborate on developing/implementing new initiatives, providing real-time feedback to providers, providing real-time follow-up of microbiologic and susceptibility reports, promoting medication safety through thorough patient evaluation, and facilitating transitions-in-care.[8] Benefits of these partnerships include reductions in medication errors, shortening of treatment duration, and decreasing cost of care.[9] In particular, real-time follow-up of microbiologic cultures results in decreased time between positive culture review and time to follow-up with patient or primary provider.[10] Nearly 1 in 4 patients discharged from an ED may require therapy modification due to pathogen non-susceptibility.[11] Further, microbiologic review results in reductions in return ED visits and 30-day hospital readmissions.[11] These data emphasize the

Table 1. Examples of ASP strategies successfully implemented in the emergency department

Stewardship approach or strategy	Description	Primary outcome measured	Results	Reference
Prospective review and feedback	Prospective cohort study of a pharmacist driven urine culture review process in the ED.	To assess the reduction in antimicrobial use resulting from pharmacist intervention.	136 patients were treated for a total of 426 antibiotic days. Pharmacist intervention resulted in 29% reduction in potential antibiotic days.	Zhang et al[24]
Use of rapid diagnostics	Single-center study of the impact on antimicrobial use of the implementation of rapid diagnostic testing (RDT) methodology in the ED for *N. gonorrhoeae* (NG) and *C. trachomatis* (CT).	To compare the percentage of patients who received appropriate antimicrobial treatment using traditional testing methods versus RDT for NG/CT.	Initial antimicrobial treatment was considered appropriate in 60% in traditional testing group vs. 72.5% in the RDT group. Additionally, median time to test results was significantly reduced in the RDT arm.	Rivard et al[21]
Development of treatment pathways or protocols	Pre- and post-study of the impact of implementation of a febrile young infant clinical pathway in the ED.	To evaluate timeliness and effectiveness of care using rates of pathway specific antibiotics and antivirals prescribed.	Post-implementation of the pathway, mean time to first antibiotic was reduced by 36 minutes. Also, use of pathway resulted in significant improvements in proportion of infants receiving pathway specific antibiotics and antivirals.	Murray et al[25]
Penicillin skin testing	Prospective study of outcomes of penicillin and amoxicillin skin testing in the ED of patients with self-reported penicillin allergy.	To determine if penicillin skin testing followed by graded oral challenge could safely delabel patients presenting for emergency care with a self-reported penicillin allergy.	Of the 100 patients who completed the study, 17 patients had evidence of IgE mediated hypersensitivity. Eighty-one percent of patients in the study safely tolerated an oral challenge of amoxicillin and were labelled as non-allergic to penicillin.	Marwood et al[26]

importance of understanding local susceptibility profiles, developing robust antimicrobial guidelines to facilitate appropriate antimicrobial selection, and establishing an effective strategy for patient/provider follow up. Implementation of such processes results in improvements in care and minimizes overuse of critical resources.

Beyond the benefits of prompt culture and susceptibility assessment, there are several additional strategies available to improve antimicrobial stewardship within the ED. These include establishing ED-specific antibiograms, developing clinical protocols/pathways, developing real-time alerts using electronic health records, and integrating rapid diagnostic testing. ED-specific antibiograms are powerful tools. Through collaboration with the microbiology department, development of antibiograms provides insight into organism frequency and susceptibility profiles needed to maximize empiric therapy selection. Drilling down on organism susceptibility by infection source, patient disposition, or presence of comorbid conditions may assist with clinical pathway development. For example, *E. coli* susceptibility patterns may vary significantly

between young healthy patients and those with comorbidities.[12] Further, ED-specific antibiograms may differ from institutional antibiograms.[13] Therefore, a thorough understanding of patient data used for antibiogram reporting assists with maximizing empiric therapy. Lastly, antibiograms allow clinicians to track susceptibility profiles over time. Following development, it is important to provide routine education and dissemination to housestaff for effective interpretation.[8]

Over the last decade, use of comprehensive electronic health records (EHR) has significantly increased.[14] Data in 2014 highlighted that nearly 97% of non-federal, acute care hospitals had adopted a certified EHR, with one-third integrating a comprehensive system.[14] Adoption of EHR allows for efficiency in communication and care coordination within a practice, thus providing an opportunity to develop real-time alerts that impact clinical care.[15,16] Fehrenbacher and colleagues identified a 15% reduction in antimicrobial use when linking diagnosis codes to treatment algorithms for acute bronchitis.[17] Further, the alert resulted in a shift towards appropriate therapy in 18% of patients. Khurana and colleagues developed an automated alert system that continuously monitors EHR, detecting patients with severe sepsis and those at increased risk for in-hospital mortality, including ED patients.[18] Overall, both strategies highlight the value of real-time assessment of patient characteristics that directs clinicians towards appropriate treatment.

An area of intense focus is the use of rapid diagnostic testing or biomarkers (i.e., procalcitonin) to optimize treatment decisions. These tools may play a substantial role in ED management by providing timely detection of infectious organisms or identifying biomarkers associated with bacterial infections. Ultimately, these tools give physicians an opportunity to initiate more targeted antibiotic selection. An analysis by Blaschke and colleagues identified a reduction in ancillary testing (i.e., cultures, chest radiographs) and antibiotic prescriptions when integrating rapid influenza testing into practice.[19] May and colleagues identified an increase in targeted antimicrobial therapy when testing for the presence of methicillin resistance in *S. aureus* cultured from skin and skin structure infections.[20] Lastly, implementation of rapid testing for *C. trachomatis* and *N. gonorrhoeae* decreased unnecessary antimicrobial use and decreased time to patient notification.[21] Consistent with rapid diagnostic testing, procalcitonin may be useful in modifying treatment decisions for patients presenting to the ED with lower respiratory infections. Available data highlight significant reductions in antimicrobial use for patients randomized to procalcitonin-guided therapy.[22,23] Currently, trials are underway in the U.S. to study these effects in non-critically ill patients presenting to the ED. (Clinical trials.gov). Additional data will assist in identifying where procalcitonin can aid in directing care.

The ED offers a myriad of opportunities for creative antimicrobial stewardship interventions impacting the healthcare continuum. Antibiotics prescribed in the ED have far-reaching consequences, therefore, attention and resources need to be shifted to this setting to ensure the delivery of appropriate therapy. The ultimate goal is to provide prompt quality care to our ED patients. Investing in strategies to improve decision making will result in maximizing outcomes and minimizing adverse events.

References

1. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic Review and Meta-analysis of Clinical and Economic Outcomes from the Implementation of Hospital -Based Antimicrobial Stewardship Programs. *Antimicrobial Agents and Chemotherapy.* AUG 2016 2016;60(8):4840-4852.

2. Malani AN, Richards PG, Kapila S, Otto MH, Czerwinski J, Singal B. Clinical and economic outcomes from a community hospital's antimicrobial stewardship program. *Am J Infect Control.* Feb 2013;41(2):145-148.

3. Aldeyab MA, McElnay JC, Scott MG, et al. A modified method for measuring antibiotic use in healthcare settings: implications for antibiotic stewardship and benchmarking. *J Antimicrob Chemother.* Apr 2014;69(4):1132-1141.

4. May L, Cosgrove S, L'Archeveque M, et al. A call to action for antimicrobial stewardship in the emergency department: approaches and strategies. *Ann Emerg Med.* Jul 2013;62(1):69-77.e62.

5. Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Danziger LH. A national evaluation of antibiotic expenditures by

healthcare setting in the United States, 2009. *J Antimicrob Chemother.* Mar 2013;68(3):715-718.

6. "*Antibiotic Use in Outpatient Settings."* Pew Reseach Center, Washington, D.C. (May 2016). http://www.pewtrusts.org/en/research-and-analysis/reports/2016/05/antibiotic-use-in-outpatient-settings. Accessed April 1, 2017.

7. Centers for Disease Control and Prevention. National Hospital Ambulatory Medical Care Survey: Emergency Department, 2011. Available at: http://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2011_ed_web_tables.pdf. Accessed April 1, 2017.

8. Trinh TD, Klinker KP. Antimicrobial Stewardship in the Emergency Department. *Infect Dis Ther.* Sep 2015;4 (Suppl 1):39-50.

9. Brown JN, Barnes CL, Beasley B, Cisneros R, Pound M, Herring C. Effect of pharmacists on medication errors in an emergency department. *Am J Health Syst Pharm.* Feb 2008;65(4):330-333.

10. Baker SN, Acquisto NM, Ashley ED, Fairbanks RJ, Beamish SE, Haas CE. Pharmacist-managed antimicrobial stewardship program for patients discharged from the emergency department. *J Pharm Pract.* Apr 2012;25 (2):190-194.

11. Dumkow LE, Kenney RM, MacDonald NC, Carreno JJ, Malhotra MK, Davis SL. Impact of a Multidisciplinary Culture Follow-up Program of Antimicrobial Therapy in the Emergency Department. *Infect Dis Ther.* Jun 2014;3 (1):45-53.

12. Hines MC, Al-Salamah T, Heil EL, et al. Resistance Patterns of *Escherichia coli* in Women with Uncomplicated Urinary Tract Infection Do Not Correlate with Emergency Department Antibiogram. *J Emerg Med.* Dec 2015;49(6):998-1003.

13. Grodin L, Conigliaro A, Lee S-Y, Rose M, Sinert R. Comparison of urinary tract infection antibiograms stratified by emergency department patient disposition. *Amer J Emerg Med.* 2017.

14. Charles D, Gabriel M, Searcy T. (April 2015) Adoption of Electronic Heath Record Systems among US Non-Federal Acute Care Hospitals: 2008-2014. ONC Data Brief, no. 23. Office of the National Coordinator for Health Information Technology: Washington DC.

15. Joos D, Chen Q, Jirjis J, Johnson KB. An Electronic Medical Record in Primary Care: Impact on Satisfaction, Work Efficiency and Clinic Processes. *AMIA Annu Symp Proc.* 2006: 394–398.

16. Price M, Singer A, Kim J. Adopting electronic medical records: are they just electronic paper records? *Can Fam Physician.* Jul 2013;59(7):e322-329.

17. Fehrenbacher L, Ravenna V, Blunt K, Rice K, Persells D, Brummitt C. Implementation of a Real-Time Electronic Health Record Alert to Optimize Antimicrobial Prescribing for Select Acute Upper Respiratory Tract Infections in the Emergency Department and Ambulatory Clinics. *Open Forum Infectious Diseases.* 2016;3 (suppl_1):1900-1900.

18. Khurana HS, Groves RH, Simons MP, et al. Real-Time Automated Sampling of Electronic Medical Records Predicts Hospital Mortality. *Am J Med.* Jul 2016;129 (7):688-698.e682.

19. Blaschke AJ, Shapiro DJ, Pavia AT, et al. A National Study of the Impact of Rapid Influenza Testing on Clinical Care in the Emergency Department. *J Pediatric Infect Dis Soc.* Jun 2014;3(2):112-118.

20. May LS, Rothman RE, Miller LG, et al. A Randomized Clinical Trial Comparing Use of Rapid Molecular Testing for Staphylococcus aureus for Patients With Cutaneous Abscesses in the Emergency Department With Standard of Care. *Infect Control Hosp Epidemiol.* Dec 2015;36 (12):1423-1430.

21. Rivard KR, Dumkow LE, Draper HM, Brandt KL, Whalen DW, Egwuatu NE. Impact of rapid diagnostic testing for chlamydia and gonorrhea on appropriate antimicrobial utilization in the emergency department. *Diagn Microbiol Infect Dis.* Feb 2017;87(2):175-179.

22. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest.* Jan 2007;131(1):9-19.

23. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med.* Jul 2006;174(1):84-93.

24. Zhang X, Rowan N, Pflugeisen BM, Alajbegovic S. Urine culture guided antibiotic interventions: A pharmacist driven antimicrobial stewardship effort in the ED. *Am J Emerg Med.* Apr 2017;35(4):594-598.

25. Murray AL, Alpern E, Lavelle J, Mollen C. Clinical Pathway Effectiveness: Febrile Young Infant Clinical Pathway in a Pediatric Emergency Department. *Pediatr Emerg Care.* Jan 2017.

26. Marwood J, Aguirrebarrena G, Kerr S, Welch SA, Rimmer J. De-labelling self-reported penicillin allergy within the emergency department through the use of skin tests and oral drug provocation testing. *Emerg Med Australas.* Apr 2017.

Post-Antibiotic Era is Business as Usual

Jack A. Heinemann and Brigitta Kurenbach
School of Biological Sciences
University of Canterbury, Christchurch
New Zealand

The post-antibiotic era[1] is more than the loss of existing antibiotics; it is the entrenchment of systems that threaten the effectiveness of new antibiotics and transition to a post post-antibiotic era. These systems include unprecedented reliance on manufactured chemical substances, where most of the ~8 million in commerce have neither been adequately evaluated for effects on human health[2] nor for effects on microbes. Another is a social priority to use profit-generating inventions to direct both public and private sector research and development.[3]

The common response to the crisis of antibiotic resistance is renewed commitment to invention of new ones. Invention of new therapeutics as a solution to the problem of infectious disease has been the dominant paradigm since the dawn of the modern antibiotic era. Yet it has for much of this history failed to keep pace with need.[4-6] Another path lies in the adoption of social structures that ensure the effectiveness of existing and new antibiotics, through stewardship. This path, however, is poor at rewarding invention of social value through capture of financial rewards.

"The same powerful socio-legal and industrial institutions will resist changes needed to help us exit the coming post-antibiotic era."

In the post-antibiotic era, as in the present,[7] each new antibiotic will be quickly countered by resistance. It becomes tempting to hypothesize that resistance is a pre-determined outcome of use. In which case, stewardship has no promise. If any use would be too much, then would prudent use ever sustain efficacy?

The direct link between the evolution of antibiotic resistant bacteria of medical importance and the scale of use of antibiotics in medicine and agriculture is sound. It is not just that antibiotics *kill* that causes resistance. It is also how we manage their development and use.[3,8] Stewardship requires us to face the social, not just biological, causes of resistance.

Chemical habitat

Industrialized societies have enormous capacity to manufacture and intentionally spread commercial chemicals,[2] including antibiotics. For example, concentrated animal feeding operations use large quantities of antibiotics to support dense animal populations.[9] Much of the antibiotic consumed by farm animals is unabsorbed and transferred to the soil.[10] The air becomes contaminated with aerosolized antibiotics, selected microbes and antibiotic resistance genes, thereafter distributed by wind and inhaled or ingested.[11] Run-off from farms also causes contamination of waterways.[9] Even concentrations too low to kill bacteria select resistance.[12] Antibiotic-resistant bacteria in animal manure may find their way to food by direct transfer or by using insect vectors.[13]

Antimicrobial compounds such as heavy metals are added to paints.[14] Antibacterials such as triclosan are in household products such as soaps.[15] Despite evidence that triclosan use increases resistance to clinical antibiotics and nasal colonization by *Staphylococcus aureus,*[16,17] hundreds of tons are released through household products and accumulate in the

waste stream.[15] Other biocides are incorporated into food packaging and cosmetics.[18,19]

There may be many more manufactured chemicals not intended to affect microbes but do.[20] Characterization of chemicals in commerce rarely includes testing for antimicrobial activity. On the bright side, unintended antimicrobial effects are occasionally pursued as a source of potential new antibiotics.[21]

Salicylates, including those used in aspirin, induce multiple antibiotic resistance in bacteria.[22] Herbicides also have been shown to induce multiple drug resistances. Observed effects were fast and required no pre-exposure to the herbicide.[23]

As with the salicylates, herbicide exposures increased the concentration needed by some antibiotics to inhibit bacteria, and decreased or had no effect on the concentration needed by others. The response pattern depended on species and herbicide, suggesting that the multiple antibiotic resistance response was due to changes in production of efflux pumps and/or porins. This was confirmed by restoration of wild type response patterns when the bacteria were treated with the efflux inhibitor PaβN.[23]

The herbicide concentration required to achieve the effect was generally above legal maximum residue limits in food and most animal feeds. However, it was significantly below recommended application rates.[23] Herbicides are among the most commonly released products in both urban and rural environments (Table 1). Worldwide, 3 billion pounds of active ingredient are used annually.[24] The U.S. accounts for 25% of global use on nearly 800,000 farms and in 52 million households.[24] Relevant rural exposures could occur in farm animals grazed on treated pastures or within spray drift areas. Relevant human and pet exposures in urban areas might occur in private lawns or public parks, where herbicide use is not controlled, leaving people and pets to be exposed as they travel through them (Figure 1).

Relevant exposures might also result from combination exposures. Some herbicides could combine with aspirin to reach an inducing concentration.[23]

The increases in resistance to various antibiotics, including ciprofloxacin, ranged from two- to six-fold. This is relevant because two- and four-fold changes in resistance to ciprofloxacin were enough to cause 21% and 75%, respectively, of patients to get a lower-than-target dose.[25]

If each antimicrobial activity could only be countered by a biochemistry unique to it, then prudent use of future antibiotics might sustain efficacy. However, the biochemistry of resistance is overlapping, sometimes in surprising ways.[26, 27] When a non-medicinal chemical has antimicrobial activity, resistance often first arises from a change in gene expression. Removing the inducer eventually restores susceptibility. However, these adaptive changes increase the potential for acquisition of spontaneous mutations or horizontal gene transfer leading to genotypic resistance.[7,28]

Innovation Environment

Prevailing intellectual property rights instruments reward anti-

Table 1. Herbicide use by sector in millions of pounds* of active ingredient.

Active ingredient	United States	
	Agriculture	Other**
glyphosate	280	13
2,4-D	35	13
atrazine	69	not reported
pendimethalin	11	6
dicamba	5	2

* Based on mid range of estimates for 2012.

**Home and garden combined with government and industry.

Source: Ref. 24

biotics with the largest market rather than a long useful life.[29] It influences what kinds of drugs are commercialized and offers few incentives for innovation in stewardship.[3, 30, 31]

Innovation in stewardship has other impediments too, especially where unrelated industries using chemicals that induce resistance may also have to change behavior, and possibly profit margins.

The post-antibiotic era comes from business as usual. The same powerful socio-legal and industrial institutions will resist changes needed to help us exit the coming post-antibiotic era. Antibiotics are precious global resources. Future innovation should treat them as such.

Figure 1. A day in the life of a pram. Hagley park is a large public area in the center of the city of Christchurch, New Zealand. It is used for exercise by people and their pets, as well as by hospital patients and their visitors.

References

1. Reardon S 2014, WHO warns against 'post-antibiotic' era. http://www.nature.com/news/who-warns-against-post-antibiotic-era-1.15135. Accessed: 15 April 2017 [Online.]
2. Egeghy PP, Judson R, Gangwal S, Mosher S, Smith D, Vail J, Cohen Ubal EA. 2012. The exposure data landscape for manufactured chemicals. Sci. Total Environ 414:159-166.
3. Amabile-Cuevas C. 2016. Society must seize control of the antibiotics crisis. Nature 533:439.
4. CDC. 2014. Antibiotic resistance threats in the United States, 2013. Centers for Disease Control and Prevention.
5. Neu HC. 1992. The crisis in antibiotic resistance. Science 257:1064-1073.
6. WHO 2015, Antimicrobial resistance. http://www.who.int/mediacentre/factsheets/fs194/en/. Accessed: 7 July 2015 [Online.]
7. Levy SB, Marshall B. 2004. Antibacterial resistance worldwide: causes, challenges and responses. Nat. Med. 10:S122-S129.
8. Davies J, Davies D. 2010. Origins and evolution of antibiotic resistance. Microbiol. Mol. Biol. Rev. 74:417-433.
9. EPA. 2013. Literature review of contaminants in livestock and poultry manure and implications for water quality 820-R-13-002. US Environmental Protection Agency.
10. Chee-Sanford JC, Mackie RI, Koike S, Krapac IG, Lin Y-F, Yannarell AC, Maxwell S, Aminov RI. 2009. Fate and transport of antibiotic residues and antibiotic resistance genes following land application of manure waste. J. Environ. Qual. 38:1086-1108.
11. McEachran AD, Blackwell BR, Hanson JD, Wooten KJ, Mayer GD, Cox SB, Smith PN. 2015. Antibiotics, bacteria, and antibiotic resistance genes: aerial transport from cattle feed yards via particulate matter. Environ. Health Pers. 123:337-343.
12. Andersson DI, Hughes D. 2014. Microbiological effects of sublethal levels of antibiotics. Nat Rev Microbiol 12:465-478.
13. Zurek L, Ghosh A. 2014. Insects represent a link between food animal farms and the urban environment for antibiotic resistance traits. Appl Environ Microbiol. 80:3562-3567.
14. Flach C-F, Pal C, Svensson CJ, Kristiansson E, Östman M, Bengtsson-Palme J, Tysklind M, Larsson DGJ. 2017. Does antifouling paint select for antibiotic resistance? Sci. Tot. Envir. 590–591:461-468.
15. Bedoux G, Roig B, Thomas O, Dupont V, Le Bot B. 2012. Occurrence and toxicity of antimicrobial triclosan and by-products in the environment. Environ Sci Pollut Res 19:1044-1065.
16. Aiello AE, Larson EL, Levy SB. 2007. Consumer antibacterial soaps: effective or just risky? Clin. Infect. Dis. 45:S137-S147.
17. Syed AK, Ghosh S, Love NG, Boles BR. 2014. Triclosan promotes *Staphylococcus aureus* nasal colonization. mBIO 5:e01015-01013.

References continued on p. 12

The Hygiene Hypothesis Misnomer and its Potential Impact on Strategies to Tackle the Global Problem

Elizabeth Scott PhD, Department of Public Health, Simmons College, Boston, MA

Sally F. Bloomfield PhD, London School of Hygiene and Tropical Medicine, London, UK

Allergic diseases including asthma, hay fever, eczema and food allergies have dramatically increased in industrialized countries over recent decades. Although evidence still supports the concept that immune regulation is driven by host-microbe interactions, the use of the term "hygiene", as in "the hygiene hypothesis", is now being seen as a misleading misnomer for this concept. Continuing use of this term means that the concept of being "too clean" persists in the minds of the public, who, as a result have lost confidence in the real meaning of hygiene. This is happening at a time when health agencies worldwide are recognizing that "hygiene must be everyone's responsibility", driven by issues such as the unacceptable levels of gastrointestinal diseases, the ongoing threats of infectious disease pandemics and the increasing numbers of immune-compromised people living in the community. Most importantly, hygiene is now seen as a key part of strategies to tackle the global problem of antibiotic resistance; reducing the level of infections results in fewer people seeking antibiotic treatment, thereby limiting the selective pressure for resistant strains.

"...the concept of being "too clean" persists in the minds of the public, who, as a result have lost confidence in the real meaning of hygiene."

Current understanding of the host-microbiome interaction and immune dysfunction is discussed in a 2016 review by a multidisciplinary group of immunologists, allergists, microbiologists and infection preventionists.[1] Evidence cited in this review indicates that increases in inflammatory disease are the combined result of lifestyle, medical and public health changes which, particularly in early life, deprive us of exposure to microbial "Old Friends". These "Old Friends" (OF) microbes are not pathogens (as argued by Strachan in proposing the hygiene hypothesis in 1989[2]), but the largely nonharmful species which inhabit the human gut and our natural environment. Although it is unclear which might be the most important, the changes which have been implicated in depriving us of exposure to OF microbes include sanitation, clean water and food, C-section rather than vaginal childbirth, bottle rather than breast feeding, fewer siblings, urbanization and less outdoor activity. It is also recognized that communication between "Old Friends" and the immune system is mediated by the human microbiome, and that excessive antibiotic use and altered diet can affect the microbiome in a way that further increases inflammatory disease risks. By contrast, the idea that "improved household amenities and higher standards of personal cleanliness" (as also argued by Strachan in proposing the hygiene hypothesis) are the culprit is not supported by the evidence. Studies show that the microbiome of our living environment is unique to each home, and largely reflects the inhabitants (including pets) and the surrounding outdoor environment.[3] It is reasonable to

suggest that, rather than excessive cleanliness, reduced microbial diversity in our homes reflects reduced diversity amongst family members due to fewer siblings, altered diet, antibiotic use, and less outdoor activity.

To explain the OF mechanism, Professor Graham Rook[1] likens the immune system to a computer program, which is present at birth but contains almost no data. After birth, exposure to a diversity of organisms is required to build memory of the diverse molecular structures present in our world. This allows not only recognition of dangerous organisms, which need to be "attacked", but also self and harmless allergens, which need to be tolerated, because attack results in the development of inflammatory diseases.

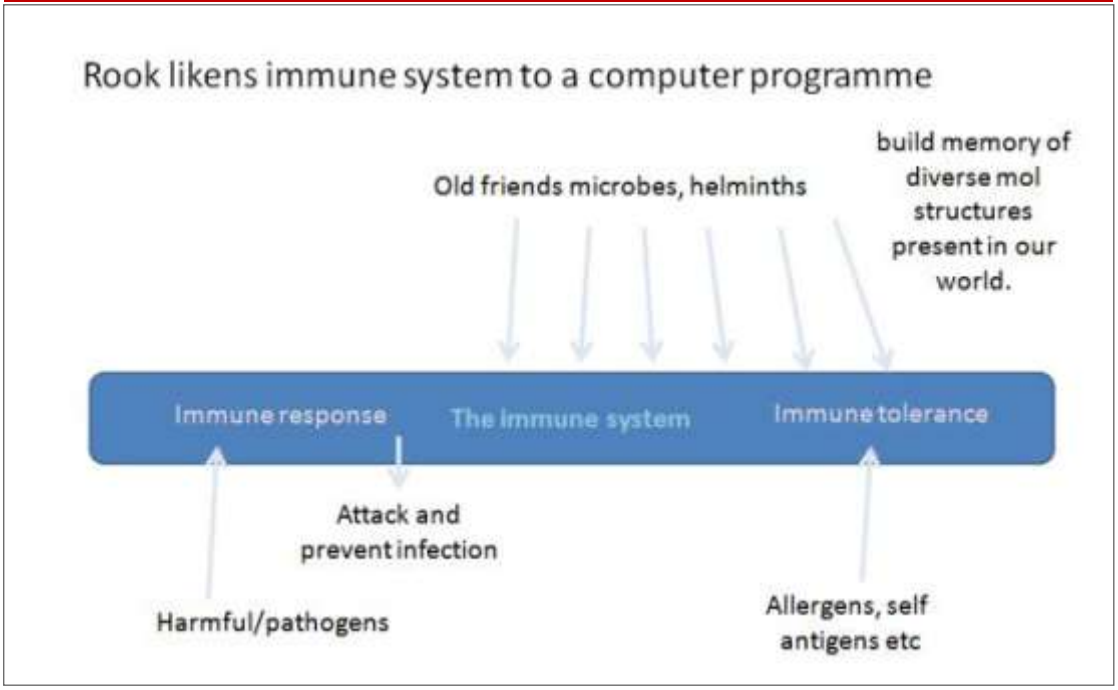
"...hygiene is breaking the chain of infection, and ... there is a difference between hygiene and cleanliness."

The question then is how to connect with our microbial world, particularly during the early months of life, whilst at the same time protecting against infectious diseases. One thing is clear — we need a smarter approach to hygiene. We need to understand that hygiene is more than "keeping ourselves and our living environment clean". It is based on understanding the key routes of infection trans-mission, and targeting hygiene practices in the places and at the times that matter to break the "chain of infection", particularly times associa-ted with food, respiratory, hand and toilet hygiene, and home-care nursing etc.[4]

Although the media now talk about the wider range of likely causes of immune dysregulation, they constantly refer to these changes collectively as "living in an over-sanitized world" and "being too clean" which continues to perpetuate the idea that obsessive home and personal cleanliness is the key factor. Attitudes to hygiene and hygiene practice will not change until we dispel public misconceptions about the hygiene hypothesis, hygiene, cleanliness and germs. Many still tend to see infection prevention/hygiene as "keeping ourselves and our environment clean and germ free." But it is important to understand that people, animals and raw foods are the main sources which "harbor" germs, that hygiene is breaking the chain of infection, and that there is a difference between hygiene and cleanliness.[5] In addition, many mistakenly believe that reconnecting with germs, i.e., infectious organisms, strengthens the immune system and reduces allergies.

There is no doubt that we are going to have to view our microbial world very differently. The idea that the human

Figure 1. Perception of the immune system as described by Professor Graham Rook[1]



microbiome is essentially an organ as vital for our health as our liver and kidneys is a very different concept from the germophobic idea of living quite separately from our microbial world, which followed acceptance of the germ theory of disease in the late 19th century. But at the same time, we will need to continue to guard against infectious disease and protect antibiotic resources.

References

1. Bloomfield SF, Rook GAW, Scott EA, Shanahan F, Stanwell-Smith R, Turner P. Time to abandon the hygiene hypothesis: New perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene *Perspect Public Heal.* 2016;136 (4):213– 224

2. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299(6710):1259–1260

3. Barberán A, Dunn RR, Reich BJ, Pacifici K, Laber EB, Menninger HL, Morton JM, Henley JB, Leff JW, Miller SL, Fierer N. The ecology of microscopic life in household dust *Proc. R. Soc. B.* 2015;282:0151139

4. Bloomfield SF. Exner M, Signorelli C, Nath KJ, Scott EA. 2012. The chain of infection transmission in the home and everyday life settings, and the role of hygiene in reducing the risk of infection. International Scientific Forum on Home Hygiene. http://www.ifh-homehygiene.org/review/chain-infection-transmission-home-and-everyday-life-settings-and-role-hygiene-reducing-risk

5. Breaking the chain of infection – an e-learning resource. International Scientific Forum on Home Hygiene https://www.ifh-homehygiene.org/e_learning/breaking_the_chain/story.html

Heinemann & Kurenbach references continued from p. 9

18. Molina-Gonzalez D, Alonso-Calleja C, Alonso-Hernando A, Capita R. 2014. Effect of sub-lethal concentrations of biocides on the susceptibility to antibiotics of multi-drug resistant *Salmonella enterica* strains. Food Control 40:329-334.

19. Orús P, Gomez-Perez L, Leranoz S, Berlanga M. 2015. Increasing antibiotic resistance in preservative-tolerant bacterial strains isolated from cosmetic products. Int. Microbiol. 18:51-59.

20. Jin Y, Wu S, Zeng Z, Fu Z. 2017. Effects of environmental pollutants on gut microbiota. Environ. Pollut. 222:1-9.

21. Kristiansen JE, Dastidar SG, Palchoudhuri S, Sinha Roy D, Das S, Hendricks O, Christensen JB. 2015. Phenothiazines as a solution for multidrug resistant tuberculosis: from the origin to present. Int Microbiol 18:1-12.

22. Rosner JL. 1985. Nonheritable resistance to chloramphenicol and other antibiotics induced by salicylates and other chemotactic repellents in *Escherichia coli* K-12. 82:8771-8774.

23. Kurenbach B, Marjoshi D, Amabile-Cuevas C, Ferguson GC, Godsoe W, Gibson P, Heinemann JA. 2015. Sublethal exposure to commercial formulations of the herbicides dicamba, 2,4-D and glyphosate cause changes in antibiotic susceptibility in *Escherichia coli and Salmonella enterica* serovar Typhimurium. mBIO 6:e00009-00015.

24. Atwood D, Paisley-Jones C. 2017. Pesticide industry sales and usage 2008-2012 market estimates. United States Environmental Protection Agency.

25. Haeseker M, Stolk L, Nieman F, Hoebe C, Neef C, Bruggeman C, Verbon A. 2013. The ciprofloxacin target AUC : MIC ratio is not reached in hospitalized patients with the recommended dosing regimens. Br. J. Clin. Pharm. 75:180-185.

26. Heinemann JA. 1999. How antibiotics cause antibiotic resistance. Drug Discov. Today 4:72-79.

27. Heinemann JA, Ankenbauer RG, Amábile-Cuevas CF. 2000. Do antibiotics maintain antibiotic resistance? Drug Discov. Today 5:195-204.

28. AAM. 2009. Antibiotic resistance: an ecological perspective on an old problem. American Society for Microbiology.

29. Overbye KM, Barrett JF. 2005. Antibiotics: Where did we go wrong? Drug. Discov. Today 10:45-52.

30. Heinemann JA. 2001. Can smart bullets penetrate magic bullet proof vests? Drug Discov. Today 6:875-878.

31. Heinemann JA, Goven J. 2006. The social context of drug discovery and safety testing, p. 179-196. *In* Amábile-Cuevas CF (ed.), Multiple Drug Resistant Bacteria, 2 ed. Horizon Scientific Press.

APUA in Action

Transitions:
APUA welcomes new board members; Bids farewell to Dennis Signorovich

APUA is pleased to announce the addition of five new members to its board of directors:

- Robert Gaynes, MD, Professor – Dept. of Medicine – Emory School of Medicine;
- Shahin Gharakhanian, MD, – Cambridge Innovation Center;
- Cristina Larkin, Chief Commercial Officer – Spero Therapeutics;
- Margaret Riley, PhD, Professor, – Dept. of Biology – University of Massachusetts, Amherst; and
- David White, PhD, Associate Dean, Research – University of Tennessee School of Agriculture.

APUA appreciates the willingness of these individuals to commit their time and expertise to the missions of APUA.

APUA extends its deepest thanks to **Dennis Signorovich** as he completes 10 years of outstanding service as a member of APUA's Board of Directors. His leadership, advice and enthusiasm have aided the organization immeasurably in forwarding its mission to preserve the power of antibiotics. As he leaves our Board we wish him well in all his future endeavors.

Thank you Dennis!

APUA receives grant from Allergan

APUA thanks Allergan for its recognition of the antibiotic resistance problem and for its generous gift in support of furthering the work of the organization. The $10,000 award will be utilized to revitalize and build APUA's chapter network overseas.

5K "Run from Resistance" supports APUA

On a sunny, but windy, early April Sunday in Boston, students from Northeastern University's School of Pharmacy gathered with their supporters to host the 3rd annual *School of Pharmacy 5K: Run From Resistance* in Boston's Back Bay Fens.

Recognizing the role of pharmacists in preserving antimicrobials for future generations, the students selected APUA, with its goals of promoting prudent antibiotic use and preserving antibiotic effectiveness, as its 2017 beneficiary. APUA Administrative Director Barbara Lapinskas and board member Arnold Reinhold attended the event, which featured a brief update by Dr. Lapinskas on the current state of antibiotic resistance. A post-race Field Day featured interactive games, posters with appropriate antibiotic messaging, literature on the topic of antibiotic resistance, and complimentary refreshments. APUA applauds the efforts of NU's School of Pharmacy students and extends its gratitude for the donation of their generous gift to further APUA's efforts towards preserving antibiotic efficacy.

The *Run From Resistance* started in 2015 as collaboration between three student pharmacy organizations at Northeastern University (Northeastern University Society of Health-System Pharmacy [NUSHP], Phi Delta Chi [PDC] Beta Chi chapter, and Phi Lambda Sigma [PLS] Gamma Kappa chapter) after students spawned the idea of bringing the school together to accomplish a larger goal – raising awareness for a cause that is lesser known by the community, while combining it with a passion for running. A few of the School's faculty are heavily involved in antibiotic re-

sistance research, and students who learn about the problem in the classroom and at work, desired to bring greater attention and education to the developing crisis. Since its creation, the event has raised over $3,000 with over 600 runners and 1,000 in attendance.

As the role of the pharmacist continues to expand clinically, it is only fitting that pharmacy students become more involved with advocating for greater education and stewardship in a growing public health dilemma. This led the School to involve the wider community in the event by expanding its advertising throughout Boston.

This year's 5K engaged over 150 runners with several hundred in attendance. With the continued success of the event and the growing awareness of antibiotic resistance, it is hoped that other pharmacy schools and communities will expand on Northeastern's efforts to make antibiotic resistance a prominent topic in every household. With more education, the problem is preventable, and that is what the *Run From Resistance* aims to achieve.

Run From Resistance **thanks it sponsors:** NEU Student Government Association, NEU Center of Community Service, NEU Crossroads, NEU School of Pharmacy, Whole Foods, Trader Joe's, Dunkin Donuts, IDstewardship.com, El Pelon Tacqueria

PYA revisits pioneering farm study by APUA president Dr. Stuart Levy

PYA is a nation-wide leader in healthcare and other consulting services. In a recent issue of the *APUA Newsletter*, (Vol 34:1) PYA consulting specialists James Keegan and Aaron Elias co-authored a feature article titled *Achieving Results by Implementing an Antibiotic Stewardship Collaborative.* The two authors have now teamed up with colleague Michael Levesque to publish *A Conversation with the Pioneer Behind the Groundbreaking Study in Antibiotic Resistance—Dr. Stuart Levy.* The Q&A style interview reflects back on the novel farm study conducted in 1975 that launched Levy's career as a pioneer in the field of antibiotic resistance. It also provides a perspective on the attitudes of the times with regard to antibiotic resistance and compares them with those of the present.

APUA News continued next page

Upcoming Events

June 14-16, 2017:
Association for Professionals in Infection Control and Epidemiology (APIC) Annual Conference. Portland, Oregon

June 20 – 23, 2017:
ICPIC 2017, 4th International Conference on Prevention and Infection Control, Geneva Switzerland

June 20-21, 2017:
Combating Antimicrobial Resistance: A One Health Approach to a Global Threat—A Workshop, sponsored by the National Academy of Sciences Engineering Medicine, Washington, DC

July 31-August 01, 2017
3rd World Congress and Exhibition on Antibiotics and Antibiotic Resistance**;** The Future of Antibiotics: Key Opportunities & Emerging Therapies. Milan, Italy

September 6-8, 2017
ASM/ESCMID Conference on Drug Development to Meet the Challenge of Antimicrobial Drug Resistance, Boston, MA, USA

September 14-16, 2017
ISAAR and ICIC 2017: Combating Antimicrobial Resistance and Emerging Infectious Diseases: Today and Tomorrow. Busan, Korea

September 25, 2017
7th Annual Congress on Clinical Microbiology, Chicago, Illinois, USA

October 4 – 8, 2017
ID Week 2017, San Diego, California

October 10-11, 2017
Uppsala Health Summit: Tackling Infectious Disease Threats—Prevent, Detect, Respond with a One Health Approach; Uppsala, Sweden

October 29 November 1, 2017
Antimicrobial and Resistance; Opportunities and Challenges (T4), A Keystone Symposia Conference, organizers: Gautam Dantas and Jennifer Leeds, Sante Fe, New Mexico, USA

APUA supports letter to U.S. Secretary Tom Price

APUA has joined multiple stakeholders in signing on to a letter to recently appointed U.S. Secretary of Health and Human Services, Tom Price (Rep), thanking him for his participation in the World Health Assembly in May. The letter urges Price to continue working domestically and internationally to "advance a robust response to antimicrobial resistance (AMR) that reflects the U.S. commitment to infection prevention, antimicrobial stewardship, surveillance and innovation".

APUA Chapter News

APUA-Nepal reports participation in the WHO expert consultation meeting on health workforce education and antimicrobial resistance control, held March 2017 in Geneva, Switzerland.

APUA-Ethiopia

Since 2014, APUA-Ethiopia has been engaged in surveillance of antimicrobial use and AMR trends as well as measurement of the effectiveness of interventions. In Jan 2017, a workshop was held to revise the AMR Intervention Detailed Implementation Plan. Other activities include the following:

- Chapter coordinator Tenaw Andualem has been serving as member and secretary of the Ethiopian AMR Containment Advisory Committee.
- "Antimicrobial Resistance Prevention and Containment: Ethiopian Experiences" was presented at the Innovative Approaches to Establishing and Strengthening Regional Laboratory Networks for Disease Surveillance and Clinical Care in Africa, March 27–29, 2017, Addis Ababa, Ethiopia
- "More than a decade of Ethiopia's Action on Antimicrobial Resistance Prevention and Containment" was presented at the MSH organized symposium "Combating Antimicrobial Resistance (AMR) in Ethiopia: Progress, Challenges and the Way Forward" on April 20, 2017.
- "Ethiopia AMR Containment Strategies and Experiences—lessons for the future" was presented at the World Veterinary Day celebration with the theme "From Awareness to Action" on 4th May 2017.

Contributed by Tenaw Andualem, who is seeking collaborators for sharing experiences and forming synergy.

APUA-Bangladesh

Dr. Wasif Ali Khan and Sabeena Ahmed report working as contributing members of the GARP-Bangladesh National Working Group, which became active in Bangladesh in 2016. The Global Antibiotic Resistance Partnership (GARP), funded by the Gates and Merck Foundations, is a project of the Center for Disease Dynamics, Economics & Policy (CDDEP), with the aim of empowering countries to tackle antibiotic resistance issues by establishing local, in-country policy analysis and policy development capacity.

In July 2016, Bangladesh undertook the study INDEPTH ABACUS in one of its rural communities. The multi-country study, supported by the Wellcome Trust, aims to evaluate antibiotic access and use in low-and middle-income countries and to find targets for social interventions to improve rational antimicrobial use. This study is a part of a multicenter project operating in five other low and middle income countries in Asia and Africa. Dr. Khan and Ms. Ahmed are acting as the site-specific Principal and Co-Principal Investigators in this collaborative project with icddr,b.

Contributed by Chapter leaders Dr. Wasif Ali Khan and Sabeena Ahmed

Tackling antimicrobial resistance in Uruguay

At the May, 2015 World Health Assembly, participating member countries signed an agreement to establish national guidelines for control of a dramatically escalating antibiotic resistance problem. While waiting for national regulations and following APUA recommendations, a variety of stakeholders in Uruguay have undertaken initiatives to warn of the danger. The National Medicine and Veterinary Academies are working together to raise awareness of the importance of limiting antibiotic use in both arenas. The National Reference Laboratory for Animal Health has introduced a pharmacological-surveillance software such that all aspects of antibiotic management—from production to final application (UNASUR, 2017)—can be tracked and registered. In addition, a revision of the manuscript *Antibiotic Resistance: A Complex Challenge* will be published in a local medical journal. Uruguay looks forward to encouraging the involvement of interested individuals in helping curb the rise of antimicrobial resistance and its associated consequences.

Submitted by: Maria Hortal

Antibiotic Resistance in the News

Policy Updates

CDC issues guidelines for antibiotic use in dentistry

To date, no national guidelines have been developed for treatment of dental infections in the U.S. and no formal antibiotic stewardship program exists for dentistry. Noting that dentists prescribe an estimated 10% of outpatient antibiotics and that approximately 30-50% of prescribed antibiotics are unnecessary or inappropriately prescribed, CDC guest author Marie T. Fluent, DDS has provided some updated clinical tips (see Table) to help dentists support responsible prescribing practices (March 28, 2017 Safe Healthcare Blog).

Many of the recommended messages that have been promoted to other healthcare professionals are equally applicable in the practice of dentistry.

CDC issues new guidance for antibiotic-resistant *Shigella*

Generally, infections caused by *Shigella* are self-limiting—lasting from five to seven days—and do not require antibiotic treatment. Nonetheless, all U.S. cases must be reported to local health departments. When needed, ciprofloxacin has been the key agent for immunocompromised patients and those with severe illness. However, instances of minimal inhibitory concentration (MIC) values between 0.12 and 1µg/ml to this drug of choice have been emerging,

Clinical Tips for Responsible Antibiotic Prescribing in Dentistry*

Dos	Don'ts
DO prescribe antibiotics only for a documented diagnosis of an oral bacterial infection	**DON'T** prescribe for viral infections, fungal infections or oral ulcerations related to trauma or aphthae
DO recognize that antibiotics are not always necessary	**DON'T** prescribe in lieu of dental interventions
DO prescribe only for patients of record	**DON'T** prescribe based on demand or expectations from patients
DO prescribe only for bacterial infections you have been trained to treat	**DON'T** prescribe based on non-evidence-based historical practices
DO review patient's medical history to assess medical allergies, potential for adverse drug events, and medical conditions that would affect antibiotic selection	**DON'T** prescribe based on pressure from another health care provider
DO prescribe only when clinical signs and symptoms of bacterial infection suggest systemic spread	
DO use the most narrow-spectrum antibiotic for the shortest duration possible (after clinical signs and symptoms subside) for otherwise healthy patients	
DO advise patients to take antibiotics exactly as directed	
DO ensure antibiotic expertise or references are available during patient visits	
DO collaborate with referring specialists about prescribing protocols	
DO provide training to staff members to improve probability of patient adherence	
DO keep up to date on appropriate management of oral infections (continuing education courses, conferences, accessing dental journals, pharmacology texts)	
DO revise antibiotic regimens on basis of patient progress and, if needed, culture results	
DO advise patients that they should NOT take antibiotics prescribed for someone else	
DO advise patients that they should NOT save antibiotics for future illnesses	

*Source: CDC

indicating reduced susceptibility and probable resistance to other commonly used antibiotics as well. In mid-April, the CDC issued a health advisory regarding the new trend. In cases of suspected *Shigella*, the CDC recommends stool culturing and susceptibility testing for ciprofloxacin and avoiding administration of fluoroquinolones if the ciprofloxacin MIC exceeds 0.12 μg/ml – even if reported "sensitive." The CDC's complete recommendations for diagnosis and treatment of *Shigella* can be accessed here.

Call for overhaul of antibiotic resistance language

Leaders in the discourse on antibiotic resistance are concerned over surveys showing that the public fails to grasp the implications and seriousness of the antibiotic resistance problem—in large part due to the terminology that is used to convey these concepts. Commenting in *Nature* (Antibiotic resistance has a language problem), Marc Mendelson and colleagues call upon the United Nations Interagency Group on AMR to undertake a review of, and develop more, standardized antimicrobial resistance vocabulary. Specifically, the authors favor use of the term "drug-resistant", and the words "antibiotic" and "antifungal" in lieu of "antimicrobial" where applicable. Due to emerging perspectives that lean towards seeking the ecological balance proposed by the *One Health* paradigm, they also argue against use of the words, "war", "conflict" and "fight" which are less relevant than in previous decades when the roles played by native microbiomes were less evident.

Advances in antimicrobial therapy

Ridinilazole — a promising candidate for control of *C. difficile* infection

Currently, just three drugs are viable treatments for *Clostridum diffficile* infection: metronidazole, vancomycin, and the newer fidaxomycin. Resistance to these is inevitable and is already emerging against metronidazole, indicating the need for new therapies for this debilitating infection. In a small, phase-two trial published in Lancet, 66% of patients achieved a sustained clinical response to ridinilazole, compared with only 44% for vancomycin. The findings clearly support progression to a larger phase-3 trial.

MRSA infections in mice respond to new antimicrobial compounds

A new class of fatty acid compounds called LANAS (lysine-conjugated aliphatic norspermidine analogues), is showing promise as a potent antibacterial. Their membrane-bursting capacity caught the attention of scientists M.M. Konar and J. Halder in India, who undertook tests of LANAs against 4 different MRSA strains, both in vitro and in mice. In both cases, the compounds were effective and eliminated the difficult-to-treat biofilms caused by MRSA skin infections in mice—all without the usual liver, kidney and nervous system damage caused by current last-resort antibiotics. Importantly, because LANAs target the bacterial membrane instead of the protein synthesis machinery, MRSA failed to develop resistance, even after 20 passages of exposure to the LANA compounds.

Personalized probiotic lotions help curb pathogenic staph

Approximately 32 million people in the U.S have eczema—an itchy, scaly skin condition that is aggravated by an overabundance of *Staphylococcus aureus.* In an investigation of 10,000 colonies of skin flora, researchers at the University of California San Diego found that normal skin bacteria—*S. hominus* and *S. epidermidis*—produce a natural antimicrobial peptide that inhibits the growth of *S. aureus*. In a small, one-day trial of five eczema patients, lotions containing these select strains achieved remarkable results in diminishing or entirely eliminating the offending staph. The success of the study indicates promise for creating highly targeted, personalized antibiotics that avoid the massive systemic destruction of host microbiomes found with traditional oral or lotion-based antibiotics. A larger clinical trial is underway to test the impacts on the eczema itself.

Buckwheat honey shows bactericidal activity against superbugs

The antibacterial activity of honey has been known for decades, and presumed to be due to its very high sugar content. In seeking an alternative approach to traditional antibiotics, scientists at the University of Wisconsin have used in vitro

assays to test the efficiency of four Wisconsin honeys, as well as artificial honey, with thirteen different pathogens, including *Clostridium difficile*, MRSA, *Pseudomonas aeruginosa*, vancomycin-resistant enterococcus, *Enterococcus faecalis* and *Klebsiella pneumoniae*. All Wisconsin honeys demonstrated bactericidal action against the pathogens, with *C. difficile* being the most sensitive. The artificial honey (at 50% w/v) showed no killing activity, indicating that some factor other than high sugar content is responsible for the observed pathogen death.

Epidemiology news

Global-PPS tracks antibiotic use

A Biomerieux-supported project known as GLOBAL-PPS (The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance) is an ambitious attempt to monitor the rates of antimicrobials prescribed in hospitals. Participation in this global network of point prevalence surveys requires a one-day survey of all patients who are admitted to the hospital at 8 o'clock and who are also receiving antibiotics. The project aims to include as many hospitals as possible across the globe. Participating hospitals can extract their own data for analysis and plot against national and continental data. Synthesized Global-PPS data aim to provide hospitals with a tool to evaluate antimicrobial prescribing practices, to identify targets for quality improvement, to influence practice, and to measure impacts through repeated PPS surveys. Sixty countries are currently participating and data for 2017 can be entered up through June.

Nursing homes carry high rates of MDR gram-negatives

It is estimated that 70% of nursing home residents receive one or more courses of antibiotics annually, and that 40-70% of such prescriptions are inappropriate. In a first-of-its-kind meta-analysis of 12 nursing homes covering the years 2005-2016, researchers Elaine Larson and team found an average of 27% of 2,720 residents carried multidrug-resistant gram-negative bacteria (most commonly *E. coli* in the rectal sites). U.S. averages were higher (38%) than those found abroad in Korea and Germany (14%).

The study results came only months after the U.S. government mandated that antibiotic stewardship programs be implemented in nursing homes and assisted living facilities that receive Medicaid or Medicare. The authors find the results "concerning" and suggest a re-examination of infection control practices to bring down the prevalence.

Honeybees suffer from antibiotic exposure

A University of Texas team headed by Nancy Moran has demonstrated that honeybees are adversely affected by exposure to the common antibiotic tetracycline. After five days of treatment, only half the bees survived one week, compared to a control group of untreated bees**.** Further investigation showed a disturbance of the gut microbiome: beneficial gut bacteria were missing—making colonization by a pathogen much easier. The treated bees also became more susceptible to *Serratia* colonization, which likewise escalated bee death.

The study provides some insight into the possible mechanism behind colony collapse disorder—a devastating condition that has caused massive bee loss with no known cause. Large scale bee operations are known to use antibiotic applications several times annually to help stave off bacterial foulbrood infection that afflicts the larvae. It is now believed that the antibiotic treatment may be at least partially responsible for the devastating disorder.

Ares Genetics acquires most comprehensive antibiotic resistance database to date

A new Vienna-based biotech, Ares Genetics (a subsidiary of Curetis), is positioned to investigate the genetic basis of antibiotic resistance. Its core technology will focus on the newly acquired 30 Terabyte GEAR database, which assembles the complete DNA sequences of more than 11,000 bacterial strains and their antibiotic susceptibility profiles to 21 different antibiotics. The company plans to publish a series of articles that describe the database and also potential approaches towards rapid diagnosis of patient infections and tools that will accelerate antibiotic research.

Advances in Diagnostics

Lung probe speeds bacterial diagnosis in ICU

A team of UK-based scientists has developed a fiber–optic probe that can diagnose bacterial infections in the intensive care unit. The new diagnostic tool utilizes Proteus technology that can reveal within minutes whether a patient needs antibiotic treatment. The new tool is expected to revolutionize the management of critically ill patients who often receive unnecessary prophylactic antibiotics while waiting for standard x-ray and blood test results.

The project is funded currently by the Wellcome Trust, and will receive an additional infusion of support from CARB-X—the antibiotic resistance project designed to accelerate and broaden the implementation of much-needed point-of-care diagnostics, such as that provided by Proteus technology.

Procalcitonin diagnostic gets FDA upgrade

Procalcitonin (PCT) is a blood protein biomarker that is undetectable in healthy individuals, but tends to rise in response to inflammation—particularly that of bacterial cause—although it cannot determine the origin of infection. It was initially approved by the U.S. FDA in 2007 as a diagnostic tool in critically ill patients to assess the risk of progression to severe sepsis and septic shock. More recently, clinical studies have demonstrated that the PCT marker can help in reducing antibiotic use in patients with lower respiratory tract infections (i.e., community–acquired pneumonia, acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease) and with sepsis, without reducing safety. The FDA has now expanded its approval of the Vidas Brahms PCT Assay™ for use with patients having lower respiratory tract infections in order to distinguish between bacterial and viral infections. A high PCT level is indicative of a bacterial infection, while a low level indicates a viral or noninfectious cause. The new ruling is seen is as advancement in the quest to distinguish viral and bacterial infections and reduce the overuse of antibiotics for these common conditions. The test is intended for hospital or emergency room use and should be used in consideration with

Publications of Interest

- White Paper: Developing Antimicrobial Drugs for Resistant Pathogens, Narrow-spectrum Indications, and Unmet Needs by HW Boucher, et al, J Infect Dis. May, 2017.

- A Guide to Infection Control in the Hospital, 5th Edition, by RP Wenzel et al. is the latest pocket-sized manual with key principles and guidelines for reducing nosocomial infection, improving quality of care and reducing costs. 2017 International Society for Infectious Diseases

- Emerging trends in the antibiotic resistance: Implications for emergency medicine, by A Pourmand et al; a review that summarizes current trends in the most clinically relevant resistant organisms encountered in emergency medicine. Mar 7, 2017 Am J Emerg Med

- Can we really halve Gram-negative BSIs (GNBSIs) by 2021?, A debate between Jon Otter (pro) and Martin Kiernan (con), moderated by A Voss and M Bonten, on the recent UK announcement to halve GNBSIs. March 29, 2017. Go here to view the final vote by the public.

- Mcr-1 and the end of the world, a blog entry from Reflections on Infection Prevention and Control by Marc Bonten, Feb 28, 2017

- The epidemiology of carbapenem-resistant *Entero-bacteriaceae:* The impact and evolution of a global menace, by LK Logan and RA Weinstein. J Infect Dis, Feb 15, 2017 Discusses evolution, epidemiology, risk factors for colonization and infections, and strategies for halting spread of the most common transmissible CPE

- How breast milk could help prevent the antibiotic apocalypse. in The Conversation by AP Håkansson, March 30, 2017; A discussion of a milk compound called HAMLET (Human Alpha-lactalbuminMade lethal to Tumour cells) that shows promise against pathogenic bacteria such as MRSA

- Winning isn't Everything: A review of University of Aberdeen professor Hugh Pennington's book *Have Bacteria Won?* (2016), in Tracking Zebra, April 2, 2017

the patient's clinical status and other laboratory tests. It is also authorized for the discontinuation of antibiotics in patients with suspected or confirmed sepsis.

Drug-resistant microbes rapidly identified with new mass spec method

Scientists attending the April 2017 ECCMID conference reported on a new use of a mass spectrometer to rapidly identify clinical samples containing carbapenem-resistant bacteria. The researchers tested 134 different colonies of *E coli* and *Klebsiella pneumoniae* using a simplified electrochemical assay called the BYG Carba test (v2.0) to quickly check the strains for resistance to colistin. Because most hospitals already own and use mass spec technology, the new diagnostic could be implemented quickly and inexpensively. The rapid identification of colistin-resistant strains would mean that patients could be quarantined to prevent further spread of organisms.

Updates in hygiene

Innovations in hygiene reduce superbug spread in hospitals and sports facilities

An American Journal of Infection article has reported that ultraviolet-C light can reduce environmental contamination with MRSA from 34.3% down to 3.3%—as well as aid in elimination of *C. difficile* spores. Now, a new robotic cohort, which incorporates the Surfacide Helios system, is being used at Olath Medical Center to reduce multidrug-resistant organisms (MDRO's) from patient rooms and surgical sites. Following standard room cleaning, the 3-tower robotic unit is introduced. It then proceeds to laser map each room and subject it to 10-30min of UV-C exposure. The new technology is expected to raise confidence in providing a safe environment for patients.

Outside of the hospital, a number of athletic training facilities are beginning to adopt another kind of technology to enhance safety for their student and professional athletes—incorporation of EPA-registered CuVerro®—an antimicrobial copper alloy that continuously kills 99.9% of bacteria on contact. As in hospitals, cleaning can go only just so far in reducing contact-acquired bacteria such as MRSA. The copper alloy has now been introduced into a number of products including weight training equipment, removable hand railing systems, door pulls, athletic trainer treatment carts, light switches and wall plates, cabinet pulls and sink, drain and faucet handles.

To view the impacts of drug-resistant infections in professional sports, see this Mar 21 update posted by ContagionLive .

Paper-based sanitizers expand hygiene applications

Inspired by the desire to create personal protective equipment that could halt the spread of dangerous infections such as the Ebola virus, a Rutgers-based research team has led the way in creating paper-based sanitized surfaces. The new technology is the first to utilize stacked sheets of honey-comb pattern metallized paper, combined with high voltage to generate plasma. Plasma is a combination of heat, UV radiation and ozone that can kill microbes.

In experimental assays, the new technology effectively killed more than 99% of the yeast *Saccharomyces cerevisiae* and *E. coli*, and could also eliminate bacterial spores. Because of its bendable nature, it is envisioned that the new paper-based technology could be applied to creating protective, wearable clothing; to 'smart bandages' for slow healing wounds; and to robotic devices that enter and exit contaminated environments.

Hydrogel wound dressing rendered antibacterial

A team of researchers in Poland have extracted a fiber from crustacean shells in order to develop an antibacterial bandage that also helps stop bleeding. They first isolated chitin from the shells and modified its structure by removing select chemical branches—creating chitosan. By dissolving the chitosan in lactic acid, it could be incorporated into the chemical structure of durable elastic hydrogel dressings without changing its crosslinking capabilities or adversely affecting other properties. The novel hydrogel dressings can conform readily to affected body parts and are particularly useful for long-term treatment of wounds in which there is a high probability of bacterial infection that would otherwise require antibiotic treatment.

APUA

"Preserving the Power of Antibiotics" ®

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.

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

APUA global chapter network of local resources & expertise

136 Harrison Ave, M&V Suite 811, Boston, MA 02111
Phone: 617-636-0966 | Fax: 617-636-0458 | E-mail: apua@tufts.org

www.apua.org