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Clumps of MRSA bacteria, magnified 2390x
Source: CDC
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Staphylococcus aureus has proved to be a versatile pathogen—having emerged with penicillin resistance in 1942, erythromycin, streptomycin and tetracycline resistances in the 1950s, followed by resistance to methicillin in 1961. By the early 2000s, it manifested as a multidrug-resistant super pathogen exceeding 50% of all S. aureus in US intensive care units, Latin America and the Asia-Pacific. The responsible culprit was a mobile genomic element—the staphylococcal cassette chromosome (SCC), carrying mecA and a PBP2a transpeptidase gene with reduced affinity for beta-lactam antibiotics.

The appearance of VISA (vancomycin-intermediate S. aureus) in 1996 was also of growing concern and ultimately heralded the onset of full-blown resistance to vancomycin—a drug of last resort for multi-resistant staph. Currently still rare (13 cases of VRSA reported in the US since 2002), its occurrence appears predisposed by chronic underlying conditions such as skin ulcers and diabetes, prior infections, colonization by MRSA or Enterococcus and previous treatment with vancomycin. Appearing some 40 years after the advent of vancomycin, this resistance was mediated by the vanA gene, acquired from Enterococcus.

Concurrently, a new pandemic was spreading outside the hospital, starting with the appearance in the 1990’s of distinct strains that caused purulent skin infections or pneumonia within Australian youth having no health-care contact. While generally more susceptible to antibiotics, community-associated S. aureus (CA-MRSA) commonly carried the highly virulent Panton-Valentine leukocidin gene (PVL gene). With their considerable propensity for evolution, these strains soon entered hospitals and began causing invasive infections, thus blurring the “community” distinction.

Currently MRSA clones are identified by pulsed-field gel electrophoresis (PFGE) patterns (e.g., USA 100), by multilocus sequence typing and by spa typing, which indicates variants of the polymorphic X region of the protein A gene (spa). Five major pandemic clones account for ~70% of hospital MRSA: Iberian, Brazilian, Hungarian, New York/Japan (or USA100) and Pediatric. The major MRSA clones are believed to have arisen from successful epidemic methicillin-sensitive S. aureus (MSSA). Strain USA 300, which spread rapidly across the US, is now the predominant cause of skin and soft tissue infections in the community setting. With the identification of a distinguishable cluster of genes known as ACME (arginine catabolic mobile element), it is now postulated that these genes were assembled in the commensal skin bacterium Staphylococcus epidermidis and only recently transferred horizontally into the ancestor of the current USA 300 strain. The speG gene of this cluster reportedly confers a set of multiple selective advantages over other clones, including enhanced adhesion and biofilm properties, resistance to antibiotics and also to polyamines.
The Cost of Methicillin-resistant Staphylococcus aureus in Pediatric Neck and Pharyngeal Infections

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The incidence of methicillin-resistant Staphylococcus aureus (MRSA), especially community-acquired-MRSA (CA-MRSA), infections has been increasing over the last decade.1,2 Not confined to adults, the troubling trend of increased MRSA in the pediatric population is the focus of a great deal of research.3 While MRSA obviously presents treatment challenges with regard to antimicrobial resistance, there exists another growing problem associated with the rise of MRSA: the socioeconomic implications. Studies have demonstrated an overall increase in resource utilization associated with MRSA.4 Most of this increased burden comes from longer hospital stays, inadequate or delayed antibiotic use, and the use of newer, more expensive antimicrobial agents needed to treat patients with MRSA appropriately.

The overall increased incidence of MRSA in children has been paralleled by a rise in the incidence of MRSA in head and neck infections, including cellulitis and deep neck abscesses.5-7 We recently published our database analysis of more than 3500 children treated across the United States for MRSA cervical infections.8 The average cost of each child’s hospitalization was more than $20,000, and almost twenty percent of children had hospitalization charges in excess of $25,000. Most stayed in the hospital more than 4 days, especially younger ones. Sixty percent of children required at least one surgical procedure during their hospitalization, most commonly incision and drainage of an abscess.

One of the keys to combating rising costs when fighting a particular disease or illness is being able to identify patients who may require additional resources to treat that disease. There exists a known increase in the prevalence of MRSA in non-white communities in the United States.9,10 It has been proposed that this difference may be confounded by factors such as socioeconomic status or the increased prevalence of comorbid conditions in certain populations. For instance, diabetes mellitus and HIV infection are more prevalent in blacks in the United States. These illnesses are known to be associated with compromise of the patient’s native immune functions.

Issues with access to care have also been described for lower socioeconomic groups, and it is plausible that this discrepancy in access to care can explain the increased severity and mortality associated with MRSA infections in some of these populations. Our study found longer hospitalizations and an increased need for surgical drainage in non-white children. In addition, children from lower socioeconomic backgrounds also required surgical drainage more frequently than other children. We can potentially explain this finding by suggesting that children from lower socioeconomic groups who might have issues with access to care are presenting to the hospital with more advanced MRSA infections. Therefore, they are potentially undergoing surgical drainage procedures at an earlier point in their hospitalizations.

Healthcare in the United States will be undergoing major changes in 2013 and 2014 (and beyond), primarily as a result of the Affordable Care Act and budget sequestration.11 More than ever, the “cost” of the care we provide will be scrutinized and analyzed. The growing incidence and associated cost of MRSA in today’s medical environment will remain a microbiological and socioeconomic challenge in both adult and pediatric medicine. Understanding the socioeconomic aspects of a disease like MRSA can allow researchers and healthcare providers to quickly identify and treat patients infected with, carrying, or at risk for MRSA.

References


References Continued on Page 8
which are native skin compounds that confer a natural tolerance to other MRSA clones.

In the landscape of life-threatening “superbugs,” only MRSA infection trends have demonstrated some reason for encouragement: recent surveillance reports suggest an actual decline in the national rate of invasive MRSA (31.2% between 2005-2011). For the first time, the incidence of invasive hospital-onset MRSA has fallen below that among community residents who lack significant health-care contact. In contrast, community-associated MRSA (CA-MRSA) infections remain stable or have declined only slightly (5%).

Nonetheless, MRSA remains a challenging pathogen and a major cause of morbidity and mortality worldwide, with significant economic consequences. In the US alone, >80,000 invasive MRSA infections still occur each year, the majority of which have community or outpatient onset. In-hospital mortality of MRSA bloodstream infections is ~30%, and in some centers, as high as 65%, resulting in >11,000 deaths annually.

This issue of the APUA Newsletter features several diverse examinations of the S. aureus resistance problem. McCormick presents a perspective on the escalating costs of community-based infections localized to the head and neck. The article by Gould looks at the phenomenon of “MIC creep” and the problems it poses in treatment of MRSA with vancomycin—one of few remaining drugs for the most resistant MRSA strains. Casey and Schwartz examine the impacts of antibiotic use in high-density livestock farming on the incidence of MRSA infections in the farming community. The articles by Nashev and by Peraza and Lopez present international perspectives of the MRSA problem from Bulgaria and Cuba, respectively. These studies examine more closely the specific strains that are circulating in non-industrialized countries on two different continents. Lastly, this issue takes an in-depth look at the tracking of procalcitonin levels as a new diagnostic tool for the recognition and management of bacterial sepsis. Procalcitonin testing is one approach to addressing the nagging problem of discerning between bacterial- and viral-mediated illnesses. Reliable differentiation of these two is crucial to antimicrobial stewardship decision-making and can be highly instrumental in reducing the unnecessary use of antibiotics for infections by viruses and other non-bacterial agents.

Sources


Planet PJ, LaRussa SJ, Dana A et al. (2013) Emergence of the epidemic methicillin-resistant Staphylococcus aureus strain US300 coincides with horizontal transfer of the arginine catabolic mobile element and SpeG-mediated adaptations for survival on skin. mbio online. 4(6)
The term “MIC creep” has come to be associated with the complicated issues around the dose response to vancomycin when used in the treatment of staphylococcal infection, most usually due to methicillin-resistant *Staphylococcus aureus*. The MIC (minimum inhibitory concentration) is a standard measurement for assessing bacterial susceptibility to an antibiotic and indicates the likely clinical response if the antibiotic is used to treat infection. While it is a well-established measurement, the MIC has its limitations, particularly in the limits of reproducibility. An additional problem when considering vancomycin MIC creep is the breakpoint (BP), which is currently 2mg/L vancomycin for both CLSI and EUCAST.

“Creep” has come to mean elevated MICs within the breakpoint—so technically still susceptible. The question arises: elevated from what? Here is the first difficulty, as there is no clear evidence of what the vancomycin MIC should be for a wild-type strain of staphylococcus—that is, one that has never been exposed to vancomycin (or another glycopeptide). As vancomycin has been in use since 1955, it is not even certain that such strains exist anywhere and so one must assume that such a figure would be the lowest that is currently measured in community isolates (with presumably only a small potential for exposure to glycopeptides), which would be an MIC of 0.25/0.5mg/L. Unfortunately, as the reproducibility of standard doubling dilution MIC tests is ± 1 dilution, it is difficult to identify MIC creep with confidence. An MIC of 1 mg/L one day may be as low as 0.5mg/L on another day or as high as 2mg/L i.e. exactly on the BP. With the understanding that different, commonly used, MIC tests all have bias up or down from the reference micro-dilution test, and that storage of organisms (as often happens prior to testing in surveys) can affect the MIC, one can see nothing but increasing confusion! But it is important that we try to resolve these issues, as the response of serious staphylococcal infections seems quite critically dependent upon the MIC. Perhaps the problem is the actual MIC, rather than MIC creep; however understanding whether creep actually exists will help us understand the dynamics of the organism’s response to antibiotics, the ways in which resistance can develop and the likely future utility of vancomycin. The latter is immediately important as that utility seems to be balanced on a knife’s edge at the moment. With a BP of 2mg/L and most series showing modal MICs of 1, 1.5 or 2mg/L, we can see immediately that there is little room for maneuver. Indeed many experts now hold that it is already too late for vancomycin as the BP should really be reclassified to 1.0 or 1.5mg/L, depending on the method used to measure the MIC. I would certainly concur with this position for treatment of life-threatening infection. The evidence here is uniformly consistent and weighty that organisms with such an MIC respond poorly to vancomycin (or teicoplanin). However, this also may be partly explained by the other changes (e.g. in autolysis, accessory gene regulation and biofilm formation) that occur simultaneously in such organisms with an elevated MIC.

Figure 1. E test MIC of *S. aureus* on Mueller Hinton agar

The antibiotic test strips above are vancomycin (VA) and teicoplanin (TP). The MIC is read from the gradient scale at the point of complete inhibition of bacterial growth; thus the MIC of VA is 1.5mg/L and TP is 1.0mg/L.

*CLSI: Clinical Laboratory Standards Institute (U.S); EUCAST: European Committee of Antimicrobial Susceptibility Testing*
Some authors have maintained that the observed elevated MICs are actually a demonstration of MIC leap—i.e., a strain change—but the evidence for this is weak. On the other hand there is mounting evidence that creep is an ongoing process over years of persistent vancomycin exposure in hospital strains, and represents sequential acquisitions of multiple mutations in several areas of cell wall manufacture that ultimately lead to intermediate or full GISA status.\(^7\) Such strains can accumulate up to 20 or 30 mutations through several different pathways, which has prevented the development of any single molecular detection tests so far. There is mounting evidence that storage of such organisms, even just for a few months, leads to either loss of expression of the mutations or loss of the mutations themselves.\(^4,5\)

So what can we do to clarify the situation and ensure the best treatment for our patients? A few suggestions for further research are included in Table 1. One interesting debate centers on the quest for accuracy versus reproducibility or precision. Traditionally, the latter has been the gold standard in susceptibility testing, particularly in surveillance surveys of strains, and represents sequential acquisitions of multiple isolines are stored. This, we now understand, may well affect the results obtained from such studies and have important implications for many future surveillance studies, even for other classes of antibiotics.\(^4,5\)

In conclusion, much work is required before we achieve clarity on these issues. In the meantime, I recommend use of the E test gradient MIC measurement in serious staphylococcal infection and a BP of 1mg/L for conventional dosing schedules and 1.5 mg/L for high-dose schedules. A loading dose of either vancomycin or teicoplanin is also necessary to rapidly achieve therapeutic levels, as well as trough serum monitoring for teicoplanin. New agents such as daptomycin\(^9-10\) and linezolid are costly, but these and other drugs will almost certainly provide benefits to critically ill patients, providing they too are dosed properly. Lastly, if it is not possible to measure an E test MIC, then a risk factor analysis can be performed on the patient.\(^11\)

**Table 1. Research Issues in MIC Creep**

- Relationships between different MIC testing methods and clinical outcome
- Storage of organisms before testing versus testing at time of isolation
- Strain types versus MIC
- Should the break point be reduced?
- Can increased vancomycin dosing compensate for MIC creep?
- Do new antibiotics give better outcomes?; are they cost effective?
- Better define the PK/PD target for glycopeptides
- MICs/resistance mechanisms versus different glycol/lipo peptide
- Does MIC creep occur with other antibiotic groups?
- Better define mutations/expression/stability; develop molecular tests
- Compare E test with other gradient methods

**References**


McCormick references, continued from Page 4


Swine livestock production as a risk factor for community-associated MRSA in Pennsylvania

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Over 80% of antibiotics in the United States are sold for use in livestock feeds, most commonly in very large, industrial operations with a high density of animals, but with insufficient land acreage on which to spread, and thus dispose of, the produced manure (Fig. 1). Because of this antibiotic use, the manure produced at these operations contains antibiotics, antibiotic-resistant bacteria, and resistance genes. This manure, spread on crop fields, sometimes near human dwellings, may put people at risk for antibiotic-resistant infections; however, no prior studies have formally evaluated this question.

Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization was first linked to high-density livestock operations in studies from Europe. A landmark 2005 study reported that the pre-valence of MRSA colonization in Dutch farmers was 760 times that of the general population. In Europe, a strain of MRSA called sequence type 398 (ST398) has been the most common colonizer of swine and their owners. In the United States, the incidence of community-associated MRSA (CA-MRSA) infection appeared to increase throughout the early 2000s, without good explanation or understanding of the drivers of the epidemic. Genetics has proven useful to the epidemiologic investigation of MRSA, and shown that nearly all CA-MRSA in the US carries the Panton-Valentine leukocidin (PVL) genes. We hypothesized that high-density livestock operations could play a role in the CA-MRSA epidemic.

Methods

To evaluate this, we first used electronic health records (EHR) from 2001 to 2010 from the Geisinger Health System (GHS) in Pennsylvania to characterize MRSA infection in a large, geographically diverse population with urban and rural areas and many animal feeding operations. The EHR dataset included over 150 million records on 450,000 patients. Incident MRSA cases were identified using EHR data, classified as CA-MRSA or healthcare-associated (HA-MRSA) and frequency-matched to randomly selected controls and patients with skin and soft tissue infection (SSTI) but without a history of MRSA. We then estimated the incidence of CA-MRSA, HA-MRSA, and SSTIs.

To assess high-density livestock production as a risk factor for MRSA infection and SSTIs, we conducted a nested case-control study. Using nutrient management plans, two individual-level exposure variables were created, based on the distance between patients’ home addresses and: (1) the location and number of animals (livestock model); and (2) the location of crop fields, their acreage, and the volume of manure applied (crop field model). We used multilevel logistic regression to assess the association between exposure and case status, while adjusting for potential confounding variables: age, sex, race/ethnicity, smoking status, antibiotic order in the two years preceding diagnosis, Medical Assistance for health insurance as a surrogate for low family socioeconomic status, residential community (city, borough, or township), and community-level socioeconomic deprivation.

We also prospectively collected MRSA isolates from a subsample of GHS patients with MRSA infections throughout 2012 and collaborated with New York University to characterize them molecularly. Here, the goal was to identify particular strains of MRSA infection associated with high-density livestock production in Pennsylvania.
Findings

We identified 1,734 CA-MRSA cases, 1,519 HA-MRSA cases, and 78,216 SSTI cases during the study period. CA-MRSA incidence increased from 69.5 to 204.3 per 100,000 person-years between 2005 and 2010 (the period of complete data), an average annual increase of 34% (Fig. 2). Age, season, community socioeconomic deprivation, obesity, smoking, and antibiotic use were identified as risk factors for CA-MRSA. Compared to patients with all other strains of MRSA, community-onset-PVL-negative MRSA was significantly associated with swine livestock and dairy/veal crop field exposures, comparing quartile 4 to quartiles 1-3, with adjusted odds ratios of 4.24 (95% CI: 1.60, 11.25) and 4.88 (95% CI: 1.40, 17.00), respectively. This is of interest because few community-onset infections are PVL-negative and almost no MRSA isolated from swine carries the PVL genes.

Interestingly, we did not isolate any ST398.

Implications and recommendations

CA-MRSA infection costs Americans between $0.5 and $2.2 billion annually. Despite recent evidence that CA-MRSA incidence is declining in cities, we found no such evidence across a large and varied geography in 38 counties in Pennsylvania.

Prior studies have reported associations of MRSA colonization and high-density livestock production, which does not directly contribute to this healthcare burden. We conducted the first study of MRSA infection in the community and high-density livestock production. We found that both livestock operations where swine were raised, as well as crop fields where their manure was applied, were associated with increased risk of CA-MRSA infection and SSTI.

Our work suggests that studies of colonization could potentially lead to erroneous conclusions about infection risk. While there is ample evidence that those in contact with livestock have increased prevalence of ST398 MRSA colonization, data suggest ST398 MRSA infection is rare. We demonstrated that other molecular types of MRSA beyond ST398 might be associated with these practices.

Our findings have implications for the role of livestock operations in the MRSA epidemic, the different roles of colonization and infection studies, and the identification of other MRSA strains that may be arising from high-density livestock production. Our data suggest that beyond the established risk of MRSA in underserved urban populations, livestock production may pose risk to residents in a range of residential settings, from rural to suburban and small town settings. We used novel, inter-disciplinary methods and collaborated among multiple institutions to add to the mounting evidence that antibiotic use in livestock feeds bears these previously unrecognized public health externalities.
Based on our results, we recommend three actions, ranging from simple to more difficult:

1. Replication of our findings
2. Communication of the results to the agricultural sector to help them understand the public health externalities of current practices
3. Removal of antibiotics from livestock feeds

References


**APUA’s Antibiotic Stewardship Webinar Series**

**Past webinar available for viewing:**

**Containing Healthcare Associated Infections Through Antibiotic Stewardship**

Presenters:

Stuart Levy, MD and Shira Doron, MD, MS
Tufts University School of Medicine

**This webinar:**

- Describes trends of major HAIs including MRSA, ESBLs and *C. difficile*
- Reviews the causes and mechanisms driving antibiotic resistance problems
- Explains the link between antibiotic overuse and the emergence of resistant infections
- Reviews effective ASP practices and the importance of diagnostics in improving antibiotic treatment and minimizing resistance
- Illustrates specific examples to enhance hospital-based antimicrobial stewardship

[VIEW HERE]
Biomarkers and antibiotic utilization

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Procalcitonin and Antibiotic management

Respiratory tract infections (RTI) remain the most common illness in humans, responsible for the most physician or emergency room visits and the most frequent cause of sepsis. While mortality is primarily associated with bacterial pneumonia or severe influenza, most patients have a mild viral illness. Interestingly, 75% of all antibiotic doses are prescribed for acute RTI, the majority of which are viral and not bacterial in etiology. Early differentiation between viral and bacterial, as well as severity of infection, are key to managing acute RTI, especially given evidence from studies that demonstrate that early and appropriate antibiotic use improves survival. Concurrently, the need for prudent antibiotic utilization avoiding overuse and prolonged use—is important for minimizing antibiotic-related complications, including side effects, drug interactions, development of resistance, and secondary infection such as Clostridium difficile colitis. Initial history, physical signs, imaging studies and current laboratory data do not reliably differentiate viral from bacterial infection.

Blood cultures have a low sensitivity, and sputum cultures, if available, have a low specificity due to quality, contamination and colonization issues.

An innovative approach to assessing the likelihood and severity of a bacterial infection is the use of blood biomarkers that reflect the host response to infection. Although there are many markers of an acute inflammatory response, only a few have undergone rigorous, randomized clinical trials that evaluate the clinical outcome associated with antibiotic management strategies. Procalcitonin (PCT) has been evaluated in numerous such studies and has been shown to be more specific for bacterial infection than traditional white cell count and C-reactive protein. In response to a bacterial infection, PCT is released from multiple tissues via direct stimulation of cytokines, including interleukin-1β, interleukin-6, and tumor necrosis factor 1α (TNFα). The degree of up-regulation of PCT correlates with the severity of bacterial infection. Conversely, interferon γ is the cytokine released in response to a viral infection. This blocks up-regulation of PCT, resulting in a higher specificity of PCT for bacterial infections. Quantitatively, PCT may help distinguish severe bacterial infections from mild viral syndromes. PCT shows a consistent kinetic profile over time with rapid up-regulation within 6-12 hours of a severe bacterial infection and a predictable daily decrease by 50% as infection is controlled by host defenses, source control and antibiotics (Fig. 1).

Given these characteristics, many studies have evaluated the usefulness of PCT for improving clinical management of patients with respiratory tract infection in four important areas: diagnosis, initiation of antibiotics, severity of illness and antibiotic duration.

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Figure 1. PCT plasma concentrations (ng/ml) in infection

PCT plasma concentrations (ng/ml) following infusion of a patient with a solution that was accidentally contaminated with Acinetobacter baumanii. During the first phase of induction (<6h), PCT increased by approximately 0.5 ng/ml per hour after a latency phase of about 2-3 hours, followed by massive PCT production at the rate of approximately 50 ng/ml per hour.

Adapted from Brunkhorst F.M. et al.
PCT for diagnosis of significant bacterial respiratory tract infection

Numerous studies have investigated the PCT for initial diagnosis of a bacterial infection and differentiation from viral infection. In one study of 925 patients with community-acquired pneumonia (CAP), 7.9% of patients were bacteremic. PCT was significantly increased in bacteremic patients compared to non-bacteremic patients. Less than 1% of patients had a positive blood culture if the initial PCT level was <0.25mg/L, which increased to greater than 20% in patients with initial PCT >2.5mg/L. Another study investigated 103 patients with confirmed influenza A (H1N1). PCT had an area under the curve (AUC) of 0.90, differentiating the 48 patients with bacterial super-infection from patients with viral pneumonia only (PCT cut off of 0.8 mg/L). The negative predictive value was 91% for excluding bacterial co-infection.

Prognostic value for prediction of adverse outcomes

Clinical risk scores, such as APACHE or SAPS II, are somewhat limited in assessing disease severity and these scores are only validated when admission values are available. Indeed, the utility of monitoring these scores over the course of sepsis is not well-established. Thus, there is interest in predictive use of biomarkers that: 1) are objectively and rapidly measurable; 2) respond to clinical recovery and 3) add relevant, reliable, real-time information. A recent derivation-validation cohort study using retrospective data from two independent U.S. critical care institutions found a high prognostic value when considering the 72-hour PCT kinetic for sepsis mortality. A PCT decrease of >80% over 72 hours had a negative predictive value of 90% (and 91% to exclude ICU mortality) which may aid in identifying individuals at reduced risk—thus good early ICU discharge candidates. Conversely, no decrease, or an increased PCT, had a positive predictive value of 35-50%, helping to flag patients who were at high mortality risk and likely to require treatment escalation.

PCT and antibiotic management

To date, a total of 14 randomized controlled trials with over 4,000 patients have assessed the efficacy and safety of using PCT for antibiotic initiation, duration and cessation in a range of respiratory illnesses—including acute exacerbation of COPD, bronchitis, asthma, community acquired pneumonia, sepsis, ventilator associated pneumonia and postoperative pneumonia. All studies used somewhat similar protocols, which recommended initiation or discontinuation of antibiotics based on PCT levels. Several cutoff ranges were used reflecting the increase in likelihood of bacterial infection with higher PCT levels. Cutoff levels were adapted to the clinical setting or acuity of the patient.

In low-acuity settings (primary care) and low-acuity conditions (bronchitis), PCT levels were used to withhold or prescribe antibiotics. In higher acuity patients with more severe findings (patients with pneumonia requiring hospitalization and ICU patients with sepsis), PCT was used not for initiation of antibiotics, but rather for discontinuation when a predetermined drop in PCT levels was achieved with concordant clinical improvement.

In all 14 studies this strategy proved to be highly effective in reducing antibiotic exposure. In patients with a lower risk of recurrent infection, PCT guidance reduced antibiotic prescription rates by 40-75% in primary care patients with upper and lower respiratory symptoms; by 60-75% in patients with bronchitis; and by 30-45% in patients with an acute exacerbation of COPD. In higher acuity patients with community-acquired pneumonia, PCT guidance reduced antibiotic duration by 35-55% and by about 35% in patients with ventilator-associated pneumonia. Crucially, there was no increase in mortality or other adverse events during the course of the various studies. In addition, a prospective real-life multicenter, multinational evaluation of a PCT guidance algorithm study also found significant reduction in antibiotic usage, without increase in adverse outcomes.

Utilization of PCT in the antibiotic management of patients with respiratory infection

Algorithms for the diagnosis, prognosis and therapy of both low-acuity and high-acuity patients are presented in Figure 2. In general, for the low-acuity patient with a PCT <0.25mg/L, antibiotics can be withheld—or withdrawn, if the PCT remains stable (Fig. 2A). For high-risk patients with severe respiratory infection, empiric antibiotic therapy should not be delayed, even with a low initial PCT (0.25mg/L). The progression and response to effective treatment of severe infection is dynamic, and serial PCT measurements at 0, 12, 24 and 48 hours help with assessing severity of infection. PCT usually peaks within 12-48 hrs.—as the patient responds to treatment, the levels drop by 50% per day. Catching the peak level is important for 3 reasons:

1. Prognostication—the higher the peak level, the higher the morbidity;
2. Treatment duration can be optimized (see Fig. 2B therapy);
3. Failure to drop by 50% every 1-2 days suggests treatment failure. Reassessment of infection source and treatment are strongly recommended.
AB = antibiotic; CAP = community-acquired pneumonia; PCT = procalcitonin

For patients already on antibiotics: If PCT <0.25mg/L, repeat PCT at 12-24 hours; if again <0.25mg/L, consider discontinuing antibiotics and look for nonbacterial source of infection. If PCT >0.25mg/L, reassess PCT every 2 days. Discontinue antibiotics if patient shows clinical recovery and PCT decreases to 0.25 mg /L (or by at least 80% to 90% from the peak level). With suspected pneumonia showing pulmonary infiltrates and >2 PCT levels <0.25mg/L over 24-48 hours, consider antibiotic discontinuation and investigate other causes (e.g., viral pneumonia, fungal infections—including pneumocystis jiroveci pneumonia, Bronchiolitis Obliterans Organizing Pneumonia (BOOP), atelectasis, heart failure and pulmonary emboli. If PCT levels are <0.25mg/L and bacterial infection is strongly suspected based on clinical, imaging and or microbiological data, continue antibiotics, but consider early discontinuation and diagnostic workup for alternative causes.

Figure 2. Clinical Use of Procalcitonin

A. Low acuity patients
(upper respiratory infection, bronchitis, primary care, ED)

<table>
<thead>
<tr>
<th>Procalcitonin (µg/L)</th>
<th>Diagnosis</th>
<th>Prognosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1µg/L</td>
<td>Bacterial infection highly unlikely → consider alternative diagnosis</td>
<td>Very low risk for sepsis related complication</td>
<td>Withhold initial AB</td>
</tr>
<tr>
<td>&lt;0.25µg/L</td>
<td>Bacterial infection unlikely → consider alternative diagnosis</td>
<td>Low risk for sepsis related complication</td>
<td>Consider withholding AB → recheck PCT</td>
</tr>
<tr>
<td>≥0.25µg/L</td>
<td>Bacterial infection likely</td>
<td>High risk for bacteremic infection</td>
<td>Start AB → monitor PCT for stopping AB treatment if PCT &lt;0.25µg/L</td>
</tr>
<tr>
<td>&gt;0.5µg/L</td>
<td>Bacterial infection highly likely</td>
<td>High risk for adverse outcome</td>
<td>Start AB → monitor PCT for stopping AB treatment if PCT &lt;0.25µg/L</td>
</tr>
</tbody>
</table>

B. Moderate and high acuity patients
(CAP patients in ED, hospital ward or ICU setting)

<table>
<thead>
<tr>
<th>Procalcitonin (µg/L)</th>
<th>Diagnosis</th>
<th>Prognosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1µg/L</td>
<td>Bacterial infection highly unlikely → consider alternative diagnosis</td>
<td>Low risk for mortality despite high clinical risk score</td>
<td>Consider AB treatment if high clinical suspicion of infection (“overruling”) → monitor PCT for early stop of AB treatment</td>
</tr>
<tr>
<td>&lt;0.25µg/L</td>
<td>Bacterial infection unlikely → consider alternative diagnosis</td>
<td>Low risk for sepsis related complication</td>
<td>Consider AB treatment if high clinical suspicion of infection (“overruling”) → monitor PCT for early stop of AB treatment</td>
</tr>
<tr>
<td>≥0.25µg/L</td>
<td>Bacterial infection likely</td>
<td>High risk for bacteremic infection</td>
<td>Start AB → monitor PCT for stopping AB treatment if decrease &gt;80-90% or PCT &lt;0.25µg/L (ward) or &lt;0.5µg/L (ICU)</td>
</tr>
<tr>
<td>&gt;0.5µg/L</td>
<td>Bacterial infection / sepsis highly likely</td>
<td>High risk for bacteremic infection and adverse outcome → monitor PCT for treatment response</td>
<td>Start AB → monitor PCT for stopping AB treatment if decrease &gt;80-90% or PCT &lt;0.25µg/L (ward) or &lt;0.5µg/L (ICU)</td>
</tr>
</tbody>
</table>
In patients suspected of respiratory infection complicating major surgery, trauma or cardiogenic shock, PCT levels may reflect the underlying cytokine response to major tissue injury, and not necessarily reflect an infectious process alone. Serial procalcitonin levels may be suggestive of infection when a secondary elevation is seen if the underlying condition is stable or improving.  

These recommendations and guidelines are valid only with highly sensitive PCT assays and should not be applied to patient populations that have not been studied, e.g., immune-compromised patients, neonates and pregnant females. Importantly, no diagnostic test should be used in isolation, out of clinical context, for decision-making. PCT does not replace good clinical evaluation and judgment. The correct understanding of PCT levels is predicated on the physician’s pretest probability for the test. Given the appropriate clinical situation, the addition of the highly sensitive PCT biomarker appears to help in the diagnosis of upper and lower respiratory tract bacterial infection and more importantly, aids in guiding antibiotic duration, based on its strong negative predictive value.

References

Characterization of methicillin-resistant *Staphylococcus aureus* isolated in Bulgarian hospitals, 2005-2011

Dimitar Nashev, MD, PhD

Staphylococcal Reference Lab at the National Center for Infectious and Parasitic Diseases, Sofia, Bulgaria

*In collaboration with:* L. Bizeva, D. Merdzhanov, E. Keuleyan, T. Kantardjiev

1Microbiology Dept., National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria

2Microbiology Dept., Medical Institute of Ministry of Interior, Sofia, Bulgaria

Reports documenting the clonal spread of MRSA in Bulgaria are still limited in number and focused mainly on single hospital outbreaks, isolates collected in a short period of time or sporadic cases of community-associated MRSA infections.1,2

We aimed to define the most prevalent spa types of MRSA found in Bulgarian hospitals in the period 2005-2011 and to associate them with the corresponding sequence types (ST), SCCmec type, PVL (Panton-Valentine leukocidin) production and phenotype of antibiotic resistance.

A total of 293 MRSA isolated between 2005 and 2011 from 31 hospitals in 20 cities were studied. The isolates were grouped according to their antibiotic resistance phenotypes and 104 representative isolates were selected for further genotyping, including spa sequence typing, SCCmec typing3 and PCR detection of the genes encoding PVL.4 The existing sequence database for spa types (http://spa.ridom.de) and literature data were used to associate spa types with a particular MLST sequence type (ST).

Among 18 spa types defined, the most prevalent was t010 (33.7%), followed by t037 (28.8%), t030 (14.4%), t1143 and t1368 (2.9%). The remaining spa types were sporadically isolated. The isolates belonging to spa types t030 and t037 possessed SCCmec type III, whereas all other isolates were found to carry SCCmec type IV. Only isolates with spa types t1143, t300 and t1368 were positive for PVL genes. (Table 1)

Using the BURP (Based Upon Repeat Pattern) algorithm integrated in Staphytype software v.2.2.1, two spa-clusters were defined: spa-clonal complex (CC) 1143 (t030, t037, t300, t1143, t1507, t3140) and spa CC 010 (t002, t010, t442, t855, t2695). Among 18 spa types defined, the most prevalent was t010 (33.7%), followed by t037 (28.8%), t030 (14.4%), t1143 and t1368 (2.9%). The remaining spa types were sporadically isolated. The isolates belonging to spa types t030 and t037 possessed SCCmec type III, whereas all other isolates were found to carry SCCmec type IV. Only isolates with spa types t1143, t300 and t1368 were positive for PVL genes. (Table 1)

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Spa types t030 and t037 are associated with ST239, a pandemic MRSA lineage characterized by worldwide distribution. These two spa types comprised the majority (43.2%) of MRSA isolates in the present study. This lineage has been reported in many European countries, including those neighboring to Bulgaria. ST239 is widely distributed in Greece and is the predominant endemic clone in the University hospital in Patras.5 Spa type t030 has been described as the prevalent MRSA spa type in Turkey6 and Romania.1 Therefore, the prevalence of ST239 related spa types in Bulgaria is not surprising. The majority of Bulgarian t030/t037 MRSA strains reflected the ST239 multi-resistance pattern (Table 1).

Spa types t010 and t002, (SCCmec IV and negative for PVL-genes) were frequently associated with ST5-IV, known as Pediatric clone (http://spa.ridom.de/mlst.shtml). According to spa-server, t010 was detected in Austria, Belgium, Czech Republic, Denmark, France, Germany, Island, Ireland, Netherlands, Poland, Spain, Sweden, Switzerland and UK, but not reported in Bulgaria’s neighbors, Greece, Turkey and Romania (http://spa.ridom.de/frequencies.shtml). In the present study, most of the ST5-IV related isolates were resistant only to beta-lactams. Sporadic t010 isolates showed resistance to kanamycin, gentamicin or tetracycline.

As reported previously, spa type t300 and t1143 were associated with ST30.7,8 PVL-positive ST30-IV is an important pandemic community-associated clone known as Southwest Pacific Clone, USA1100 or West Samoan Phage Pattern (WSPP) clone. Interestingly, in the present study, t1143 isolates were found to be hospital-associated. However, CA-MRSA has been increasingly associated with nosocomial infections with various reports of CA-MRSA isolation in European hospitals.9,10

As shown above, ST239 associated spa-types t030/t037 and ST30 related t1143 and t300 were clustered together in spa CC 1143. The wrong clustering of spa types of ST239 with those found in CC30 has been reported previously and could be explained by recombinative replacement of a large stretch of
Table 1. Characteristics of MRSA spa types in Bulgarian hospitals (2005-2011)

<table>
<thead>
<tr>
<th>Spa Type</th>
<th>n (%)</th>
<th>Antibiotic resistance phenotype</th>
<th>SCCmec</th>
<th>PVL</th>
<th>Inferred ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>t010</td>
<td>35 (33.7 %)</td>
<td>Ox, K-R/S, G-R/S</td>
<td>IV</td>
<td>-</td>
<td>ST5 (Pediatric)</td>
</tr>
<tr>
<td>t037</td>
<td>30 (28.8%)</td>
<td>Ox, K, G, T, Er/Cli const, Cip, TMP/SMX</td>
<td>III</td>
<td>-</td>
<td>ST239 (Brazilian/Hungarian)</td>
</tr>
<tr>
<td>t030</td>
<td>15 (14.4%)</td>
<td>Ox, K, G, T, Er/Cli ind, Cip, Rif, Chl-R/S</td>
<td>III</td>
<td>-</td>
<td>ST239 (Brazilian/Hungarian)</td>
</tr>
<tr>
<td>t1143</td>
<td>3 (2.9%)</td>
<td>Ox</td>
<td>IV</td>
<td>+</td>
<td>ST30</td>
</tr>
<tr>
<td>t1368</td>
<td>3 (2.9%)</td>
<td>Ox, K, G, T, Er/Cli ind</td>
<td>IV</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>t002</td>
<td>2 (1.9%)</td>
<td>Ox</td>
<td>IV</td>
<td>-</td>
<td>ST5 (Pediatric)</td>
</tr>
<tr>
<td>t442</td>
<td>2 (1.9%)</td>
<td>Ox, K, G, Er/Cli const</td>
<td>IV</td>
<td>-</td>
<td>ST478</td>
</tr>
<tr>
<td>t2970</td>
<td>1</td>
<td>Ox, Er/Cli const</td>
<td>IV</td>
<td>-</td>
<td>ST398</td>
</tr>
<tr>
<td>t1531</td>
<td>1</td>
<td>Ox</td>
<td>IV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>t2695</td>
<td>1</td>
<td>Ox, K, G, T</td>
<td>IV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>t855</td>
<td>1</td>
<td>Ox</td>
<td>IV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>t1507</td>
<td>1</td>
<td>Ox</td>
<td>IV</td>
<td>-</td>
<td>CC30</td>
</tr>
<tr>
<td>t300</td>
<td>1</td>
<td>Ox</td>
<td>IV</td>
<td>+</td>
<td>ST30</td>
</tr>
<tr>
<td>t3140</td>
<td>1</td>
<td>Ox, Er/Cli ind</td>
<td>IV</td>
<td>-</td>
<td>CC30</td>
</tr>
<tr>
<td>t386</td>
<td>1</td>
<td>Ox, K, G, Er/Cli const, Cip</td>
<td>IV</td>
<td>-</td>
<td>ST1</td>
</tr>
<tr>
<td>t024</td>
<td>1</td>
<td>Ox, K, G, Er/Cli ind, TMP/SMX</td>
<td>IV</td>
<td>-</td>
<td>ST8 (EMRSA-2/6; USA500)</td>
</tr>
<tr>
<td>t2143</td>
<td>1</td>
<td>Ox</td>
<td>IV</td>
<td>-</td>
<td>ST45 (Berlin; USA600)</td>
</tr>
<tr>
<td>t1872</td>
<td>1</td>
<td>Ox</td>
<td>IV</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Ox = oxacillin, K = kanamycin, G = gentamicin, Cip = ciprofloxacin, T = tetracycline, Er = erythromycin, Cli ind = clindamycin inducible resistance phenotype, Cli const = clindamycin constitutive resistance phenotype, Chl = chloramphenicol, TMP/SMX = trimethoprim/sulfamethoxazole, PVL = Panton-Valentine leukocidin, ST = MLST sequence type
chromosomal DNA in MRSA isolates of CC8 by a stretch originating from CC30 and including the spa gene.\textsuperscript{11}

The PVL-negative spa types t3140 and t1507 were also grouped in the spa CC-1143 clonal complex. Data on their corresponding ST were not found in the spa-server, but according to BURP-clustering they could probably belong to CC30.

A PVL-positive spa type, t1368, defined as singleton by BURP, was detected in three isolates (Table 1). We have not found data on the ST association of this spa-type on the spa server or in the literature, but the closely related spa-type t9381 was associated with CC8; ST-72. However, for the exact ST identification, MLST analysis should be performed.

Along with the prevalent spa types and their relatives, several minor spa types, classified by BURP as singletons were found. Their characteristics and ST association are shown in Table 1.

In conclusion, spa types associated with ST239 and ST5-IV clones were largely predominant among MRSA isolates in 20 Bulgarian hospitals. Sporadic strains belonging to different MRSA lineages, including PVL-positive CA-MRSA showed potential for further spread of new clones in Bulgaria, although in relatively small proportions.

References


Methicillin-resistant Staphylococcus aureus in Cuba

Gilda Toraño Peraza, PhD and Alexis Monzote López, MD
Bacteriology-Mycology Department, Pedro Kouri Institute, Havana, Cuba; APUA-Cuba Members

Staphylococcus aureus is responsible for a wide variety of clinical problems, ranging from skin and soft tissue infections, to severe systemic and life threatening diseases. The organism is relevant in the community and is commonly associated with nosocomial infections. S. aureus possesses a large capacity to acquire antimicrobial resistance genes, with strains currently resistant to the majority of available antibiotics—particularly to methicillin, a resistance reported initially in the hospital environment (hospital-associated methicillin resistant S. aureus, HA-MRSA) and subsequently in the community (community-associated methicillin resistant S. aureus, CA-MRSA), has complicated the worldwide control of infection by this microorganism.1

MRSA is an increasing problem in the Americas and the Caribbean, but in Cuba very little is known about its epidemiology and even less about its behavior in the community.2 Some epidemiological data are available from independent studies of different hospital institutions and nasal carriage surveys, but the reports are infrequent and insufficient to estimate the change in the morbidity and mortality of annual national figures.3,4 However, the available evidence suggests a MRSA incidence greater than 50% in Cuban hospitals.7

A collaborative study between Hospital Canisius-Wilhelmina in Nijmegen, Netherlands, and Pedro Kouri Institute (IPK) in Havana, Cuba investigated the molecular epidemiology of 68 MRSA clinical strains (isolated from wounds, bronchial/tracheal aspirations, blood, skin, abdominal drainage and chest tissue biopsy), prospectively collected from three major hospitals in Cuba during three months in 2008. Molecular testing was performed for detection of Panton-Valentine leukocidin (PVL), meca, the Sa442 element and spa typing. Forty isolates were meca positive and confirmed to be MRSA. Spa typing identified five different spa types: t149 (n = 24), t008 (n = 8), t037 (n = 6), and one each of t4088 (closely related to t149) and t2029 (closely related to t037). All eight t008 isolates (but none of the other spa types) were PVL-positive. Multi locus sequence typing (MLST) was performed on t008 isolates and all proved to be CC8 positive.8

This is the first report of molecular typing of MRSA isolates from Cuba and shows that the predominant clone is spa-type 149, followed by CA-MRSA USA300. This clone was first described in the United States, where it has now become endemic; it’s finding in Cuba highlights the wide spread of this strain over Latin America.9

Another study in a Havana paediatric institution between 2010-2012 confirmed 333 MRSA isolates and revealed that 65.9% of MRSA isolates caused severe skin and soft tissue infections requiring hospitalization. Genes encoding PVL were detected both in community-acquired isolates (86%) and hospital-associated strains (54.5%), pointing to the possible movement of MRSA clones to the hospital environment, but also suggesting that hospital isolates could be producing the toxin, thus reducing PVL as a valuable epidemiological marker.

In conclusion, MRSA is both a hospital and community problem for Cuba and demands local surveillance on prevalence and transmission dynamics. Surveillance studies that utilize molecular typing will lead to a better understanding of its epidemiology and permit the design of more assertive control strategies. However, faced with the inability to conduct comprehensive studies of molecular characterization, we must ensure that the microbiology laboratory can accurately identify MRSA infections. Physicians must be alerted to control its spread through prudent use of antibiotics, with an emphasis on limiting the use of glycopeptides and prolonged therapy. Hospitals must also define appropriate protocols for the management or treatment of individuals colonized or infected with CA-MRSA.

References


Upcoming webinar:

Antibiotics: Managing a Medical Treasure
Live Event: Friday, January 31, 2014 1:00 PM EST
PACE® credit available

Antimicrobial agents are a remarkable class of drugs that are responsible for some of the most dramatic improvements in medical therapy in history. However, these medicines are also the only class of drugs whose efficacy diminishes as we use them. The link between antibiotic use and the development of resistance has been repeatedly made since the 1950s, yet clinicians have not learned from mistakes that have occurred with the introduction of new antibiotics. The development of resistance to carbapenems is now one of the greatest challenges to medicine since there is little on the horizon for patients suffering from carbapenem-resistant, gram-negative infections. Clinicians must realize how perilously close we are to a ‘post-antibiotic’ era.

While no one doubts the importance of infection control practices in limiting the spread of antibiotic-resistant organisms, optimizing antibiotic use, also known as antibiotic stewardship, remains essential for successful control of the antibiotic resistance. Approaches to optimize antibiotic use vary in their effectiveness; some interventions are restrictive while others are persuasive. The overriding premise that antimicrobials are medical treasures, should guide all prescribers whenever these drugs are used. Once begun, their continued use must be scrutinized. Antibiotic de-escalation is a complex concept comprised of three questions: Is the patient actually infected at all? Is the patient actually infected with bacteria? How long do you need to treat with antimicrobials?

This webinar will:

- Analyze the relationship between antibiotic use and antibiotic resistance
- Review the reasons for the dearth of new antibacterial antibiotics
- Discuss the need for antibiotic stewardship
- Describe the methods for optimizing antibiotic use including the use of biomarkers, newer diagnostic tools and approaches to de-escalate antibiotics

Presenter: Robert Gaynes, MD
Professor of Medicine
Emory University School of Medicine

Dr. Gaynes is Chair of the Antimicrobial Stewardship Committee and Infection Control Committee at Emory University School of Medicine and the Atlanta VA Hospital. Dr. Gaynes has authored and/or coauthored over 145 papers/book chapters on infectious disease topics and in 2011 published a book entitled, Germ Theory: Medical Pioneers in Infectious Diseases.

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New compounds may boost antibiotic efficacy for MRSA, anthrax

Thomas Poulos of University of California - Irvine and Richard Silverman of Northwestern University have demonstrated an approach for treating neurodegenerative diseases that may be applicable to combating bacterial diseases. By using inhibitor compounds to block neuronal nitric oxide synthase (NOS—an enzyme that appears to help bacteria resist antibiotics), the researchers believe they may be able to increase antibiotic effectiveness. By coupling antibiotics with NOS-inhibitor compounds, bacteria were killed off more effectively than they were using antibiotics alone. Testing suggests that combining the compounds with antibiotics creates a special bond that increases the efficacy of the drug. The studies, which will be extended to animal models, have implications for treatment of severe bacterial pathogens, such as MRSA and anthrax.

MRSA survivors unite for World MRSA Day Kickoff Event

On September 28, the Chicago-based non-profit MRSA Survivors Network held its 5th Annual World MRSA Day Kickoff Event & Global C. difficile Summit. The Chicago, Illinois gathering brought together MRSA survivors, physicians and lawmakers at an event designed to raise awareness in the fight against MRSA and other healthcare-acquired infections. The Network’s founder, Jeanine Thomas, declared that the U.S. CDC has underreported MRSA infection and death rates in its recent studies. Thomas also called upon Congress to “declare MRSA and C. difficile epidemics and appropriate funds for prevention and public awareness campaigns.” The MRSA Survivors Network calls for a comprehensive approach to MRSA detection and control, including patient isolation and decolonization, strict adherence to hand hygiene guidelines, vigilant decontamination of surfaces, and more prudent usage of antibiotics. The kickoff event was a precursor to World MRSA Day, (October 2), and World MRSA Awareness Month (October).

CDC: Community-associated MRSA not declining

A CDC study published in The Journal of the American Medical Association (JAMA) in September sought to estimate the burden of methicillin-resistant Staphylococcus aureus (MRSA) among US adults. The study, titled “National Burden of Invasive Methicillin-Resistant Staphylococcus aureus Infections, United States, 2011,” used laboratory-based findings to identify MRSA cultures in nine different US cities between the years 2005 and 2011. In 2011, there were 80,461 total cases of MRSA infections across the nation. Of these, 48,353 were classified as healthcare-associated community-onset (HACO), 14,156 as hospital-onset infections, and 16,560 as community-associated infections. Between 2005 and 2011, national incidence rates for HACO infections and for hospital-onset infections decreased markedly (by 27.7% and 54.2%, respectively). Community-associated infections, however, only decreased by 5% across the same six years. Overall, the decreases in MRSA infection rates are encouraging signs, but this study makes it clear that increased emphasis must be placed on decreasing the spread of MRSA outside of the healthcare setting.

CDC reports on pediatric MRSA

In September, the U.S. CDC published a new study in Pediatrics that found unexpected results regarding the incidence and prevalence of invasive MRSA infections in children. The study, titled, “Trends in Invasive Methicillin-Resistant Staphylococcus aureus Infections,” found that rates of invasive pediatric MRSA between 2005-2010 were much lower than those reported among adults. However, while national trends in invasive adult healthcare-associated MRSA have shown dramatic declines, no significant changes were found among children aged three months to 17 years. Most alarming is the CDC’s finding that community-associated MRSA infections are actually increasing among children—signaling the need for more prevention of MRSA infections outside of the hospital. Lastly, it appears that both young infants and black children are disproportionately affected by serious MRSA infections.
APUA partners with Alere Inc. to build “Test Target Treat” educational platform

Through an unrestricted educational grant from Alere, APUA has brought together multiple experts from around the world to contribute to a diverse collection of educational materials dedicated to antimicrobial stewardship. The materials will include clinical monographs, case studies addressing six different disease states, personal perspectives from stakeholders within the healthcare system, recorded interviews, and three educational webinars. APUA looks forward to the roll-out process, which will follow in the coming months. Please check here for more details and updates as new educational pieces are added.

APUA attends ID week – presents “Learning Lounge”

APUA president, Dr. Stuart Levy, and Executive Director, Kathleen Young, hosted a booth at this year’s ID Week, which took place from October 2-6 in San Francisco, CA. ID Week is an annual collaboration between the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the HIV Medicine Association (HIVMA), and the Pediatric Infectious Diseases Society (PIDS). Every year, more than 5,500 professionals from 80 different countries attend the five-day meeting, which serves as an educational and networking event for those with an interest in infectious diseases.

In addition to hosting a booth that shared APUA’s mission and recent work, Drs. Stuart Levy and Kavita Trivedi (CA Department of Public Health) held a “Learning Lounge” presentation and discussion titled, “Antibiotic Stewardship and the Role of Diagnostics: Barriers and Opportunities,” which drew over one hundred participants.

APUA participates in CDC’s Get Smart About Antibiotics Week 2013

APUA was a proud participant in the U.S. Centers for Disease Control and Prevention’s (CDC) annual Get Smart About Antibiotics Week (November 18-24). The CDC’s campaign combines non-profit partners, for-profit partners, and state-based campaigns supporting appropriate antibiotic use. The collaboration sets the stage for a week-long observance of antibiotic resistance and the need for proper usage of antibiotics. APUA contributed throughout the week with extensive social media communications, which culminated in a live Twitter chat hosted by the CDC.

Boston-area Antimicrobial Research Network (BAARN) Meeting

Posing the question ‘What does it take to succeed in antibiotic R&D?’ a group of like-minded stakeholders gathered for a day-long symposium this fall as the Boston-area Antimicrobial Research Network or BAARN. The 110 individual participants, coming from industry, academia, medical centers, and NGOs, examined the emerging regulatory landscape and available resources to develop and utilize novel approaches to target pathogen-directed therapies. APUA and the ~30 other organizations that comprise the network pledged to meet annually and maintain a website to share information towards their common goal.

Chapter update: APUA-Ecuador

APUA-Ecuador reports several significant accomplishments in its recent history. This 180-member chapter has enacted control over antibiotics and established resistance surveillance programs in five different specialty hospitals in the capital city of Quito. In a joint effort with other Ecuadorian scientific societies, the Chapter has also submitted a letter to the Presidency and National Assembly, alerting them to the growing issue of bacterial resistance. The letter serves as a call-to-action and asks for the government’s support with bacterial resistance prevention programs. In order to better educate healthcare providers and patients on the issue of antimicrobial resistance, APUA-Ecuador has developed a monthly publication that is delivered to all Specialization Public Hospitals across the country.

The Chapter also reports the hosting of two upcoming conferences in Ecuador: the Pan American Congress of Infectious Diseases, and the Pan American Association for Infectious Diseases, which will be chaired by its leader, Dr. Ana Celi de la Torre.

Chapter update: APUA-Nepal

Access the tenth annual APUA-Nepal Newsletter, here.
Obituaries

Both of these APUA Scientific Advisory Board members were instrumental in initiating and supporting the Reservoirs of Antibiotic Resistance project.

Dr. Donald Low, an internationally recognized Canadian microbiologist and member of APUA’s Scientific Advisory Board, passed away on September 18, 2013 at the age of 68. Low led an active and meaningful career as microbiologist-in-chief at Mount Sinai Hospital in Toronto. He was diagnosed with a brain tumor earlier this year. Low was most known for his tireless efforts responding to the 2003 Toronto outbreak of severe acute respiratory syndrome (SARS), during which he became a public figure for the city’s response to the outbreak that claimed 44 lives in Toronto. Over his lifespan, he co-authored over 400 peer-reviewed articles for scientific journals and made a name for himself as an expert in necrotizing fasciitis (flesh-eating disease) caused by Group A Streptococcus. As evidenced by his role at APUA, Low dedicated himself to combating the rise of antimicrobial resistance by championing the appropriate use of antibiotics.

Dr. Abigail Salyers, a world renowned research scientist, author and professor at the University of Illinois at Urbana-Champaign, passed away at the age of 70 on November 6, 2013. In 1983, Salyers became the first female tenured professor in microbiology at Illinois. She quickly went on to become a full professor, and received a multitude of awards in the three decades she taught and researched there. Dr. Salyers wrote five books and published over 200 peer-reviewed research articles, book chapters, and reviews that were widely read and cited. From 2001 to 2002, Abigail was president of the American Society for Microbiology, where she shone as a leader and championed her interest in the diversity of microorganisms on the planet. She was also one of the original members of APUA’s Reservoirs of Antibiotic Resistance project.

Upcoming Events


May 10-13, 2014: European Congress on Clinical Microbiology and Infectious Diseases (ECCMID 2014), Barcelona, Spain.

May 17-20, 2014: American Society for Microbiology’s Annual Meeting (ASM 2014), Boston, MA, USA.

June 7-9, 2014: Association for Professionals in Infection Control and Epidemiology’s Annual Conference (APIC 2014), Anaheim, CA.


July 6-9, 2014: The Australasian Society for Infectious Diseases (ASID) Annual Scientific Meeting, Melbourne, Australia.


• XIVth International Congress of Mycology
• XIVth International Congress of Bacteriology and Applied Microbiology
• XVIIth International Congress of Virology

September 5-9, 2014: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2014), Washington, DC, USA.

October 8-12, 2014: Infectious Diseases Society of America (IDSA), the HIV Medicine Association (HIVMA), and the Pediatric Infectious Diseases Society (PIDS)’s ID Week 2014, Philadelphia, PA, USA.

Leadership Award: Dr. Keith Klugman

The distinguished recipient of this year’s 2013 APUA Leadership Award is Dr. Keith Klugman, who was honored at a dinner held in San Francisco, CA during ID Week 2013. Chosen from a pool of highly qualified individuals nominated for this year’s award, Dr. Klugman received the award for his work on the pneumococcal vaccine. His research has focused on the emergence of antibiotic-resistant pneumococci and factors that spread this resistance. He has published more than 450 scientific papers on pneumonia, meningitis, antimicrobial resistance, and vaccines for bacterial pathogens and served as an expert on antimicrobial resistance for numerous committees, including at the WHO and the CDC. APUA also commends him for his recent appointment as the Director of Pneumonia Studies at the Bill and Melinda Gates Foundation.

Chapter Award: APUA-Cuba

The Alliance for the Prudent Use of Antibiotics was pleased to bestow its 2013 APUA Chapter Award on APUA-Cuba, in recognition of the chapter’s exemplary efforts to improve antibiotic stewardship and awareness in Cuba and throughout Latin America. In just six years of existence, APUA-Cuba has enrolled over 2,000 members from 63 medical specialties and has established 9 provincial chapters nationwide, including a newly established sub-chapter in San Cristobal.

November 14-16, APUA President Dr. Stuart B. Levy attended and presented at the 2nd IUMS (International Union of Microbiological Societies)-sponsored international conference on antibiotic resistance in Havana, Cuba where he had the honor of personally presenting APUA’s 2013 Chapter Award. The conference on resistant bacteria and fungi addressed pressing problems related to antibiotic use in Cuba. The visit provided an opportunity to share perspectives on important global issues and congratulate Cuban colleagues on their impressive multi-faceted approach to fighting antimicrobial resistance.

As part of these efforts, APUA-Cuba has hosted multiple symposia on antimicrobial resistance and the need for new antibiotics. The chapter’s electronic database allows for daily communication and serves as an important venue for discussion of scientific issues. APUA-Cuba has also utilized four television appearances to educate the public on the importance of proper use of antibiotics and the consequences of inappropriate use.

Recently APUA-Cuba unveiled its new San Cristobal sub-chapter, with an enrollment of 150 members. Before an audience of almost 200 medical professionals, five specialists from APUA-Cuba presented updated information and led discussions on antibiotic stewardship, childhood pneumonia, the human microbiome, treatment of multi-resistant infections, and surgical prophylaxis.
New Chinese policies promote rational use of antibiotics

A PLOS Medicine study titled, “Changes in Chinese Policies to Promote the Rational Use of Antibiotics” evaluates the success of a recent antimicrobial stewardship program in China. The Chinese campaign, motivated by the high rates of morbidity and mortality due to antimicrobial resistance in China, was designed to promote more rational use of antimicrobials in healthcare settings. The campaign, implemented by the Chinese Ministry of Health in 2011, was coupled with new healthcare reforms and established new mandatory management approaches, such as the development of audit and inspection systems, target-setting, and task force organization. According to the study, the campaign successfully decreased antibiotic sales by eight percentage points in one year and reduced prescriptions for antimicrobials for both outpatients and hospitalized patients. Despite promising results, the study highlights the need to improve antimicrobial use in other settings, including over-the-counter sales and animal husbandry.

Netherlands and Russia to collaborate on antibiotic resistance effort

In a recently announced partnership, the Netherlands and Russia are joining forces to combat antibiotic resistance. A Dutch-Russian commission will be established to examine the issue of antimicrobial resistance and the best policies for reducing its impact. The agreement between these two countries signifies that both governments acknowledge the serious nature of this growing problem and the potential public health consequences it may hold for each.

FDA releases guidelines to limit use of antibiotics in meat production

On Wednesday, December 11 the FDA released the final FDA Guidance for Industry 213 and the draft Veterinary Feed Directive (VFD). This is the first time since 1977 the FDA has taken broad action against the use of antibiotics in livestock. The two sets of guidelines are designed to encourage agriculture to voluntarily stop using sub-therapeutic growth-promoting dosing, and to involve veterinarians in the administration of antibiotics to farm animals. Although only voluntary, the FDA guidelines do demonstrate progress towards the goal of eliminating sub-therapeutic antibiotic use in food animal production. This positive step will help the US catch up with EU regulations on agriculture.

APUA played a major role in promoting this policy change by documenting the science as evidence and publishing in journals such as Clinical Microbiology Reviews. APUA’s comprehensive FAAIR (Facts About Antibiotics in Animals and their Impact on Resistance) report, published in Clinical Infectious Diseases (CID) was used as evidence and expert opinion in testimony by advocacy groups. Current legislation in Congress, the Preservation of Antibiotics for Medical Treatment Act, would go much further towards eliminating the use of medically important antibiotics for growth promotion.

Antibacterials questioned by the FDA

In the face of mounting evidence that questions the safety of antibacterials in soaps, toothpastes and a multitude of other household products, the U.S. FDA has moved to require manufacturers to demonstrate the safety and efficacy of such chemicals. The antibacterials of concern, triclosan and triclocarban, are accumulating in groundwater and soils and have been found in 75% of US urine samples and 97% of breast milk samples. Following proliferation of these agents in non-hospital-based products over previous decades, evidence has accumulated showing hormone disturbances in children (e.g., decreasing thyroid function). Furthermore, worries over escalating antibiotic resistance have fueled concerns over the possible promotion of cross-resistance to antibiotics. The proposed FDA rule will provide a 1-year period for manufacturers to demonstrate product safety and efficacy before requiring removal of the antibacterial components.
Salmonella outbreak exposes weaknesses in monitoring of US food chain

A recent news article highlights the weaknesses in the U.S. Food and Drug Administration (FDA) and U.S. Department of Agriculture (USDA)’s methods for ensuring the safety of the food supply. Beginning in October, a virulent, antibiotic-resistant Salmonella outbreak, traced to three poultry plants in California, sickened over 300 people across the U.S. Surprisingly, none of the plants in question failed salmonella testing in October because inspectors do not test chicken after processing into parts, such as drumsticks, thighs, and breasts. It is believed that the Salmonella contamination spread during this secondary processing step. Under current federal rules, no more than 7.5 percent of broilers should test positive for the bacteria, but no rules govern the quantities of salmonella that are acceptable in chicken parts. The government estimates that 24% of chicken parts are positive.

Even if inspectors had detected an alarming amount of the bacteria before the outbreak, USDA authority could only have pressured the plants to improve the processes—not force plant closure. Such federal policies are just some of many that expose Americans to the risks of food-borne illnesses that are becoming increasingly resistant to antibiotics.

Taiwan reports successes of antimicrobial stewardship program

An antimicrobial stewardship program in a Taiwan community public teaching hospital has demonstrated marked success in reducing unnecessary antibiotic use and costs. In a study published in the American Journal of Infection Control, researchers examined the effects of a three-year stewardship program on antibiotic consumption, costs, and quality of patient care in a 415-bed hospital. The three primary strategies implemented were: clinical pharmacist-based intervention, education of prudent antimicrobial use, and regular announcements of outcomes. The program lowered consumption of aminoglycosides, first-generation cephalosporins, and aminopenicillins and successfully reduced hospital antibiotic costs by 43.4% over the three-year period—from $21,464 to $12,146 per 1,000 patient-days. $2.5 million was saved in total hospital costs despite an estimated labor cost of $3,935 per month. Lastly, patients’ quality of care did not decline, as measured by length of stay, incidence of healthcare-associated infections, and mortality.

Harmony Institute endows antibiotic resistance research

In a recent press release The University of Central Florida College of Medicine and the Harmony Institute announced a partnership with the goal of creating an endowed “Harmony Scholars” chair to embark upon longitudinal studies in Harmony, Florida, a planned community specifically designed to accommodate such studies. Because of the critical nature of antibiotic resistance and the opportunity for a population study, the Harmony Institute and UCF College of Medicine are investigating antibacterial resistance as one of several beginning studies.

This project was first reported in the APUA Newsletter, Volume 31. For further information contact Martha E. Lentz, President and Founder, The Harmony Institute at mlel@harmonyinstitute.org.

CDDEP researches free antibiotics programs

Are “free antibiotic programs” doing more harm than good? Health Economics recently published a new study from the Center for Disease Dynamics, Economics and Policy (CDDEP) that gives evidence to the concerns that free antibiotic programs are contributing to unnecessary drug prescriptions and possibly to the problem of antibiotic resistance. The study, co-authored by CDDEP Director Ramanan Laxminarayan, looked at the consequences of the first free antibiotic program in the U.S., started in 2006 as an effort by the Meijer supermarket chain to improve access to valuable drugs. Researchers found that across four states, zip codes in which the program operated had 5% higher rates of antibiotic prescription than those without the program. Low-income areas, which the program would ostensibly aid the most, showed a 12% increase in antibiotic prescriptions. This study shows that such well-intentioned programs may be inadvertently contributing to over prescription and overconsumption of antibiotics in the U.S.
About us

Antibiotics are humanity’s key defense against disease-causing microbes. The growing prevalence of antibiotic resistance threatens a future where these drugs can no longer cure infections and killer epidemics run rampant. The Alliance for the Prudent Use of Antibiotics (APUA) has been the leading global non-governmental organization fighting to preserve the effectiveness of antimicrobial drugs since 1981. With affiliated chapters in more than 65 countries, including 33 in the developing world, we conduct research, education and advocacy programs to control antibiotic resistance and ensure access to effective antibiotics for current and future generations.

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

The APUA Clinical Newsletter has been published continuously three times per year since 1983.

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