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*Scanning electron micrograph of the characteristic diplococci of *Neisseria gonorrhoeae*. These type IV pilus filaments, control movement, attachment, immune escape, and natural transformation. Pili are attractive targets for vaccines and therapeutics because of their prominent cell surface exposure and role in bacterial virulence. (See news item page 21)*

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Neisseria gonorrhoeae (the gonococcus) is one of the 11 species of the genus Neisseria, which colonizes humans, and along with N. meningitidis, holds the distinction of causing human infection. As a human-specific pathogen, the gonococcus is an ancient scourge—dating back in recorded history to the early 13th century in France. Despite our antibiotic resources, the gonococcus has persisted into the current century, causing an estimated 106.1M adult cases globally per year. In the United States, it is the second most common notifiable communicable disease, causing 820,000 cases, of which 246,000 are resistant—and costing $162 million annually.

Gonorrhea is a sexually transmitted infection (STI), and in its uncomplicated form, causes urethral inflammation (urethritis) in both females and males. The infection may appear symptomatic or remain largely asymptomatic in multiple body sites (urethra, pharynx, rectum). However, if left untreated it can progress to pelvic inflammatory disease, ectopic pregnancy and infertility in women. Neonates may also acquire gonococcal conjunctivitis during passage through the birth canal. Additionally, there is strong evidence that gonococcal infections facilitate HIV infection.

N. gonorrhoeae is a prime example of a bacterial agent that was once acutely antibiotic-susceptible and fully treatable, but now makes the “post-antibiotic era” appear ominously close. A resourceful and evolutionarily adept organism, the gonococcus has successfully outwitted four classes of antibiotics over the past 70 years, beginning with the sulphonamides in the 1940s. The history of these successive failures and prevalence trends (US) are depicted in the figures presented by Shafer and Jerse (page 5) and by Kirkcaldy and Kidd (page 13). In 2011, the gonococcus was elevated to a new and alarming “superbug” status with the reporting of strain H041 in Japan, a strain that demonstrates resistance to high-level ceftriaxone and to most other antibiotics as well, leaving only untested options for treatment. Experts predict that this MDR strain could spread globally within decades. Multidrug-resistant N. gonorrhoeae is now ranked third and designated “urgent” on the CDC’s list of seven antibiotic threats—just under Clostridium difficile and carbapenem-resistant Enterobacteriaceae.

The gonococcus is highly receptive (i.e., “competent”) to the uptake of extracellular, naked DNA throughout its entire life cycle, and thus this process of transformation coupled with bacterial conjugation, play a significant role in mediating resistance—both within the same species, and to a lesser extent, between closely related species—for example N. meningitidis.
and the non-pathogenic (commensal) *Neisseria*. The varied molecular mechanisms for antibiotic resistance in the gonococcus are described in more detail in the article by Shafer and Jerse in this issue (see Table 1, page 6).

Historically, rising MICs (minimal inhibitory concentrations) are an ominous indicator of impending resistance problems and this story is repeated once again with cephalosporin resistance (Figure 1). As the prevalence of resistance to a front-line antibiotic exceeds 5%, treatment guidelines are altered to focus on more effective agents. The article by Kirkcaldy and Kidd describes the history and evolving treatment strategies for outmaneuvering the gonococcus. As recommended by the CDC, treatment options in the US are now limited to the third-generation cephalosporins. While no treatment failures to the third-generation agent cefixime have been reported in the US, a recent study in Canada has found a 7% failure rate using the standard dose. Aside from the development of new antibiotics, the best way to block further development of resistance is to treat with two or more families of drugs simultaneously—a tactic which has been employed successfully for TB treatment and now forms the basis for the newly revised CDC guidelines for gonorrhea (Figure 2). A long sought-after vaccine solution to end the scourge of gonorrhea has so far remained elusive.

The history, difficulties and prospects for a vaccine solution to the gonorrhea problem are described in detail in the article by Rice (page 16).

The gonococcus is a fastidious organism and is traditionally detected using culture-based diagnostics. Phenotypic typing methods are employed to determine antimicrobial susceptibility, resulting in a 24-48 hour time requirement for diagnosis and drug susceptibility. The expertise required and the delays in diagnosis impede rapid treatment, which allows further spread and exacerbates the drug resistance problem. As described in the case study by Dillon and Lewis (page 9), rapid diagnostics—in particular, nucleic acid amplifications tests (NAATS)—are increasing in popularity due to their speed and sensitivity, especially in asymptomatic body sites. However, these tests cannot yet provide susceptibility results, which are deemed essential for surveillance efforts and for monitoring resolution of treatment failures. Paradoxically, susceptibility testing of gonococcal isolates has declined in high-income countries where these molecular methods have been adopted.7

Shafer and Jerse provide a comprehensive, 8-point action plan (Table 2, page 7) for halting the imminent threat of untreatable gonorrhea. While an immediate priority is to replenish the drug pipeline, there is also an urgent need to enhance molecular diagnostics to include expanded testing for a wide spectrum of antimicrobials. As emphasized by Dr. Anthony Fauci, Director, NAIAD, “A point-of-care drug susceptibility test would help providers know—at the time of diagnosis—which treatment regimen will be most effective. Progress toward a vaccine is urgently needed.”8

References (cont. page 8)

Mechanisms and implications of gonococcal antibiotic resistance in the 21st century

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Sounding the Alarm

“It is time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense, threatening our ability to cure gonorrhea and prevent severe sequelae.” This recent sobering message from Bolan et al.1 succinctly warned of the impending public health crisis due to the emergence of Neisseria gonorrhoeae (GC) strains with decreased susceptibility to the extended spectrum cephalosporins (ESCs), cefixime (CEF) and ceftriaxone (CTX). Remarkably, forty years earlier, one of the co-authors (P.F. Sparling) recognized the potential problem of antibiotic resistance expressed by GC,2 which is testimony to his prescience. Given the >100 million cases of gonorrhea worldwide each year (2011 WHO estimate),3 the public health implications of untreatable gonorrhea are worrisome and represent an immediate challenge that demands a coordinated international response.

GC as a “Super Bug”

In 2007 the Centers for Disease Control and Prevention (CDC) placed GC on the infamous “Super Bug” list due to high prevalence (>5%) of strains in the USA resistant to penicillin (PEN), tetracycline (TET) or fluoroquinolones (FQs).4 In many underdeveloped countries, particularly in Asia,7,8 the problem of antibiotic-resistant GC is more acute with Pen-, Tet- or FQ-resistant strains predominating. The emergence of strains in the US exhibiting decreased susceptibility to CEF, particularly in men who have sex with men (MSM) or isolates from the west coast, also observed with FQ-resistant GC,5 resulted in a change in the treatment guidelines such that this oral antibiotic

Figure 1. Timeline of gonorrhea antibiotic therapies and loss of antibiotics due to resistance

<table>
<thead>
<tr>
<th>Sulphonamides</th>
<th>Tetracycline</th>
<th>Cephalosporins</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
</table>

Source: Adapted from Unemo M & Shafer W, (2011) Ann NY Acad Sci. pE21

Shown above the timeline are dates (arrows) when certain antibiotics (color-coded) were introduced for treatment of gonorrhea. Dates below the line indicate when they were removed from recommended treatment guidelines due to resistance (blocked lines) or when the first cephalosporin resistant Gc was identified in 2009 (solid vertical line). Additional antibiotic treatment regimens consisting of chloramphenicol, streptomycin, or azithromycin were also used previously (reviewed in reference 8).
Evolution, Spread and Mechanisms of Antibiotic Resistance

The emergence of drug resistant GC began in the late 1930s with the use of sulfonamides (Figure 1), which was only briefly effective for treatment of gonorrhea. This was a predictor of the future because GC resistance to newly introduced antibiotics continued, albeit less rapidly, over the next seventy years (Figure 1). While initially sensitive to new antibiotics, some GC strains develop single or multi-step mechanisms of resistance and then spread the determinants to other GC by genetic exchange. Resistant GC often have their origin in Asia and first appear in the USA in Hawaii and western states.\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Mechanism</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamides</td>
<td>Mutations in folP</td>
<td>Reduction in target affinity to the sulfonamide target dihydropteroate synthase</td>
</tr>
<tr>
<td>Penicillin G or Ampicillin</td>
<td>Plasmid-encoded beta-lactamase</td>
<td>Breakage of beta-lactam ring: high-level resistance</td>
</tr>
<tr>
<td></td>
<td>5 genetic alterations and 1 undefined &quot;Factor X&quot;</td>
<td>Reduced drug uptake, increased efflux, decreased acylation of PBP2 and PBP1 - resulting in lower-level, but clinically relevant resistance</td>
</tr>
<tr>
<td>Ceftriaxone/Cefixime</td>
<td>Acquisition of a mosaic penA allele from commensal Neisseria</td>
<td>Extensively remodeled PBP2</td>
</tr>
<tr>
<td></td>
<td>Promoter mutations impacting mtrR and/or mtrCDE expression</td>
<td>Increased levels of the MtrC-MtrD-MtrE efflux pump</td>
</tr>
<tr>
<td>Tetracycline or Doxycycline</td>
<td>tetM resistance gene (present on conjugal plasmid)</td>
<td>Blocked binding of drug: high-level resistance; high level resistance</td>
</tr>
<tr>
<td></td>
<td>Protection of 30S ribosomal subunit</td>
<td>Increased expression of MtrC-MtrD-MtrE efflux pump, decreased entry and decreased binding to ribosomal protein target; and low level resistance</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Missense mutations in:</td>
<td>Decreased drug binding to DNA gyrase and Topoisomerase IV: high-level resistance; both needed for high-level resistance</td>
</tr>
<tr>
<td></td>
<td>a) gyrA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) parC</td>
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</table>

Antibiotic resistance expressed by GC arises from gene acquisition and/or mutation (summarized in Table 1 for antibiotics shown in Figure 1). As an example of how GC develops antibiotic resistance, it is now clear that two genetic events are required for resistance to the ESCs, CEF and CTX. Thus, susceptible strains acquire a penA allele from commensal Neisseria spp., which encodes the essential peptidoglycan transpeptidase termed penicillin-binding protein (PBP) 2. The extensively remodeled PBP2 encoded by the imported penA allele is poorly acylated by beta-lactam antibiotics (including ESCs) and can differ from the wild-type protein by > 60 amino acids.\(^8\)\(^,\)\(^9\) It now appears that for clinical and microbiologic levels of such resistance, GC must also develop a cis-acting mutation in promoter sequences that results in over-expression of genes encoding a multidrug efflux pump termed MtrC-MtrD-MtrE (Golparian et al., unpublished). This efflux pump is essential for
GC PEN-resistance\textsuperscript{10} and GC survival during experimental infection of female mice.\textsuperscript{11} Moreover, mutations that increase pump levels also enhance GC fitness in the murine infection model\textsuperscript{12} and were present before introduction of ESCs for gonorrhea treatment;\textsuperscript{8} these mutants are frequently found in isolates from MSM.\textsuperscript{13}

What can we anticipate in the future? We should expect the appearance of extended spectrum beta-lactamases (ESBLs) produced by GC. ESBLs may evolve from existing beta-lactamase-encoding genes or GC may acquire such genes as they did earlier for beta-lactamase plasmids.\textsuperscript{14} We should also be vigilant for strains with compensatory mutations that enhance fitness of GC bearing resistance determinants as they may have a competitive advantage in the community. Thus, recent work on FQ-resistant GC showed that while resistance imposes a fitness defect in vivo this can be mitigated by compensatory mutations that develop during experimental infection.\textsuperscript{15} We should also expect continued emergence of AZI-resistant GC, which will impact the current therapy regimen. Finally, history informs us that resistance will develop to new drugs brought into clinical practice (Figure 1).

Can knowledge regarding resistance systems be exploited in drug development efforts? The short answer is a hopeful yes. For instance, the MtrC-MtrD-MtrE efflux pump seems to be critical survival of gonococci in vivo, due to export of host-derived antimicrobials.\textsuperscript{8,12} Hence, efforts to develop safe efflux pump inhibitors should continue as they may have the benefit of augmenting host defenses and could allow restoration of PEN for treatment of gonorrhea. A second example is that by understanding how resistance to FQs developed, it has been possible for Melinta Therapeutics to develop a promising new drug (delafloxacin) now in Phase III clinical trials that recognizes the same target (DNA gyrase) as ciprofloxacin, but seems to be refractory to mutations that result in GC resistance to ciprofloxacin.\textsuperscript{16} In addition, the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, offers services to assist investigators in the design and testing of new antimicrobials.\textsuperscript{17} These services have supported promising candidates for the treatment of GC, some of which are now in the product development pipeline.

**An Action Plan is Needed**

In the absence of a vaccine, antibiotic usage is the most effective way for both curing the afflicted and halting local spread of GC. Failure to cure can result in severe complications in the reproductive tract (especially for women) and other organs. Importantly, repeated GC infections increase HIV acquisition of and transmission by individuals.\textsuperscript{17} Hence, GC antibiotic resistance may hinder efforts to combat the HIV/AIDS epidemic. Table 2 summarizes action points to combat antibiotic resistant GC. Time is of the essence if an era of untreatable cases of gonorrhea is to be avoided.

<table>
<thead>
<tr>
<th>Table 2. Proposed international action plan to combat antibiotic-resistant GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Continued and increased federal and commercial/private funding for drug development and vaccine efforts.</td>
</tr>
<tr>
<td>➢ Continued evaluation of new treatment regimens that involve existing antibiotics recently examined in clinical trials (dual use of an aminoglycoside and a macrolide).</td>
</tr>
<tr>
<td>➢ Increased funding for development of rapid point-of-care molecular diagnostic techniques (e.g., PCR/DNA sequencing and MALDI-TOF mass spectrometry) to identify resistance determinants so as to better guide antibiotic usage and making these techniques available in under-developed countries especially where resistance is high.</td>
</tr>
<tr>
<td>➢ Increased and sustained funding for basic research on mechanisms of resistance to augment efforts in drug development and molecular diagnostics.</td>
</tr>
<tr>
<td>➢ Making effective antibiotics readily and cheaply available in poor countries where resistance often develops.</td>
</tr>
<tr>
<td>➢ Increased efforts in promoting antibiotic stewardship, especially in developing countries where antibiotic usage may be poorly regulated or supervised.</td>
</tr>
<tr>
<td>➢ Increased surveillance efforts to identify emergence of resistant strains in communities which may guide local empiric antibiotic treatment options.</td>
</tr>
<tr>
<td>➢ Increased efforts in training clinical microbiology staff in detecting antibiotic resistant GC using conventional culturing and newly developed molecular diagnostics.</td>
</tr>
</tbody>
</table>
References


Case Study: Diagnosis and treatment of antibiotic resistant Neisseria gonorrhoeae

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PS is a 45-year-old unmarried male who presented to a sexually transmitted infection (STI) clinic at his local hospital. His interview indicated a history of persistent urethral discharge with dysuria over a period of three weeks. He indicated that he had been treated on two occasions during the past three weeks without a clinical response, once with single-dose oral ciprofloxacin and once with single dose oral cefixime at private clinics near his home. He was uncertain about the status of microbiological testing but indicated that urethral cultures had been taken. He did not return to the private clinics for test of cure or follow-up. He indicated that he did not have a steady partner but acknowledged multiple sexual contacts with male partners in the past year. Within the past three months, he reported engaging in unprotected receptive and insertive oral intercourse including oro-anal contact, as well as protected receptive, but unprotected insertive anal intercourse. He stated that he had no sexual contact after his second treatment with cefixime. He had no sexual contacts with females. The client used recreational drugs periodically and alcohol. He had travelled extensively throughout South East Asia recently.

Pharyngeal, rectal and urethral specimens were taken for culture-based identification of the pathogen. In addition, a request was made for Gram staining of the urethral and rectal exudate to be performed prior to culture plate inoculation as well as antimicrobial susceptibility testing (AST) if Neisseria gonorrhoeae was cultured. The client agreed to provide first-pass urine, rectal and oro-pharyngeal specimens for a N. gonorrhoeae and Chlamydia trachomatis nucleic acid amplification test (NAAT), as well as blood for HIV, syphilis and hepatitis B serological testing. While dual antibiotic therapy is the current model for treatment in many countries, given the client’s history of possible treatment failure with cefixime and his clinical risk assessment, PS was treated with azithromycin alone (2 gm, single oral dose) and asked to return to the clinic after one week for a test of cure. In addition, he was asked to inform as many of his partners from the previous three months as possible about his STI and to encourage his partners to seek treatment as sexual contacts.

Vital signs normal:
- Blood pressure: 110/70,
- Heart rate: 72 bpm,
- Respiratory rate: 15 bpm,
- Tmax: 37.2°C

Physical exam:
- Respiratory, cardiovascular, abdominal, musculoskeletal and dermatological exams within normal limits
- Genital exam revealed a reddened urethral meatus with a purulent discharge
- Normal scrotal examination
- No inguinal/generalized lymphoadenopathy
- Normal ano-rectal and oro-pharyngeal examination

Through an unrestricted educational grant, the Alliance for the Prudent Use of Antibiotics (APUA) has developed a series of non-commercial health provider educational materials for the Test Target Treat™ antimicrobial stewardship initiative. Test Target Treat is an antibiotic stewardship initiative providing health practitioners with expert guidance on drug resistance trends. These materials discuss resistance, stewardship and the role rapid diagnostics play as part of the solution.

This case study was produced by the Alliance for the Prudent Use of Antibiotics (APUA) for the Test Target Treat initiative through an unrestricted educational grant from Alere, Inc.
Labs/Blood Tests:
- CBC: normal
- HIV: anti-HIV antibody - negative
- Hepatitis B: Hepatitis B surface antigen - negative
- Syphilis: rapid plasma reagin and Treponema pallidum particle agglutination assays* — negative

Microbiology:
- Gram stain: Intracellular gram-negative diplococci and >20 pus cells per high power field in the urethral smear; no abnormalities were detected in the rectal smear
- Urethral culture and identification: N. gonorrhoeae. AST profile: Resistant to penicillin (Minimum Inhibitory Concentration (MIC) 4.0 µg/ml; non β-lactamase producing); resistant to tetracycline (MIC ≥ 16.0 µg/ml); resistant to cefixime (MIC 0.25 µg/ml); resistant to ciprofloxacin (MIC 16.0 µg/ml); susceptible to azithromycin (MIC 0.25 µg/ml); susceptible to ceftriaxone (MIC 0.064 µg/ml).
- Pharyngeal rectal cultures: no growth
- NAATs: Pharyngeal: Positive N. gonorrhoeae; Rectal: positive N. gonorrhoeae; Urine: Positive N. gonorrhoeae
- Molecular typing: Reported one month later, N. gonorrhoeae isolate belonged to NG-MAST (N. gonorrhoeae multi-antigen sequence typing) strain type 1407.

Discussion

Several issues are relevant in consideration of this client and the treatment of his infection. Men who have sex with men (MSM), especially those of older age with a history of travel abroad, are at high risk for the acquisition and transmission of antibiotic-resistant N. gonorrhoeae. In addition, the client also indicated several other high risk behaviors associated with increased risk of STI acquisition, i.e. multiple potentially high risk partners coupled with a history of recreational drug and alcohol use. Although the NG-MAST results are usually reported retrospectively because rapid molecular testing for strain type is not available, the NG-MAST strain type (1407) of the client’s N. gonorrhoeae isolate is one which has been linked with the international spread of antibiotic resistant N. gonorrhoeae, particularly isolates with reduced susceptibility or resistance to cefixime. Such isolates have also been reported to be simultaneously resistant to ciprofloxacin and some may carry plasmid-mediated resistance to tetracycline, i.e. TRNG – tetracycline resistant N. gonorrhoeae (the isolate from PS is a putative TRNG because its MIC is ≥16.0µg/ml). This antimicrobial susceptibility phenotype and NG-MAST strain type should alert the clinician or public health officials to the possible spread of this clone within the region. It calls for an antimicrobial alert and further suspected treatment failures with cefixime should be followed up with a test-of-cure and contacts of the index case should be followed.8

MSM often have asymptomatic anal or pharyngeal infections with N. gonorrhoeae. Although culture for N. gonorrhoeae at pharyngeal and rectal sites may often be negative, recent reports indicate that such specimens may be positive upon nucleic acid amplification testing (NAAT).9,11 In many resource challenged settings neither test format is performed and diagnosis of gonorrhea and its empiric treatment may depend upon the syndromic management approach. Thus there is the potential to under-diagnose infections at body sites which may be asymptomatic. Pharyngeal isolates of N. gonorrhoeae are notoriously resistant to treatment, mostly because antibiotics may not reach this site at a sufficient dose.12,13 Further, isolates carried in the oro-pharynx may exchange DNA with commensal Neisseria species. It has been shown that DNA from these species contributes to cefixime resistance by DNA exchange such that the gonococcal penA gene, implicated in resistance to cefixime, is a mosaic of DNA from several species.14,15

Many international jurisdictions change their treatment guidelines regularly in response to the threat of potentially untreatable gonorrhea. These changes are generally informed by on-going or periodic gonococcal antimicrobial susceptibility programs (GASP).8,16 Since the introduction of sulphonamides in the 1930s, the gonococcus has developed resistance to each class of antibiotic introduced for treatment.17 Guidelines generally recommend single-dose therapies as primary treatment to ensure a cure and compliance with the antibiotic regimen. The N. gonorrhoeae isolate from client PS was resistant to all antibiotics except ceftriaxone and azithromycin. Treatment failures with cefixime have been reported in many countries and have been correlated with decreased susceptibility or resistance to this antibiotic. It is not unusual for isolates resistant to cefixime to be susceptible to ceftriaxone. However, ceftriaxone-resistant isolates associated with treatment failures have also been reported in a number of countries.17 In the United States and elsewhere, in response to the emerging threat of resistance to third-generation cephalosporins, treatment regimens include increased dosages of ceftriaxone in combination with other antibiotics.16 These include 250/500 mg of ceftriaxone as a single intramuscular dose, plus either 1 g of azithromycin as a single dose, or 100 mg doxycycline orally twice daily for 7 days. Alternative options for urogenital or
rectal gonorrhea include cefixime 400 mg as a single oral dose and either azithromycin (1 g as a single dose) or doxycycline (100 mg bid for 7 days); or, if the client is allergic to cephalosporin, azithromycin (2 g) as a single oral dose. Although efficacy data are relatively few for single-dose intramuscular gentamicin (240 mg) as therapy for cefixime-resistant \( N. \) gonorrhoeae infections, it may also be a useful agent in combination with azithromycin. 18

In many countries, ciprofloxacin may still remain the antibiotic recommended for treatment of gonorrhea. 19 This may reflect an inability to perform on-going gonococcal antimicrobial susceptibility surveillance that would inform the development of up-to-date, effective treatment guidelines. Regions still using ciprofloxacin as primary therapy face a double threat—the use of antibiotics to which the gonococcus is resistant and a lack of up-to-date antimicrobial surveillance information regarding which antibiotics may be effective. Interestingly, however, some regions retain a high percentage of isolates that are susceptible to antibiotics such as ciprofloxacin. 20 Treatment guidelines would preclude its use as primary therapy for gonococcal infections given that national treatment guidelines are generally based on aggregated data from multiple regions within a country masking regional trends. In the case of patient PS, a rapid test to determine antimicrobial susceptibility status would have been most advantageous.

Although leukocyte esterase dipsticks or immuno-chromatographic devices that detect specific gonococcal antigens have been used as a point-of-care test (POCT) for \( N. \) gonorrhoeae, it is recognized that there is a need to improve the performance and format of POCTs for diagnosis of gonorrhea. 21 Currently available POCTs are usually not recommended for the diagnosis of gonococcal infections because of their low sensitivity and specificity. 15 There are no POCTs at present to detect antimicrobial susceptibility to direct an effective treatment at the time of diagnosis. More expensive molecular NAATs are regularly used for diagnosis in resource-advantaged settings and they have been shown to be highly sensitive and specific. Moreover, in a comparison of NAAT testing with standard off-site lab testing for gonorrhea and chlamydia diagnosis, a simulated model using 1.2 million cases demonstrated a baseline cost savings of 10% (£11.7 million) using NAAT. Same-day testing and treatment could avoid 95,000 inappropriate treatments and the point-of-care model projected the prevention of nearly 200 cases of pelvic inflammatory disease and ~17,500 cases of onward transmission annually. 22

At present, organism culture is still required for AST, and therefore, the use of a rapid molecular diagnostic, including NAATs, will often eliminate the possibility of receiving simultaneous identification and susceptibility results in a single report. The development of rapid, inexpensive, accurate, sensitive and specific test formats, useful at the client point-of-care, both for the diagnosis of \( N. \) gonorrhoeae and its antimicrobial susceptibility has become a pressing priority.

*While many laboratories still use one of the non-treponemal tests for screening (i.e., RPR or VDRL), some are moving toward the current European model—the highly sensitive and specific, automated chemiluminescence immunoassay (CLIA), which is both simple to perform and cost-saving.

**References:**


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**Empowering appropriate antimicrobial use with rapid diagnostics**

Test Target Treat, the antimicrobial stewardship initiative from Alere, empowers healthcare professionals to make targeted treatment decisions sooner with rapid diagnostics—reducing antimicrobial misuse and the spread of resistance. Alere has a wide range of rapid tests for infectious diseases, including influenza, RSV, Strep A, \( C. \) difficile and MRSA, which can all aid quick and accurate clinical treatment decisions.

Discover more about Test Target Treat and the APUA educational collaboration at [TestTargetTreat.com](http://TestTargetTreat.com) where you can find additional case studies, webinars, stewardship perspectives and much more.


Prompt detection and effective antimicrobial therapy are the foundations of public health control of gonorrhea and prevention of reproductive complications from gonorrhea. However, antimicrobial treatment of gonorrhea has been complicated by the remarkable ability of Neisseria gonorrhoeae to acquire resistance. The organism has developed resistance to each antimicrobial that has been used for treatment and has managed to retain these resistance phenotypes (Figure 1). In a pattern observed with penicillinase-producing and, two decades later, fluoroquinolone-resistant strains, gonococcal resistance has often been detected first in East Asia or among patients with recent travel links to East Asia, and then has spread globally.1 Following the emergence of fluoroquinolone-resistant N. gonorrhoeae in the United States during the 2000s, cephalosporins (cefixime [oral] and ceftriaxone [injectable]) were the only remaining antimicrobials recommended by the US Centers for Disease Control and Prevention (CDC) as first-line treatment for gonorrhea.2 By that time, however, gonococcal cephalosporin minimum inhibitory concentrations (MICs) were already increasing in East Asia and several reports from the region described unsuccessful gonorrhea treatment with oral cephalosporins.1 More recently, unsuccessful treatment with oral cephalosporins has been identified in Europe and North America (Canada), and isolates with high ceftriaxone MICs were detected in Japan and Europe.3-6 In the US, surveillance data from CDC’s Gonococcal Isolate Surveillance Project demonstrated that cefixime MICs increased between 2006 and 2011 (Figure 2).7 In an epidemiological pattern reminiscent of the initial emergence of fluoroquinolone resistance in the US, cefixime MICs increased sharply in Hawaii and the western US, and among men who have sex with men. Cephalosporin treatment failures have not been identified in the US. The CDC currently recommends that pharyngeal, urogenital or rectal gonorrhea in the US be treated with combination therapy: ceftriaxone 250 mg as a single intramuscular dose and either azithromycin 1 g orally or doxycycline 100 mg orally twice daily for a week.7 Because of the high prevalence of tetracycline resistance (20-25% in recent years), azithromycin is preferred.

Following recent changes to treatment recommendations in the UK and US, cefixime MICs declined in the UK and may be declining the US.8,9 However, we cannot afford to become complacent. We are on our last first-line treatment option and given the history of N. gonorrhoeae, it is likely just a matter of time before cephalosporin resistance emerges. It is critical that clinicians, public health officials, policy makers, and drug developers prepare for the emergence of cephalosporin-resistant and multidrug-resistant gonorrhea by ensuring adequate treatment of patients with gonorrhea and their partners, detecting and
effectively treating resistant infections, supporting surveillance and public health control, and supporting antimicrobial development.

For clinicians to effectively treat multidrug-resistant gonococcal infections, they must first identify such infections. In the case of gonorrhea, antimicrobial susceptibility testing (AST) is not widely available to clinicians in the US. This is due in large part to the decline in use of culture (which is necessary for AST) for diagnostic testing and expanded use of nucleic acid amplification tests (NAATs). Although NAATs have excellent sensitivity and specificity and allow for non-invasive or patient-collected samples, NAATs do not allow AST to be performed. Although reliable molecular tests for resistance hold potential for supporting treatment and surveillance in the future, the current PCR-based tests for gonococcal resistance that are commercially available in the US rely on incomplete knowledge of molecular determinants of resistance (especially for the currently recommended antimicrobials) and the tests have not been validated against “gold standard” phenotypic susceptibility testing. Clinicians should interpret results of such tests with caution. In the absence of AST, clinicians often must rely on identification of persistent infection despite treatment. CDC’s Cephalosporin-resistant Neisseria gonorrhoeae response plan outlines proposed criteria that clinicians and public health officials can use to classify suspected (Figure 3) and potentially resistant infections. If a clinician suspects that a gonococcal infection may be resistant to recommended therapy, he/she should obtain a careful sexual history, with attention to whether the patient had sex without a condom since the patient was treated. Tips on taking a sexual history can be found on CDC’s website. Specimens from all exposed anatomic sites should be collected for culture and phenotypic AST (i.e. disc diffusion, Etest®, or agar dilution); however, interpretive criteria for ceftriaxone, cefixime, and azithromycin resistance have not yet been established by the Clinical and Laboratory Standards Institute. Because suspected treatment failures may be due to re-infections, CDC recommends re-treating with ceftriaxone 250 mg as a single intramuscular dose and 2 grams of oral azithromycin. The patient should abstain from sex and return in 7–10 days for repeat testing with culture (preferred) or NAAT to ensure cure. Recent sexual partners should be evaluated and treated.

What if the infection persists after recommended treatment with ceftriaxone and azithromycin? First, clinicians should promptly notify their local or state health department STD program and ask that the STD program quickly notify CDC’s Division of STD Prevention. AST, if available, can guide therapy. A recently completed clinical trial provides clinicians with potential treatment options for empiric therapy. In a multisite trial conducted by CDC and the National Institute for

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**Figure 2: Proportion of urethral Neisseria gonorrhoeae isolates with elevated cefixime MICs (≥ 0.25 µg/ml)**

![Figure 2](image_url)

Source: CDC Gonococcal Isolate Surveillance Project (GISP), US: 2000–2011

**Figure 3. Clinical criteria for suspect case of cephalosporin-resistant N. gonorrhoeae**

The patient experienced possible cephalosporin treatment failure with the following specific components:

- Patient had laboratory-confirmed N. gonorrhoeae infection
- Patient received CDC-recommended cephalosporin-based antimicrobial regimen as treatment
- Patient subsequently had a positive N. gonorrhoeae test result (positive culture ≥72 hours after treatment or positive NAAT (≥7-10 days after treatment)
- Patient did not engage in sexual activity after treatment (was not re-exposed)

Allergy and Infectious Diseases at NIH, patients with uncomplicated urogenital gonorrhea were randomized to either (1) gemifloxacin 320 mg orally and 2 grams of oral azithromycin, or (2) gentamicin 240 mg intramuscularly and 2 grams of oral azithromycin. The primary outcome was microbiological cure (negative culture) at 10–17 days. All but one of the 199 (99.5%) patients treated with gemifloxacin/azithromycin were cured and 100% of the 202 patients treated with gentamicin/azithromycin were cured. Mild-moderate gastrointestinal side effects, including vomiting, were common in both arms. Looking down the road, two promising new compounds have demonstrated in vitro activity against *N. gonorrhoeae* and are in different stages of clinical testing. Solithromycin demonstrates robust in vitro activity and cured 41/41 patients with uncomplicated gonorrhea. Delafloxacin also demonstrates robust in vitro activity, including against ciprofloxacin-resistant strains. Clinical testing is planned. Despite these developments, we still have only a single first-line regimen and antimicrobial resistant *N. gonorrhoeae* remains an urgent and growing public health threat. New drugs are urgently needed.

**References**


10. Kirkcaldy RD. Treatment of gonorrhea is an era of emerging cephalosporin resistance and results of a randomised trial of new potential treatment options. STD & AIDS World Congress 2013; Vienna, Austria, July 14-17.


**Recommended CDC Resources**


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**Call for papers for special issue on “Antibiotic Resistance of Bacteria”**

An upcoming (December 2014) special issue of BioMed Research International in Microbiology and Antibiotic Resistance of Bacteria is open to the submission of original research articles and review articles. Deadline for submission in July 18, 2014. You can find the call for papers for this Special Issue [here](#).
Introduction

The widespread emergence of resistance to currently used antimicrobials, ceftriaxone in particular, and the potential for spread of resistant gonococci threaten to herald an era of untreatable disease, worldwide.\(^1\) There is an urgent need to develop novel vaccines against \textit{Neisseria gonorrohoeae}. However, development of effective vaccines against gonococcal infection is challenging because the correlates of immune protection are not fully known.\(^2\) Furthermore, gonococcal surface molecules that may be appropriate targets often are antigenically variable. Unfortunately, adaptive immune responses to highly conserved gonococcal antigens that result from infection have not been shown to elicit protection against future infections; in fact repeat infections are common because of continuing behavioral risk factors but also perhaps because prior infection may enhance susceptibility.\(^3,4\) Levels of genital and serum antibodies, taken as a whole, in men and women with uncomplicated gonococcal urethritis and cervicitis are modest and it is unclear how responses targeted to specific antigens influence future susceptibility.

A proposed human vaccine model

A proposed predictor of protection against gonococcal infection, and therefore a surrogate for vaccine efficacy, has been an increased level of complement (C)—dependent bactericidal antibody activity directed at \textit{N. gonorrhoeae}. Bactericidal antibodies, in addition to killing gonococci directly, promote binding to and ingestion by phagocytes via Fc and complement receptors (CRs), which may dispose of infecting organisms.\(^5,6\) However, numerous variables contribute to the efficacy of bactericidal antibodies. In the context of natural infection, for example, the major antigenic targets of bactericidal antibodies are porin (Por) and lipooligosaccharide (LOS) components of the gonococcal outer membrane, which themselves may vary antigenically and in their ability to induce bactericidal antibodies during infection. In addition, effective bactericidal function of antibodies directed against these antigens is regulated (downward) by the presence of other antibodies—so-called blocking antibodies—directed against reduction-modifiable protein (Rmp),\(^3\) which is conserved across gonococcal strains.\(^7,8\) Bactericidal antibody function is further regulated by soluble C regulators that include at a minimum, C4b binding protein (C4BP), the major regulator of the classical pathway of complement and factor H (FH), the counterpart alternative pathway regulator; both selectively bind to specific forms of Por.\(^9,10\) \textit{N. gonorrhoeae} whose LOS molecules are sialylated also bind FH.\(^11\) Together, regulatory events appear to make bactericidal antibody activity a variable parameter; however, regulation of low levels of antibodies that occur in natural infection can be overcome by higher levels of bactericidal antibodies, a condition that rarely occurs in natural infection, but which may be achievable with an appropriate vaccination strategy.

Vaccines that induce bactericidal antibody activity

A number of gonococcal surface components that elicit bactericidal antibodies have been identified and are being pursued as vaccine candidates. Some of these targets do not promote bactericidal antibody activity in natural infection, and based on this parameter, were not predicted as potential candidates from immune responses occurring during infection; they represent examples where “nurture trumps nature” because an immune response can be forced under conditions of vaccination that are not seen in natural infection. In addition, immune responses to several of the antigens may target and interfere with import physiologic functions that further compromise survival of \textit{N. gonorrhoeae}. These include: interfering with colonization and nutrient acquisition and, separately, the promotion of immune evasion. The discussion herein will focus on antigens that are known to elicit bactericidal antibody activity, in some cases directed against the related species, \textit{N. meningitidis}. This function is elicited by several successful meningococcal vaccines and can be coupled with other immune responses directed against critical functions. Vaccine candidates that target function but are not known to elicit bactericidal antibody activity are discussed in two recent reviews.\(^12,13\)

Common antigenic targets (Table 1)

\textit{Colonization:} Interfering with adherence to, or uptake by host cells constitutes an ancillary approach to gonococcal vaccine design. Surface molecules such as PilQ, the secretin through which pili are extruded,\(^14\) serve this function. The conserved C-
terminal portion (364 aa) of PilQ also elicits murine bactericidal antibodies against *N. meningitidis*.\(^9\)

Eight to ten antigenically distinct (phase variable) Opa (Opacity associated) proteins exist per strain of *N. gonorrhoeae*. Variable, but not semi-conserved or highly conserved peptide antigens derived from Opa, elicit bactericidal antibodies.\(^16-18\) Opa antibodies also interfere with binding of bacteria to eukaryotic cells.\(^19\)

OpcA is an integral outer membrane adhesion protein that binds to sialic acid (SA)-containing polysaccharides\(^20\) on the surface of epithelial cells and elicits bactericidal antibodies against *N. meningitidis*.\(^21\)

Gonococcal porin (PorB) is also involved in adherence and invasion of host cells.\(^22,23\) Use of the conserved domains within the surface-exposed portions of PorB loops to elicit an immune response that interferes with Por function and also elicit bactericidal antibodies could lead to the development of a broadly cross-reactive vaccine candidate.\(^24\)

**Nutrient acquisition:** Targeting nutrient acquisition constitutes a separate ancillary approach to gonococcal vaccine development. Gonococcal transferrin receptor (TbpA and TbpB) or lactoferrin receptor (Lf) is required for (male) experimental urethral infection.\(^25\) TbpA and TbpB work together to extract and import iron across gonococcal outer membranes. When fused to cholera toxin subunit B, TbpA and TbpB proteins induce high titer, specific vaginal IgG and IgA antibodies, serum bactericidal antibody activity and antibodies that also inhibit growth of *N. gonorrhoeae* in media containing Tf as the sole source of iron.\(^26\)

Half of *N. gonorrhoeae* strains express an Lf receptor. The semiconserved LbpA subunit of the meningococcal Lf receptor induces bactericidal antibody activity, but it has limited cross-reactivity.\(^27\)

ZnUD, a Ton-dependent function transporter (Tdf) facilitates zinc acquisition in *N. meningitidis* and is regulated by the putative zinc-dependent regulator, Zur. Expression of ZnUD in *N. meningitidis* does not require iron regulation. Antiserum to the meningococcal homologue ZnUD is bactericidal.\(^28\) Similar studies have not been reported for gonococcal TdfL, so the function of this protein and its contribution to growth of *N. gonorrhoeae* are not yet known.\(^29\)

**Immune evasion:** PorB binds C down regulators, C4BP and FH through the variable surface-expressed loops and evades the bactericidal action of normal human serum (termed serum-resistance).\(^9,10\) Organisms whose LOS molecules are sialylated bind FH.\(^11\) Serum-resistance can be overcome and *N. gonorrhoeae* killed by immune anti-Por antibodies.\(^30\) NspA (Neisserial surface protein) binds FH and contributes to serum-resistance of *N. gonorrhoeae*;\(^31\) murine anti-gonococcal NspA is bactericidal.\(^32\)

**Vaccine efficacy in humans**

Only two vaccines have entered full-fledged clinical trials in humans. The first was a crude whole cell vaccine used in a population of Inuits in northern Canada.\(^33\) The second, a single-antigen pilus (Pil) vaccine was used in a large-scale field trial conducted in high-risk US military personnel stationed in Korea\(^34\)— neither showed efficacy.

In the most recent American trial that took place in 1985,\(^35\) a placebo/control, human challenge trial was performed. Sixty-three male volunteers either were immunized with a vaccine prepared from the outer membranes of a single strain of *N. gonorrhoeae*, or were given a placebo. Men were challenged intraurethrally with viable organisms 2-4 weeks after completing the vaccination course. No significant difference in infection after challenge was observed in the two groups, but resistance to infection was high: 46% of vaccinees and 36% of placebo recipients resisted infection. The goal for the outer membrane derived vaccine preparation was enrichment for the Por protein. The proposed mechanism of protection, had it occurred, was to elicit bactericidal (and perhaps opsonophagocytic) antibodies against Por\(^30\) in the urethra. Methods for preparing pure Por were not totally reliable at the time, and preparations were contaminated with other outer membrane constituents, particularly LOS and Rmp, which together with Por, also stimulated antibody responses. Not completely appreciated in 1985, were the complex interactions of antibodies directed against these antigens that resulted in a net effect upon complement-dependent bactericidal activity.

A graded risk of acquiring gonorrhea in both vaccine and placebo recipients was not considered prospectively in choosing the cohorts, because at that time, natural protective immunity against gonorrhea, while in some cases recognized,\(^36-39\) was not defined in specific enough terms that would have permitted immunologic stratification of volunteers into different categories. In a “look back” at that vaccine trial, volunteers were retrospectively stratified for immunologic risk, and the question asked whether susceptibility to infection after intraurethral inoculation was influenced by the vaccine. The ratio of the concentration of Por and LOS antibodies, summed, to Rmp antibody concentration was positively correlated with protection both in vaccine and placebo recipients, but none of these antibody levels alone correlated with protection against challenge. Furthermore, changes in bactericidal activity, both
### Table 1: Neisseria gonorrhoeae Vaccine Candidates

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Function</th>
<th>Expression</th>
<th>Variability</th>
<th>Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colonization and Invasion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PiQ</td>
<td>Outer membrane channel for pilus extrusion</td>
<td>Stable</td>
<td>Conserved at C-terminus</td>
<td>Abs against <em>N. meningitidis</em> homologues are bactericidal</td>
</tr>
<tr>
<td>Opa</td>
<td>Adherence, invasion</td>
<td>Phase variable</td>
<td>Variable</td>
<td>Bactericidal Ab</td>
</tr>
<tr>
<td>OpcA</td>
<td>Adherence, invasion</td>
<td>Stable</td>
<td>Conserved</td>
<td>Abs against <em>N. meningitidis</em> homologues are bactericidal</td>
</tr>
<tr>
<td>PorB</td>
<td>Adherence, invasion</td>
<td>Stable, essential</td>
<td>Variable</td>
<td>Bactericidal Ab</td>
</tr>
<tr>
<td><strong>Nutrient Acquisition</strong></td>
<td></td>
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<tr>
<td>TbpB, TbpA</td>
<td>Transferrin receptor</td>
<td>Induced in iron limiting conditions</td>
<td>TbpB-variable</td>
<td>Bactericidal Ab</td>
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<td></td>
<td></td>
<td></td>
<td>TbpA-conserved</td>
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<tr>
<td></td>
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<td></td>
<td>LbpB-variable</td>
<td></td>
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<tr>
<td>LbpA, LbpB</td>
<td>Lactoferrin receptor</td>
<td></td>
<td>LbpA-semiconserved</td>
<td>Abs against <em>N. meningitidis</em> homologues are bactericidal</td>
</tr>
<tr>
<td>ZnuD</td>
<td>Zinc transporter</td>
<td>Induced by zinc limitation</td>
<td>Conserved</td>
<td>Abs against <em>N. meningitidis</em> homologue (ZnuD) are bactericidal</td>
</tr>
<tr>
<td><strong>Immune Evasion</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PorB</td>
<td>Binds C4BP and FH [see text]; (also critical for nutrient acquisition)</td>
<td>Stable, essential</td>
<td>Variable</td>
<td>Cyclic loop peptides induce cross-reactive bactericidal Abs</td>
</tr>
<tr>
<td>NspA</td>
<td>Binds FH [see text]</td>
<td>Stable</td>
<td>Highly conserved</td>
<td>Abs against <em>N. meningitidis</em> homologues are bactericidal</td>
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<tr>
<td><strong>Protective in experimental mice</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Outer membrane (OM)</td>
<td></td>
<td></td>
<td></td>
<td>OM immunization elicits bactericidal Abs and accelerates clearance of infection</td>
</tr>
<tr>
<td>2C7 epitope</td>
<td>Inner glycose core of LOS; lactose substitution on HepI and HepII and are required for <em>in vivo</em> fitness</td>
<td>Phase variability but expressed by &gt;95% of isolates <em>in vivo</em> (human)</td>
<td>Common epitope in otherwise variable LOS</td>
<td>2C7 bactericidal Abs are also opsonophagocytic; active and passive immunization accelerates clearance of infection</td>
</tr>
<tr>
<td>MtrE</td>
<td>Surface-exposed channel of the MtrC-MtrD-MtrE and FarA-FarB-MtrE active efflux pumps</td>
<td>Stable</td>
<td>Highly conserved</td>
<td>rMtrE immunization elicits bactericidal Abs and accelerates clearance of infection</td>
</tr>
</tbody>
</table>

1 Adapted from refs. (12) and (13)
2 Bactericidal Abs (antibodies) are directed against *N. gonorrhoeae* unless otherwise stated that they are directed against *N. meningitidis*
positive and negative (blocking), elicited by the vaccine, correlated with enhanced protection or increased susceptibility respectively, to infectious challenge, when this variable was considered independently. This study emphasizes that the use of a placebo group and stratification for pre-existing immunity will be important considerations in the future design of gonococcal vaccine trials that involve vaccine candidates to which there may already be partial immunity.40

**Experimental mouse model vaccines**

While female mice are only transiently susceptible to *N. gonorrhoeae* infection during proestrus, administration of 17β-estradiol and antibiotics can prolong colonization.41 Immunization of mice with gonococcal outer membrane elicits vaginal and serum antibodies against several outer membrane proteins. Immune serum antibodies are bactericidal and accelerate clearance of gonococcal organisms, which are maintained at lower numbers throughout the period of infection.42

Antibodies against a peptide mimic of the 2C7-LOS epitope, a structure required for *in vivo* fitness, are highly bactericidal and promote opsonophagocytic killing of *N. gonorrhoeae*.5, 6, 43 Immunization of mice with a multiantigenic form of the 2C7-LOS peptide mimic elicits vaginal and bactericidal serum antibodies and accelerates clearance of gonococcal organisms. Passive administration of a monoclonal antibody directed against the epitope also enhances clearance.44

*N. gonorrhoeae* expels hydrophobic antimicrobial substances that bathe mucosal surfaces (e.g., fatty acids, long-chain fecal lipids, antimicrobial peptides, progesterone, bile salts) through the MtrC-MtrD-MtrE or FarA-FarB-MtrE active efflux pumps.12 The MtrC-MtrD-MtrE system is required for murine infection and plays an important role in antibiotic resistance.45 MtrE, the outermost component of the MtrC-MtrD-MtrE and FarA-FarB-MtrE pumps, each have two surface-exposed loops. Immunization of mice with recombinant MtrE elicited bactericidal antibody activity against a variety of gonococcal strains. Vaccinated mice that were then challenged exhibited a significant reduction in the percentage of mice colonized over time.46

**Future approaches**

*N. gonorrhoeae* possess numerous mechanisms to allow for redundancy in escaping immune attack and for promoting adhesion and circumvention of certain nutritional pathways.12, 13 One approach that has been applied to the development of new group B *N. meningitidis* vaccines,47,48 would be to develop outer membrane vesicle (OMV) vaccines, deleted of antigens such as Rmp that may undermine efficacy3, 4 and supplemented with several antigens that constitutively express transcriptionally regulated proteins, known to be expressed during infection and that may elicit efficacious immune responses against *N. gonorrhoeae*. Several such candidates have been reviewed above.

**References**


Neisseria gonorrhoeae news

New molecular tests detect antibiotic-resistant gonorrhea

University of Queensland experts have molecular detection of DNA mutations to identify gonorrhea outbreaks with antibiotic-resistant strains. Associate Professor David Whiley and his team successfully used the new DNA detection tools to confirm susceptibility to penicillin in Australian gonorrhea strains. Traditionally, resistance is detected in bacterial growth cultures and subsequent testing for susceptibility to different antibiotics. While successful, this method is complex, technically demanding, and subject to viability loss from long distance transport of cultures.

Whiley, the WHO, and the CDC urge improved surveillance methods to guide treatments and to control pandemic outbreaks of the sexually transmitted infection. Whiley proposes that molecular methods will complement existing diagnostics and improve the ability to detect resistance in order to provide patients with appropriate treatment and prevent further transmission.

CDC reports strong positive association between ciprofloxacin resistance and gonorrhea incidence rates

A CDC review of gonorrhea incidence rates in 17 U.S. cities from 1991-2006 has found a strong positive association between ciprofloxacin resistance and new gonorrhea infection rates. The study, led by Chesson et al., adds to the growing evidence of the effects on antimicrobial drug resistance and infectious disease outbreaks at the population level. Two possible mechanisms may explain the observed association: 1) treatment delays or failures due to ciprofloxacin resistance may increase the duration of infectivity and thereby increase transmission, and 2) resistance mutations in the organism support gonococcal transmission. The results highlight the need to monitor increases in gonorrhea outbreaks caused by emerging cephalosporin resistance. *N. gonorrhoeae* acquires resistance differently to ciprofloxacin and cephalosporins, but with limited treatments available, the effect of ceftriaxone (a third generation cephalosporin) resistance could be more detrimental. These results quantify the association between ciprofloxacin resistance and gonorrhea incidence outbreaks and warn of the emerging resistance to current treatments.

Gonorrhea becoming impossible to treat?

Today’s gonorrhea patient has very few treatment options left as the most prevalent form of the bacterium has developed resistance to penicillin and various tetracyclines. Citing evidence from the CDC study by Chesson et al. and other epidemiologic data, “the emergence and spread of cephalosporin-resistant gonorrhea in the United States appears imminent.” Since 2007, the CDC has changed its recommended gonorrhea treatment twice—instituting drug combination changes and increasing doses. However, there are no current recommended treatments for patients who already have the cephalosporin-resistant strain of gonorrhea. Reports of cephalosporin-resistant strains in Japan, France, and Spain highlight the imminent pandemic and urge monitoring of this emerging resistance.

'Grappling Hooks' assist in gonorrhea transmission

A new study shows how *Neisseria gonorrhoeae* is transmitted between sexual partners. For the past 40 years, it was thought that the bacterium adhered to sperm during intercourse, but this theory did not explain female-to-male transmission. Recent data and imaging reveal that the organism utilizes its pili to attach to seminal proteins. These “grappling hooks” are normally contained in a bundle, but when exposed to semen, unwind to expose more pili—increasing the organism’s ability to invade as much as 24-fold. The pili also attach the bacteria to skin cells around the genital tracts, assisting with infection. Authors Anderson et al., suggest the development of antibiotics which “unhook” the pili as a means of countering resistance in gonorrhea treatment. See image on page 1.

Proteins discovered in gonorrhea may offer new approach to treatment

Oregon State University researchers discovered new proteins that reside within or on the membrane vesicles of the gonococcus (*Molecular and Cellular Proteomics 2014*). The proteins help the bacteria acquire nutrients, provide a permeable barrier and suppress immune response. This discovery could offer and possibly aid a promising new means of attacking *N. gonorrhoeae* infection and possibly aiding in the development of a gonorrhea vaccine.
APUA names Honor Roll companies that responsibly limit antibiotic use in food products

In its first annual Honor Roll, APUA named Applegate, Bell & Evans, Chipotle, Coleman Natural, Heritage Acres Foods, Niman Ranch, Panera Bread, sweetgreen, and Whole Foods. APUA applauds these Honor Roll companies for taking the initiative to commit to more stringent controls on antibiotic use in food production. "Through their leadership and best practices, these companies strive for healthful quality and assert pressure on the food animal industry to stop overusing antibiotics for non-therapeutic purposes and growth promotion," said APUA President Dr. Stuart Levy.

APUA endorses letters from Pew and others re: Veterinary Feed Directive

Following a January teleconference among public health, consumer, and environmental protection organizations organized by the Pew Charitable Trusts’ “Save Antibiotics” campaign, APUA signed a joint letter to the FDA regarding the new Veterinary Feed Directive (VFD). The letter expresses concern that several of the proposed changes would remove or compromise important public health protections.

The FDA included a new veterinary oversight requirement for food animal antibiotics that were previously purchased over the counter; however they also removed the previous requirement of a valid veterinary-client-patient relationship and left this regulation up to the states. The working group argues that FDA should reinstate the minimum federal requirement to ensure that veterinarians have sufficient knowledge of the animals for which they prescribe. Another major problem is that the VFD does not clearly limit the number of times that a VFD order can be reissued. The letter also addresses VFD records and the definition of “distributor.”

APUA President Dr. Levy participates in Harvard forum on antibiotic resistance

On February 5th, APUA President Dr. Stuart Levy participated in the Forum at Harvard School of Public Health, which featured "Battling Drug-Resistant Superbugs: Can We Win?" Also participating on the panel were Marc Lipsitch of the Harvard School of Public Health, Aaron Kesselheim of Brigham and Women’s Hospital, and Beth Bell of the CDC. The event, was moderated by David Baron, health and science editor of “The World.”

Dr. Levy and colleagues addressed a wide range of issues—from how we talk about and address antibiotic resistance, to the genetic evolution of resistance, preventive hygiene, antibiotic use in animals, hospital stewardship programs and the antibiotic pipeline. Dr. Levy stressed that antibiotics are “societal drugs,” due to the effects that individual use has on resistance in the community.

Read more about the event here, or watch a recording here.

Senator Warren queries FDA Commissioner Hamburg on voluntary guidelines

On March 13, Massachusetts Senator Elizabeth Warren questioned FDA Commissioner Hamburg on the effectiveness of FDA Guidance #213 at a Senate hearing for the Committee on Health, Education, Labor, and Pensions (HELP). Guidance #213 calls on drug companies to phase out the use of antibiotics in food animals. Prior to the hearing, APUA President Dr. Stuart Levy briefed Senator Warren’s staff on important questions about the guidance and its impact on the problem of antibiotic resistance.

Warren pressed Commissioner Hamburg on how the guidance will ultimately be implemented. “Surely the removal of production uses is a good first step, and I’m hopeful that this is going to lead to decreasing use of antibiotics,” said Warren, “but the FDA’s guidance doesn’t guarantee the prudent use of antibiotics in the context of disease prevention. Even with every animal company agreeing to comply with the FDA’s most recent guidance, there could still be a lot of antibiotic use in animals that is ostensibly for disease prevention but is still far more than necessary and will continue increasing resistance.”

View a video recording of the hearing here.

See news update on page 28 for status of company compliance.
By Kauser Jabeen and Rumina Hasan
Department of Pathology Microbiology, Aga Khan University, Karachi, Pakistan; APUA Pakistan

While sexually transmitted Neisseria gonorrhoeae infections occur in Pakistan, most laboratories do not report them due to limited resources and lack of trained personnel. Consequently, antimicrobial resistance data from the country are limited. High resistance rates to penicillin, tetracycline and quinolones, with increasing isolation of multidrug resistant strains has been reported from our laboratory. However, despite the emergence of Neisseria gonorrhoeae strains with decreased susceptibility to ceftriaxone from South East Asian countries, these strains have not been yet been recorded in Pakistan.

This year, the World Health Organization’s Gonorrhea Antimicrobial Surveillance Program (GASP) is initiating efforts to enhance detection and reporting of Neisseria gonorrhoeae strains with decreased susceptibility to ceftriaxone. Participating laboratories will undertake ceftriaxone MICs using ceftriaxone E-strips. Aga Khan University laboratory has been participating in this program since 2012 by submitting laboratory data on gonococcal resistance to the GASP annual report.

Participation in this study, including internal and strict quality external quality assurance programs, will strengthen the antimicrobial resistance data of gonorrhoeae from Pakistan and lead to early and efficient detection of the emergence of any ceftriaxone-resistant strains.

References:


APUA-Nepal receives distinguished foreign visitors

In February 2013, APUA-Nepal President Dr. K.K. Kafle met with Ms. Hellen Gelband, Program Fellow and Study Coordinator from the Centre for Disease Dynamics, Economics and Policy (CDDEP), and in December Dr. Gaetano Marrone of the Public Health Department, Karolinska Institute, visited from Sweden. Each guest was briefed on the activities of the Nepal chapter since its establishment in 2000 and was presented with copies of the APUA-Nepal Newsletter. Commendation was expressed for the chapter’s many activities and for receiving APUA’s distinguished Chapter Leadership Award in 2011. The visitors expressed interest in further collaboration with APUA-Nepal.

Figure 1. Comparison of resistance in Neisseria gonorrhoeae strains: 1992–2006 vs. 2007–2009

There is a significant increase (P value <0.01) in resistance to penicillin, tetracycline, ofloxacin, and combined resistance to all 3 antibiotics over these two periods.

n = total number of strains.
Increases are significant for all drugs (p < 0.01)
APUA-Lebanon hosts well-received educational events

This year APUA-Lebanon has been very active providing events for people of all ages to learn about microbiology and antibiotic resistance. On March 5, the chapter hosted an event for second grade students, ages 7-8, at the Antoinine Sisters School in Ghazir, Lebanon. Group activities introduced basic information about microorganisms, hand hygiene, and the concept of germ transmission. The 180 students that participated viewed bacteria and fungi through microscopes and watched a presentation defining a microbe, its advantages and disadvantages.

Eight members of APUA-Lebanon collaborated to host this very well received event. The chapter plans to conduct other similar activities focused on microbiology education with children in the next two years.

On February 28 APUA-Lebanon hosted a workshop in collaboration with the Microbiology and Infectious Diseases Collaborative Research center at the University of Balamand. The workshop, titled “Bacterial Resistance and Phenotypic Detection in Gram Negative Bacilli” attracted 40 participants, including lab directors, microbiologists, lab technologists, infectious disease physicians, and graduate students.

Dr. Ziad Daoud presented on the different mechanisms of resistance in gram-negative bacilli and emphasized the importance of phenotypic detection in understanding resistance and targeting appropriate antibiotic therapy. Dr. Monzer Hamze reported on the increasing levels of bacterial resistance observed in Northern Lebanon.
described the Cuban healthcare system’s focus on universal primary care, public health education and prevention services. Among the achievements are: lowest infant mortality rate of developing countries and a lifespan on par with the US (Table 1). According to a summary report by the Parliament of the United Kingdom, the strengths of the Cuban healthcare system are the integration of prevention/proactive response and disease management/reactive response. Other findings include:

- “In Cuba [there is] one doctor per 175 people, in the UK the figure was one doctor per 600 people.
- There is a commitment in Cuba to the ‘triple diagnosis’ (physical/psychological/social) at all levels.
- Extensive involvement of patient and the public in decision-making at all levels.
- Integration of hospital/community/primary care via polyclinics.
- Team-work is much more evident, both in the community and the hospital sector. The mental-health and care of the elderly sites visited were very well staffed and supported.”

Problems identified in the UK study noted: Low pay of doctors; many facilities in poor state of repair and mostly outdated; and shortages of equipment and essential drugs.

In February, APUA Cuba chapter representatives briefed APUA program consultant Kathleen Young on the chapter’s success in organizing antibiotic stewardship trainings and committees at health centers throughout the country. Professor Maria Guadalupe Guzman, Director of the Central Laboratory for the Study of Dengue and chief of the Department of Virology at the Institute of Tropical Medicine “Pedro Kouri” and her associate Dr. Dianylis Quiñones Pérez, who work with APUA-Cuba president Dr. Moises Morejon Garcia, described their work to promote rational antibiotic use and expand the APUA-Cuba chapter to over 1800 members. The APUA professionals relayed their pride in and commitment to the Cuban health system’s quality and universal coverage.

Although a developing country, Cuba has prioritized universal access to health care and education. Low rates of infectious and other diseases are attributable to a strong model of community-based practice where primary healthcare practitioners and students receive training and education in cultural sensitivity, psychology, indigenous medicines, effective community relations and other public health issues influencing patient health.

While in Cuba, Ms. Young also visited a primary care polyclinic where visitors were briefed by a multidisciplinary team. They

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Cuba</th>
<th>United Sates</th>
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<tbody>
<tr>
<td>Under 5 mortality rate</td>
<td>6/1,000 live births</td>
<td>7/1,000 live births</td>
</tr>
<tr>
<td>Infant mortality rate (&lt;1yrs)</td>
<td>4/1,000 live births</td>
<td>6/1,000 live births</td>
</tr>
<tr>
<td>Neonatal mortality rate</td>
<td>3/1,000 live births</td>
<td>4/1,000 live births</td>
</tr>
<tr>
<td>Life expectancy at birth</td>
<td>79.1 yrs</td>
<td>78.8 yrs</td>
</tr>
<tr>
<td>Literacy rate (15-24yrs, male and female)</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>GDP (USD)</td>
<td>$68.23 billion</td>
<td>$16.24 trillion</td>
</tr>
<tr>
<td>GDP per capita (USD)</td>
<td>$6,051</td>
<td>$51,749</td>
</tr>
</tbody>
</table>

Source: 2012 Data from UNICEF and World Bank
Cuba’s medical schools train huge graduating classes and each of Cuba's 11 million citizens is scheduled for at least one house call per year, more if there is a chronic condition. With 15% of the Cuban budget currently devoted to healthcare, the Cuban government, like the US government, is trying to find more healthcare efficiencies to contain costs. While not without problems, the Cuban health system provides some good lessons about the value of community-based prevention and treatment to achieve the goal of effective universal health care.

References:


Recommended Resources

**Book:** One Health: People, Animals, and the Environment
Editors: Ronald M. Atlas, University of Louisville; Stanley Maloy, San Diego State University

This book, authored by interdisciplinary experts, covers a range of topics, including:
- The interconnectedness of human and animal pathogens
- Case histories of notable recent zoonotic infections
- Causes behind the emergence of antibiotic resistance
- New technologies and approaches for public health disease surveillance
- Strategies for promoting the global acceptance of One Health

Available through the American Society for Microbiology (ASM) [here](#).

**Webinar:** Preventing Infection Transmission: Moving Toward Ideal Practice
Presenter: Ruth M. Carrico, PhD, RN, FSHEA, CIC
Associate Professor, University of Louisville School of Medicine, Division of Infectious Diseases

This webinar will:
- Review the steps in blood glucose monitoring focusing on those that represent risk and contamination prevention opportunities
- Outline core infection prevention and control practices that are key to the safe blood glucose monitoring process
- Identify practice questions where data are limited or unknown

**Interview:** Modern Medicine May Not Be Doing Your Microbiome Any Favors
Between: Dr. Martin Blaser, director of NYU’s Human Microbiome Program, and *Fresh Air’s* Terry Gross

This 45 minute interview discusses the theories that food allergies and intestinal disorders are on the rise due to the overuse of antibiotics.

The interview highlights:
- Potential links between antibiotics and obesity
- How the birth process informs a baby’s microbiome
- How the microbiome determines a person’s immunity and allergies
US fiscal year 2015 budget update

The Centers for Disease Control and Prevention (CDC) has developed an initiative to outsmart the “ticking time bomb” of antibiotic resistance. The Detect and Protect Against Antibiotic Resistance Initiative (the AR Initiative) requests $30 million annually for 5 years from the President’s 2015 Budget. With this funding, the CDC aims to: detect and track patterns of antibiotic resistance; respond to outbreaks involving antibiotic-resistant bacteria; prevent infections from occurring and resistant bacteria from spreading; and discover new antibiotics and new diagnostic tests for resistant bacteria. The AR Initiative plans to improve detection through regional labs and to prevent infections and improve antibiotic prescribing practices in healthcare facilities and in the community to curb emerging resistance threats.

The seven highlighted antibiotic-resistant threats include: Clostridium difficile (C. diff), Carbapenem-resistant Enterobacteriaceae (CRE), MDR Neisseria gonorrhoeae, Extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL), MDR-Salmonella, Methicillin-resistant Staphylococcus aureus (MRSA), and MDR-Pseudomonas.

With the $30 million annual funding, the CDC’s AR Initiative could achieve the following:

- A 50% reduction in healthcare-associated C. diff infections;
- A 50% reduction in healthcare-associated CRE infections;
- A 30% reduction in healthcare-associated multidrug-resistant infections;
- A 30% reduction in invasive MRSA; and
- A 25% reduction in MDR-Salmonella infections.

APUA has signed onto a joint letter by the Infectious Diseases Society of America in support of the CDC’s proposed AR Initiative.

India aims to curb over-the-counter sales of antibiotics in five years

The Chennai Declaration is a roadmap to tackle antimicrobial resistance in India, prepared in 2012 by a group of stakeholders and experts. The same group has now created a five-year plan that will ultimately restrict 80% of antimicrobial drugs from over-the-counter sales. It also sets goals for compliance with a range of other policies to monitor and restrict antibiotic use for surgical prophylaxis, veterinary practice, and infection control in hospitals across India. The plan will require all tertiary health care facilities to have antibiotic monitoring facilities by the end of the year, and all primary and secondary health centers to have an antibiotic policy in place in two years.
Drug-makers comply with request to phase out sub-therapeutic antibiotics in animal feed

In December 2013, the Food and Drug Administration (FDA) asked 26 pharmaceutical companies to voluntarily phase out the use of antibiotics used to treat human infections in the sub-therapeutic dosing of food animals. In mid-March 2014, 25 of the 26 companies, representing 99.6% of the total sales of animal antibiotic products, agreed to the FDA’s request. The vendors intend to remove over-the-counter use of their products in animal production or switch to use by veterinary prescription only to limit the growing health problem of antibiotic resistance. The FDA is working with the industry directly in order to circumvent slow regulatory processes in its attempt to curb drug-resistant infections.

CDC Vital Signs: Varying antibiotic prescribing practices in hospitals

In March 2014, the CDC cautioned hospitals to make health care safer through prudent antibiotic prescribing practices. CDC Vital Signs reports that 1 in 2 hospital patients receive an antibiotic; some hospitals prescribe three times as many antibiotics as doctors in other hospitals; and a 30% reduction in the use of high-risk antibiotics can lower deadly infections by 30%. While antibiotics save lives, irrational prescribing practices put patients at future risk for preventable allergic reactions and super-resistant infections. To preserve antibiotic efficacy, hospitals should adopt a stewardship program, which includes: leadership commitment, accountability, drug expertise, action, tracking, reporting, and education.

The CDC declares surveillance feasible in under-resourced countries

In the journal of Emerging Infectious Diseases, the CDC provides a roadmap to introduce antibiotic resistance surveillance in under-resourced countries. Typically, antimicrobial drug resistance (ADR) is not monitored in low income countries due to lack of surveillance networks, laboratory capacity, and diagnostics. ADR is implicated in excess infant, child, and maternal mortality rates due to poor post-partum infection control practices. Living in a globalized world makes ADR surveillance pressing, as resistant microorganisms can travel faster and further than before.

WHO releases first report on global antimicrobial resistance

Providing the most comprehensive evaluation of drug resistance to date, the WHO has declared that antimicrobial resistance (AMR) is a major public health threat. Its first report on the topic, “Antimicrobial resistance: global report on surveillance” states that, without urgent, coordinated action, common infections and minor injuries will once again become potentially life-threatening. The report addresses the current surveillance status on AMR at the country level and highlights the significant gaps in surveillance, data sharing, and coordination. WHO concluded that high rates of resistance are prevalent in health care associated (E. coli, K. pneumoniae, S. aureus) and community acquired infections (S. pneumonia, Salmonella, Shigella, N. gonorrhoeae) in all WHO regions. The report also summarizes the health and economic burden due to AMR in TB, malaria, HIV, influenza and the food chain. The WHO plans to facilitate development of surveillance tools and networks to address the gaps and to contain AMR globally. In the meantime, it urges interventions to prevent infection through diligent hygiene and vaccination and tackling resistance through better antibiotic stewardship. APUA representatives Dr. Stuart Levy and Kathleen Young served on the panel of reviewers of the report.

New VRSA strain in Brazil

A new, highly vancomycin-resistant, methicillin-resistant Staphylococcus aureus (VRSA) has been identified in a Brazilian patient—the first ever reported in a bloodstream infection. It carries a novel, highly transferable plasmid bearing the vanA cluster genes that are responsible for vancomycin resistance. Of great concern, the strain belongs to the staphylococcal USA300 lineage, a clone that circulates in the community and can disseminate rapidly. Currently, vancomycin is the drug of last resort for treating severe MRSA infections. As VRSA is evolving in the same way as community-acquired MRSA, the potential dissemination of vanA in community MRSA strains poses a serious public health problem. According to co-author Dr. Barbara Murray, “the worst resistance possible has now appeared in the community-associated MRSA clone.”
Current bacterial culture diagnostics are time consuming and require sophisticated technology and highly trained staff. Molecular diagnostic testing successfully identifies resistance gene sequencing, but only for a limited number of microorganisms. These new molecular diagnostics should be used with existing culture-based diagnostics.

Resistance surveys in Africa and Southeast Asia have already successfully mapped malaria and TB resistance at the household level through rapid molecular-based tests adapted for field use and gene sequencing. Addressing insufficient laboratory capacity, use of existing networks, and standardization of resistance data will facilitate expanded interventions in these under-resourced communities.

Future research should focus on: developing appropriate technology for ADR detection; mapping of existing surveillance initiatives to coordinate under-resourced countries with existing global networks; centralizing data in public databases; developing communication plans to target health authorities at the regional, national and international levels.

Serious antibiotic-resistant infections in children up 2- to 3-fold in 10 years

In March 2014, the Journal of the Pediatric Infectious Diseases Society published a study on the increase in drug-resistant infections in US children. Chicago researchers examined the national database of bacteria retrieved from pediatric infections between 1999 and 2011 and evaluated Enterobacteriaceae for extended-spectrum beta-lactamase production (ESBL+) and for resistance to 3rd-generation cephalosporins. Only carbapenems can successfully treat ESBL+ bacteria. While the resistance frequencies are low in children, they have climbed over the last decade: from 0.28% to 0.92% for ESBL+ and from 1.4% to 3% for 3rd-generation cephalosporins. Additionally, multi-drug resistance to three or more drug classes was common in 46-74% of the two resistance phenotypes. The highest frequencies were found in children in outpatient clinics, but it is unclear if those subjects were pre-exposed to resistant bacteria in a healthcare institution. The study is one of the first to examine drug resistance data in non-staph related childhood infections and it emphasizes that, as drug resistance rises, the present antibiotics are losing their effectiveness.

Refs cont. from page 20

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 Newsletter has been published continuously three times per year since 1983.
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APUA global chapter network of local resources & expertise

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