Po-Ren Hsueh

• Professor in the Divisions of Clinical Microbiology and Infectious Diseases, Departments of Laboratory Medicine and Internal Medicine, at National Taiwan University Hospital, National Taiwan University College of Medicine.

• Graduated:
  - Department of Medical Technology at the College of Medicine
  - Department of Medicine at National Taiwan University College of Medicine and graduated

• Position:
  - President for Global Chinese Association of Clinical Microbiology and Infectious Diseases (GCACMID)
  - Past president for Taiwan Society of Microbiology (TSM)
  - Secretary-General of Western Pacific Society of Chemotherapy (WPSC)
  - The honorary treasurer of International Society of Chemotherapy (ISC)
  - Director for The Infectious Diseases Society of Taiwan (IDST)
New Antibiotics in the 21st Century
An Update

Po-Ren Hsueh
National Taiwan University Hospital
Main MDRO

Methicillin-resistant *Staphylococcus aureus* (MRSA) (also referred to as ORSA—oxacillin-resistant *S. aureus*)

Extended-spectrum beta-lactamase (ESBL)-producing bacteria

Carbapenem-resistant *Pseudomonas aeruginosa* CR-, MDR-, XDR-, PDR-PA

Vancomycin-resistant enterococci (VRE)

Carbapenem-resistant *Acinetobacter* spp. CR-, MDR-, XDR-, PDR-AB
COUNTERTHINK

MEET THE HOSPITAL STAPH

EMPLOYEES MUST WASH HANDS BEFORE RETURNING TO WORK.

CONCEPT: MIKE ADAMS
ART: DAN BERGER
WWW.NATURALNEWS.COM
Distribution of MRSA by Country

2004-6, CA-MRSA and HA-MRSA, Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>CA-MRSA (No.)</th>
<th>HA-MRSA (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sri Lanka</td>
<td>86.5 (49/377)</td>
<td>65 (270/574)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>34.8 (93/97)</td>
<td>30.1 (654/147)</td>
</tr>
<tr>
<td>The Philippines</td>
<td>38.1 (147/705)</td>
<td>30.1 (82/345)</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>74.1 (46/93)</td>
<td>56.8 (46/316)</td>
</tr>
<tr>
<td>Korea</td>
<td>77.6 (22.6)</td>
<td></td>
</tr>
</tbody>
</table>

VRE Prevalence in Asia-2010

- Korea: (10-25%)
- Japan: (<1%)
- Taiwan: (20-25%)
- China: (1-5%)
- HK: (1-5%)
- Malaysia: (1-5%)
- Thailand: (5-10%)
- Singapore: (1-5%)
- Sri Lanka: (<1%)
- Philippines: (1-5%)
THE HOSPITAL STAFF
DID THIS TO YOU?

NO, THE HOSPITAL STAPH.

MRSA
Nosocomial MRSA Bacteremia
Mortality based on Vancomycin MICs

risk factors of high MIC: Patients in the ICU, vancomycin exposure, prolonged hospitalization

Day 14 mortality × Day 30 mortality

Wang JL et al. BMC Infect Dis 2010

Lodise TP et al. 2008 JAC. Wang et al, 2010 BMCID
Prevalence Rates of hVISA and VISA among MRSA Isolates in Asia

<table>
<thead>
<tr>
<th>Region</th>
<th>hVISA (%)</th>
<th>VISA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>Singapore</td>
<td></td>
<td>12.5</td>
</tr>
<tr>
<td>China</td>
<td></td>
<td>10.7</td>
</tr>
<tr>
<td>Thailand</td>
<td>0</td>
<td>2.2</td>
</tr>
<tr>
<td>Taiwan</td>
<td>0.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Comparative Outcome
VISA, hVISA, and VS-MRSA

Increase in vancomycin treatment failure in hVISA

J Antimicrob Chemother 2011 online 26th April

Distribution of Linezolid Resistance in S. aureus and CoNS Worldwide

S. aureus
- LRSA strains with outbreak of healthcare-associated infection
- LRSA strains reported

S. aureus
- Japan 2009, 2011
- Korea 2011
- China 0.05%
- 1.4% (CoNS)

CoNS
- LRCoNS strains with outbreak of healthcare-associated infection
- LRCoNS strains reported

Daptomycin-non-susceptible VISA- Taiwan

Bacteremia and Infective Endocarditis Caused by a Non-Daptomycin-Susceptible, Vancomycin-Intermediate, and Methicillin-Resistant \textit{Staphylococcus aureus} Strain in Taiwan

Yu-Tsung Huang,\textsuperscript{1,2} Cheng-Hsiang Hsiao,\textsuperscript{3} Chun-Hsing Liao,\textsuperscript{1} Chung-Wei Lee,\textsuperscript{4} and Po-Ren Hsueh\textsuperscript{2,5,*}

\textsuperscript{1}Department of Internal Medicine, Far Eastern Memorial Hospital, Taipei County, Taiwan, \textsuperscript{2}and Departments of Internal Medicine, \textsuperscript{3}Pathology, \textsuperscript{4}Radiology, \textsuperscript{5}Laboratory Medicine, \textsuperscript{5}National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan


Fatal bacteraemia caused by daptomycin-non-susceptible, vancomycin-intermediate, meticillin-resistant \textit{Staphylococcus aureus} in a patient with chronic kidney disease

Main MDR GNB

KPC  NDM

Extended-spectrum beta-lactamase (ESBL)-producing bacteria

Carbapenem-resistant *Pseudomonas aeruginosa*
MDR-, CR-, XDR-, PDR-PA

Carbapenem-resistant *Acinetobacter* spp.
MDR-, CR-, XDR-, PDR-AB
Antibiotic Sensitivity Pattern of in an ICU
Fatmawati Hospital, Indonesia

- From 249 patients, January 2009 to March 2010
- *P. aeruginosa* (26.5%), followed by *K. pneumoniae* (15.3%) and *S. epidermidis* (14.9%)
- Susceptibility rates
  - *P. aeruginosa*: amikacin 84.4%, imipenem 81.2%, and meropenem 75.0% (*CR P. aeruginosa*, 25%)
  - *K. pneumoniae*: cephalexin 13.5%, ceftriaxone 24.3%, ceftazidime 27%, cefotaxime 32.1%
- **Conclusion:** Most bacteria were resistant to the third generation of cephalosporins and quinolone antibiotics

**Infections due to ESBL-Producing Enterobacteriaceae**

**Antimicrobial Treatment**

<table>
<thead>
<tr>
<th>Type</th>
<th>First-line</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-onset</td>
<td>Ertapenem</td>
<td>Amikacin, tigecycline, colistin</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>Imipenem/meropenem/doripenem</td>
<td>Amikacin, tigecycline, colistin</td>
</tr>
</tbody>
</table>

Pneumonia, bacteremia, intraabdominal infections, complicated UTI

Pitout J D. *Drugs* 2010; 70: 313-33.
Carbapenem-resistant Enterobacteriaceae (CRE)
Outcomes of Infections Caused by KPC-KP
According to Treatment Regimen

A: 2 active drugs with a carbapenem
B: 2 active drugs, not a carbapenem
C: Monotherapy with an aminoglycoside
D: Monotherapy with a carbapenem
E: Monotherapy with tigecycline
F: Monotherapy with colistin
G: Inappropriate therapy

Regimen A was superior to regimens B, E, F, and G (A versus B, E, F, and G, the P value was 0.02, 0.03, <0.0001, and <0.0001, respectively).
Regimens B, C, and D were superior to regimen G (B versus G, P= 0.014; C versus G, P= 0.04; D versus G, P = 0.03).

Assessment of Antimicrobial Combinations for KPC–Producing K. pneumoniae

Antimicrobial combination

- Doripenem plus amikacin
- Doripenem plus rifampin
- Levofloxacin plus rifampin
- Doripenem plus levofloxacin
- Amikacin plus rifampin
- Levofloxacin plus amikacin

Synergy and antagonism are determined by the respective log_{10} CFU/mL values.

Abbreviation: CI, confidence interval

Survival of Animals Infected with KPC-producing K. pneumoniae

<table>
<thead>
<tr>
<th></th>
<th>KPVM9</th>
<th>KP6153</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC</td>
<td>KPC-2</td>
<td>KPC-3</td>
</tr>
<tr>
<td>Others</td>
<td>SHV-11</td>
<td>TEM-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ompK35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ompK36</td>
</tr>
<tr>
<td>Doripenem</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Amikacin</td>
<td>64</td>
<td>32</td>
</tr>
<tr>
<td>Rifampin</td>
<td>&gt;64</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>128</td>
<td>8</td>
</tr>
</tbody>
</table>

Double-Carbapenem Therapy for Carbapenemase-Producing K. pneumoniae

Hypothesis: KPC's preferential affinity for ertapenem, due to the ease of hydrolysis vs. that of doripenem; thus, ertapenem acts as an KPC consumer

Bacterial densities of KPC 354 over 24 h in the in vitro chemostat model (doripenem MIC, 4 mg/L).

Comparative efficacies of various dosing regimens of doripenem with or without ertapenem against KPC 354 in the in vivo murine thigh infection model.

Antimicrob Agents Chemother 2011;55:3002–4
**Incidence of CR-, MDR-, XDR-, PDR- P. aeruginosa and Acinetobacter spp.**

HAP, VAP in Asia-Pacific

<table>
<thead>
<tr>
<th>Condition</th>
<th>P. aeruginosa</th>
<th>Acinetobacter spp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>30.1</td>
<td></td>
</tr>
<tr>
<td>MDR</td>
<td>67.3</td>
<td></td>
</tr>
<tr>
<td>XDR</td>
<td>82</td>
<td>51.1</td>
</tr>
<tr>
<td>PDR</td>
<td>0.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Few isolates from Indonesia
P. aeruginosa (n=2), A. baumannii (n=1)

Antibiotic Treatment of Infections due to MDR or PDR Superbugs

- **P. aeruginosa**
  - Combination with $\geq 2$ susceptible agents
  - Colistin alone or in combination (PDR)

- **A. baumannii**
  - A carbapenem plus sulbactam
  - Colistin in combination
  - Tigecycline in combination

Management Recommendations on Nosocomial Pneumonia caused by XDR or PDR A. baumannii

<table>
<thead>
<tr>
<th>Conventional agents</th>
<th>Alternative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Carbapenems (imipenem, meropenem, and doripenem) plus sulbactam (6-8 g/d) or sulbactam-containing agents</td>
<td>● Carbapenem plus colistin (IV, IH)</td>
</tr>
<tr>
<td></td>
<td>● Carbapenem plus tigecycline</td>
</tr>
<tr>
<td></td>
<td>● Colistin plus tigecycline</td>
</tr>
<tr>
<td></td>
<td>● Colistin plus rifampin</td>
</tr>
<tr>
<td></td>
<td>● Tigecycline plus imipenem and amikacin</td>
</tr>
</tbody>
</table>

Colistin (Polymyxin B) Nonsusceptibility Rates
SENTRY, Asia-Pacific (12 countries, 72 centers)

Colistin-R in A. baumannii:
Mainland China (1.4%), Taiwan (9.5%)

Chung DR, Hsueh PR, Song JH et al. AJRCCM 2011

Susceptibility Trends of MDRO to Tigecycline
TIST, 2006-2010, Taiwan

Old and New Antibiotics Currently in Clinical Development, or that Entered Phase 2 Clinical Development since 1995

New Antibacterial Drugs Launched Since 2000

Natural Product-derived

New Antibacterial Drugs Launched Since 2000

Synthetically-derived

- Linezolid (1)
- Prulifloxacin (13)
- Pazufloxacin (14)
- Balofloxacin (15)
- Gemifloxacin (16)
- Garennoxacin (17)
- Sitafoxacin (18)
- Antofloxacin (19)
- Besifloxacin (20)

New Systemic Antibacterial Agents

New Targets or New Mechanisms (N=66)

- 19: Same target as other licensed agents
- 39: New target likely
- 8: New mechanism of action likely

## Improving Known Classes of Antibiotics

### An Optimistic Approach for the Future

<table>
<thead>
<tr>
<th>Class</th>
<th>Original member</th>
<th>Year of identification</th>
<th>Recent compounds in development post-2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporin</td>
<td>(Cephalosporin C)</td>
<td>1948</td>
<td>Ceftobiprole, ceftaroline, ceftolozane</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>Imipenem</td>
<td>1976</td>
<td>Doripenem</td>
</tr>
<tr>
<td>β-lactamase inhibitor</td>
<td>Clavulanic acid</td>
<td>1976</td>
<td>Aibactam, MK-7655</td>
</tr>
<tr>
<td>Monobactam</td>
<td>Aztreonam</td>
<td>1981</td>
<td>BAL30072, MC-1</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>Streptomycin</td>
<td>1943</td>
<td>Plazomicin</td>
</tr>
<tr>
<td>Glycopeptide</td>
<td>Vancomycin</td>
<td>1952</td>
<td>Dalbavancin, oritavancin, telavancin</td>
</tr>
<tr>
<td>Ketolide</td>
<td>Telithromycin</td>
<td>1997</td>
<td>Cethromycin, solithromycin</td>
</tr>
<tr>
<td>Oxazolidinone</td>
<td>Linezolid</td>
<td>1995</td>
<td>Radezolid, tedizolid, PF-02341272, AZD5847</td>
</tr>
<tr>
<td>Quinolone</td>
<td>Nalidixic acid</td>
<td>1962</td>
<td>Delafloxacin, JNJ-Q2, nemonoxacin, DS-8578</td>
</tr>
<tr>
<td>Glycylcycline</td>
<td>Tigecycline</td>
<td>1998</td>
<td>Omadacycline (PTK0796), TP-434</td>
</tr>
</tbody>
</table>
Newer Ketolides

Telithromycin
- Visual disturbances (blurred vision) and liver failure

Cethromycin
- More potent against macrolide-resistant *S. pneumoniae* (Erm methylase)
- CAP, CABP (clinical efficacy?)

Solithromycin (CEM-101)
- Active against *S. aureus* with the MLSB phenotype
- CABP phase III

Anti-MRSA Quinolones

- Delafloxacin, Nemonoxacin (non-F), JNJ-Q2
- Enhanced activities against quinolone-resistant strains
  - MRSA, Ciprofloxacin-R MDR S. pneumoniae
- Lower resistance selection
- Community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin-structure infections (cSSTI)
  - Nemonoxacin (IV, oral): CAP phase III, DFI

**Tedizolid**
*(TR-700, formerly Torezolid)*

- A next-generation oxazolidinone active moiety of the prodrug tedizolid phosphate (TR-701)
- Inhibiting protein synthesis
- High oral bioavailability and once-daily dosing
- Activity against MSSA, MRSA), linezolid-resistant strains
  - MRSA: >4-fold and CoNS: >16-fold > linezolid
  - 79.2% (at ≤ 4 mg/L) and 31.4% (≤ 2 mg/L) against isolates with linezolid MICs (32 to >128 mg/L)
- 200, 300, or 400 mg/d oral tedizolid for SSTI (5-7 days)
  - Overall eradication 97.7%: MRSA (97.8%) MSSA (95.7%)
  - Clinical cure: MRSA (96.9%) MSSA (95.7%), across all dose groups

New $\beta$-lactam-$\beta$-lactamase Inhibitor Combinations

- Avibactam and MK-7655
  - Diazabicyclooctane (DABCO) inhibitors, not $\beta$-lactams
  - Spectra of activity: class A carbapenemases and class C enzymes
- Ceftazidime-avibactam (4:1), ceftaroline-avibactam (1:1), imipenem-cilastatin-MK-7655 (2:2:1 and 4:4:1)
- Ceftolozane-tazobactam (2:1)
  - Ceftolozane (antipseudomonal cephalosporin), and tazobactam protects it against extended spectrum $\beta$-lactamases to which it is labile

Imipenem-MK-7655 against Carbapenem-resistant GNB

- KPC-2- K. pneumoniae (KP6339), P. aeruginosa (PA24226, PA24227, and PA24228) with OprD porin deletions and overexpression of AmpC

- **Red mesh surface**: expected killing
- **Black dots**: observed killing
- **Synergism**: a black dot is below the mesh (observed killing is more than expected killing)
- **Antagonism**: a black dot above the mesh signifies (observed killing is less than expected killing)

Novel Agents in Development for Carbapenemase-Producing Enterobacteriaceae

- **NXL104** (a new $\beta$-lactamase inhibitor)
  - Able to withstand hydrolysis by ESBLs, class A carbapenemases

- **LK-157** (a novel tricyclic carbapenem)
  - Potent activity against class A and class C $\beta$-lactamases

- **BLI-489** (a bicyclic penem molecule)
  - Against a wide variety of enzymes (KPC ?)

- **ACHN-409** (plazimicin, neoglycoside)
  - Active against KPC-producing isolates
Plazomicin (ACHN-490)

- Synthetically derived from sisomicin
- Inhibits protein synthesis, dose-dependent bactericidal activity
- IV 15 mg/ kg, Cmax 113 μg/ml, AUC$_{0-24h}$ 239 h·μg/ml, T1/2 4.0 h
- Active against both GNB and GPC with any aminoglycoside (AMG)-modifying enzymes, but not with ribosomal methyltransferases
  - MDR (AMG-R) Enterobacteriaceae: MIC$_{90}$, 2 μg/mL
  - P. aeruginosa (like amikacin); A. baumanii (better)
- Synergistic activity
  - Daptomycin or ceftobiprole: MRSA, hVISA, VISA, VRSA
  - Cefepime, doripenem, imipenem, piperacillin-tazobactam: P. aeruginosa
- Not reported nephrotoxicity or ototoxicity
- UTI and APN (vs. levofloxacin 750 mg IV for 5 days)

**Omadacycline (PTK0796) and TP-434**

**Omadacycline**
- A novel aminomethyl-substituted derivative of minocycline with similar in vitro activity as tigecycline
- Potent activity $\text{MIC}_{90}$
  - Resistant Gram-positive bacteria 0.5 mg/ml
  - *Enterobacteriaceae* 2 mg/ml
  - No anti-pseudomonal activity
- Oral therapy

**TP-434**
- Like omadacycline
- Oral an IV for cIAI

DS-8587
A Novel Fluoroquinolone against Resistant A. baumannii

- Wild-type gyrA/parC isolates, MICs
  - 0.015 to 0.06 g/ml (4-8-fold and 8-16-fold < LVX and CIP)
- gyrA/parC mutation isolates, MICs
  - 0.5 to 1 g/ml (4-16-fold and 64-128-fold < LVX and CIP)
- Antibacterial activity of DS-8587 was less affected by adeA/adeB/adeC or abeM efflux pumps than CIP
  - MICs of MDR and CIP-R A. baumannii: 0.5 to 1 g/ml
- The frequency of single-step mutations with DS-8587 (4.2-7.3x10^{-8}) was lower than that with CIP (2.4-9.6 x10^{-6})
- DS-8587 might be an effective agent against MDR A. baumannii infection

Emerging Therapies for MDR A. baumannii
Non-antibiotic Approaches

- **Phage therapy**
  - Environmental biocontrol or infection control
  - Rapid clearance by macrophages, anti-phage antibodies

- **Iron chelation and gallium-based therapies**

- **Antimicrobial peptides**
  - Cecropin A–melittin hybrid and brevinin-2-related peptides
  - Resistant to proteolytic degradation in serum

- **Prophylactic vaccination and passive immunization**
  - Biofilm-associated protein Bap, porin OmpA

- **Photodynamic therapy**
  - Used topically, host damage

- **Nitric oxide (NO)-based therapies**
  - Wound treatment, biofilm inhibition, environmental biocontrol

USA TODAY INVESTIGATION

Planning

DRUGS CAN’T STOP THIS KILLER

In the past decade, bacteria that resist even ‘drugs of last resort’ have spread to health care facilities in 42 states

A specimen of an antibiotic-resistant, infectious bacteria — belonging to the family known as Carbapenem-Resistant Enterobacteriaceae, or CRE — sits in a laboratory petri plate.
The 7th International Congress of the Asia Pacific Society of Infection Control

March 26-29
Taipei International Convention Center, TAIWAN

Combating infection for global health

MARK YOUR DIARY
www.apsic2015.org