Emergence of MDR: Are we different from the rest of the world

Dr C. Wattal, M.D.
Chairman
Dept of Clinical Microbiology
Sir Ganga Ram Hospital
New Delhi.
Antibiotic-Resistant Bugs in the 21st Century — A Clinical Super-Challenge

• It is more difficult than ever to eradicate infections caused by antibiotic-resistant “superbugs,”

• And the problem is exacerbated by a dry pipeline for new antimicrobials with bactericidal activity against gram-negative bacteria

Cesar A. Arias. NEJM 2009, 360:439-443
Need to Identify Antibiotic Resistance?
Development of R is potentially a disastrous situation

- The consequences of resistance:
  - Higher mortality and morbidity, such as neurologic damage in children with pneumococcal meningitis not recognized as R or for which alternatives to first-line antibiotic therapy are less effective.
  - Infections with R organisms lead to longer hospitalizations and greater expense, e.g. valve replacement in enterococcal endocarditis or lung resection in pulmonary tuberculosis.
  - More virulent organism such as MRSA acquires R to vancomycin, the consequences still more devastating, because the alternatives are few or nonexistent.
A Tilting Balance in India

Gram +ve bacteria
Major problems....
MRSA
Penicillin R pneumococci
Vancomycin-R enterococci
But
Many new antibiotics

• Most Infections due to Gram -ve bacteria
  Rising problems....
  ESBL producers
  – Pan R Acinetobacter
  & P. aeruginosa

And

Few new antibiotics
# Most Common Bacteremia Pathogen: SGRH

**2008**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Pathogen</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CNS</td>
<td>20</td>
</tr>
<tr>
<td>2.</td>
<td>Acinetobacter</td>
<td>11</td>
</tr>
<tr>
<td>3.</td>
<td>E. coli</td>
<td>10</td>
</tr>
<tr>
<td>4.</td>
<td>Candida/Pse./Kl</td>
<td>9</td>
</tr>
<tr>
<td>7.</td>
<td>S.typhi</td>
<td>8</td>
</tr>
<tr>
<td>8.</td>
<td>Enterococcus</td>
<td>5</td>
</tr>
<tr>
<td>9.</td>
<td>S.paraA</td>
<td>4</td>
</tr>
<tr>
<td>10.</td>
<td>S.aureus</td>
<td>3</td>
</tr>
</tbody>
</table>

**2013**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Pathogen</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CNS</td>
<td>17</td>
</tr>
<tr>
<td>2.</td>
<td>Kleb.</td>
<td>17</td>
</tr>
<tr>
<td>3.</td>
<td>Candida</td>
<td>16</td>
</tr>
<tr>
<td>4.</td>
<td>Acineto.</td>
<td>13</td>
</tr>
<tr>
<td>5.</td>
<td>E.coli</td>
<td>11</td>
</tr>
<tr>
<td>6.</td>
<td>Enterococcus</td>
<td>9</td>
</tr>
<tr>
<td>7.</td>
<td>Pseud.</td>
<td>5</td>
</tr>
<tr>
<td>8.</td>
<td>S.typhi</td>
<td>4</td>
</tr>
<tr>
<td>9.</td>
<td>S.aureus</td>
<td>4</td>
</tr>
</tbody>
</table>

*Microbiology Newsletter 2008-2014*
You are the next class of drug-resistant bacteria. As humans continue to abuse and overuse antibiotics, your ranks will swell. So, go out there and mutate! And remember: that which does not kill us makes us stronger!!
Trends & Causes of Bacteremia In Hospitalized Patients (SGRH)

Microbiology Newsletter 1999-2014
Blood isolates from Ward Jan. - Dec., 2013

**Acinetobacter**

**E. coli**

**Enterococci spp.**

**Fungal isolates**

**Klebsiella**

**Salmonella paratyphi A**

**Salmonella typhi**

**Staph. aureus**

**Staphylococci**

**Streptococcus spp.**

**Others**

**Others**: Achromobacter spp. -1, Aeromonas-3, Burkholderia cepacia-1, Chrysochromatium-2, Enterobacter spp.-5, Ochrobactrum anthropi-4, Pantoea sps.-1, Providencia spp. -1, Pseudomonas putida-1, Pseudomonas stutzeri.-2, Salmonella enteritidis-1, Serratia marsceceus-8, Serratia spp.-1, Sphingomonas paucimobilis-3, Stenotrophomonas maltophilia-4, Strept. pneumoniae-3, Streptococcus agalactiae-1, Streptococcus yogenes Group A -1
Blood Isolates from ICU: Jan-Dec 2013

Others: Achromobacter spp. 4, Aeromonas 4, Alcaligenes faecalis 1, Burkholderia capaica 6, Chrysobercteria spp. 8, Citrobacter spp. 2, Cryptococcus neoformans 2, Elizethkingia meningoseptica 8, Group A Streptococce 1, Ochrobactrum anthropi 3, Pantoea spp. 1, Proteus spp. 2, Providencia spp. 2, Pseudomonas spp. 2, Pseudomonas stutzeri 4, Ralstonia manitoliyctica 2, Ralstonia picketti 1, Salmonella spp. 2, Salmonella typhi 1, Salmonella typhimurium 1, Serratia marscecens 6, Serratia spp. 1, Sphingomonas paucimobilis 1, Strept. Pneumoniae 3, Streptococcus pyogenes Group A 2, Streptococcus spp. 6
Original article

Ecology of blood stream infection and antibiotic resistance in intensive care unit at a tertiary care hospital in North India

Chand Wattal\textsuperscript{a,*}, Reena Raveendran\textsuperscript{a}, Neeraj Goel\textsuperscript{a}, Jaswinder Kaur Oberoi\textsuperscript{a}, Brijendra Kumar Rao\textsuperscript{b}

\textsuperscript{a} Department of Clinical Microbiology & Immunology, Sir Ganga Ram Hospital, New Delhi 110060, India
\textsuperscript{b} Department of Critical Care Medicine and Emergency, Sir Ganga Ram Hospital, New Delhi 110060, India
Blood & Pus- GPC (OPD) 2013

% Resistance

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Staph aureus (254)</th>
<th>Staph CNS (303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Microbiology Newsletter vol. 20, No 1, 2014
Blood & Pus- GPC (Ward) 2013

% Resistance

- Clindamycin
- Gentamycin
- Oxacillin
- Penicillin G
- Vancomycin
- High Dose Genta
- Ampicillin
- Linzolid
- Daptomycin

- Staph aureus (122)
- Staph CNS (244)
- Enterococcus spp. (98)

Microbiology Newsletter vol. 20, No1, 2014
Sample Source & MRSA at SGRH : 2013

Blood | Urine | Pus | Body Fluid | Respiratory

%  

Microbiology Newsletter vol. 20, No.1, 2014
Time Series Analysis of AMR at a Tertiary Care Hospital Delhi. India.
Ongoing Trend Analysis: SGRH

% Resistance - S. aureus - Blood Isolates - IPD

Ongoing Trend Analysis: SGRH

% Resistance - S. aureus - Pus Isolates - IPD

- Penicillin
- Oxacillin
- Clindamycin
- Gentamicin
- Erythromycin

Graph showing the percentage resistance of S. aureus pus isolates over the years 1999 to 2013, with Penicillin showing a steady increase, Oxacillin showing fluctuations, Clindamycin and Gentamicin showing varying trends, and Erythromycin showing a decreasing trend.
% Resistance - Staph CONS - Blood Isolates - IPD

- Penicillin
- Oxacillin
- Clindamycin
- Gentamicin
% Resisance - E.coli - Blood Isolates - IPD

- Ampicillin
- Ceftriaxone
- Gentamicin
- Amikacin
- Ciprofloxacin
- Piperacillin + Tazobactum
- Cefapirazone + Sulbactum
- Imipenem
% Resistance - Klebsiella - Blood Isolates - IPD

- Ceftriaxone
- Gentamicin
- Amikacin
- Ciprofloxacin
- Piperacillin + Tazobactum
- Cefaperazone + Sulbactum
- Imipenem

Years: 2001 to 2013
% Resistance - S. Typhi - Blood Isolates-IPD

- Ampicillin
- Chloramphenicol
- Co-trimoxazole
- Nalidixic Acid
- Ciprofloxacin

Blood Isolates: Klebsiella - ICU

- Imipenem / Meropenem
- Ceftriaxone
- Amikacin
- Cefaperazone + Sulbactum
- Ceftazidime
- Colistin
- Ertapenem
- Piperacillin + Tazobactam
- Quinolones
- Tigecycline

Blood Isolates: Klebsiella - ICU
Blood Isolates: Pseudomonas - ICU

- Imipenem / Meropenem
- Amikacin
- Cefaperazone + Sulbactum
- Ceftazidime
- Colistin
- Piperacillin + Tazobactam
- Quinolones

Blood Isolates:
- Pseudomonas - ICU

Blood Isolates: Acinetobacter - ICU

% Sensitivity

2008 2009 2010

Imipenem / Meropenem
Ceftriaxone
Amikacin
Cefaperazone+Sulbactum
Piperacillin+Tazobactam
Ceftazidime
Colistin
Quinolones
Tigecycline

MDR organisms: increasing threat

• Gram negative organisms show multi-drug resistance by production of numerous beta-lactamases
  – Extended-spectrum β-lactamases (ESBL)
    • TEM, SHV & CTX-M types
  – AmpC
    • Derepressed chromosomal e.g Enterobacter
    • Plasmid-mediated in E. coli & Klebsiella
  – Carbapenemases
    • Metallo- (MBL) & non-metallo- (KPC) types
ESBL, OXA: Co-production

Multicenter study in 6 Indian cities in 2007

doi:10.1093/jac/dkl532
Advance Access publication 9 February 2007

**Comment on: Occurrence, prevalence and genetic environment of CTX-M β-lactamases in Enterobacteriaceae from Indian hospitals**

T. R. Walsh¹,* M. A. Toleman¹ and R. N. Jones²

<table>
<thead>
<tr>
<th>Klebs. spp. (n=24)</th>
<th>OXA</th>
<th>42%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=23)</td>
<td>CTX-M-15</td>
<td>75%</td>
</tr>
<tr>
<td>E. coli.</td>
<td>65%</td>
<td>83%</td>
</tr>
</tbody>
</table>

In India bacteria are frequently co-producing OXA along with ESBL (CTX-M-15) Which are Resistant to penicillins & 3rd gen cephalosporins cephamycins & BLIs (Cefepime is sensitive)
“PROBLEM” GRAM-NEGATIVE PATHOGENS

• ESBL-producing GNR
  – E. coli
  – Klebsiella pneumoniae
  – Enterobacter spp.

• Acinetobacter spp.

• P. aeruginosa

• Stenotrophomonas maltophilia

Wattal et al, Microbiology Newsletter 1997-2005; www.sgrh.com
Carbapenemases

1. MBL- VIM-1 in *K.pneumoniae* in Greece.
2. KPC in US, Greece, Israel
3. OXA-48 in Turkey
4. **NDM-1** Swiftly emerging - India

Antibiotic Consumption at SGRH: 1998-2013

- Total antibiotics
- Total cephalosporins
- Imipenem/Meropenem/Ertapenem
- Aminoglycosides
- Fluoroquinolones
- Macrolides
- Lincomycins
- Glycopeptides
- Linezolid

DDD/100 Bed Days

## 2008
Carbapenemases in Enterobacteriaceae: 35.8%

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of isolates screened</th>
<th>ESBL positive %</th>
<th>Imipenem Resistance %</th>
<th>Ertapenem Resistance %</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>211</td>
<td>61%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>263</td>
<td>40%</td>
<td>52%</td>
<td>55%</td>
</tr>
</tbody>
</table>

## Tigecycline: SGRH Experience

### Jan- Dec: 2013

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of isolates screened</th>
<th>Tigecycline Resistance %</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>298</td>
<td>4</td>
</tr>
<tr>
<td><em>Klebsiella spp.</em></td>
<td>157</td>
<td>42</td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td><em>Enterococci</em></td>
<td>89 (38 GRE)</td>
<td>0%</td>
</tr>
<tr>
<td><em>Staph aureus</em></td>
<td>46 (15 MRSA)</td>
<td>0%</td>
</tr>
</tbody>
</table>
Association between carbapenem consumption and resistance in *P. aeruginosa* and *A. baumannii* (SGRH)

*p* value for *A. baumannii* < 0.5
Trend analysis of antimicrobial consumption and development of resistance in non-fermenters in a tertiary care hospital in Delhi, India

Neeraj Goel, Chand Watta*, Jaswinder Kaur Oberoi, Reena Raveendran, Sanghamitra Datta and Kamal Jeet Prasad

Department of Clinical Microbiology & Immunology, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi-110060, India

*Corresponding author. Tel: +911-42251049; Fax: +911-25736022; E-mail: chand_watta@yahoo.com

Received 16 July 2010; returned 28 October 2010; revised 9 December 2010; accepted 3 April 2011

Objectives: Multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii are becoming increasingly important nosocomial pathogens worldwide. To study the evolution of non-fermenters in a tertiary care hospital, we undertook a retrospective 10 year (1999–2008) trend analysis of antimicrobial consumption and resistance in non-fermenters causing bacteraemia.

Methods: Antibiotic consumption and resistance were analysed by linear regression. The Pearson correlation coefficient was used for assessing correlation between them.

Results: A total of 69010 blood cultures were performed, which grew 15465 isolates (22% positivity rate), of which 1525 isolates (771 isolates of P. aeruginosa and 754 isolates of A. baumannii) were non-fermenters. Overall antibiotic consumption showed an increasing trend, from 158 to 319 defined daily doses (DDDs)/100 bed-days ($r^2=0.62$, $P=0.007$). The largest relative increase in antibiotic consumption was seen for carbapenems ($r^2=0.68$, $P=0.022$), followed by β-lactam/inhibitor combinations ($r^2=0.45$, $P=0.033$), whereas third-generation cephalosporins, fluoroquinolones and aminoglycosides showed no significant changes. A significant increase in resistance in A. baumannii to fluoroquinolones ($r^2=0.63$, $P=0.006$), aminoglycosides ($r^2=0.63$, $P=0.011$) and carbapenems ($r^2=0.82$, $P=0.013$) and in P. aeruginosa to aminoglycosides ($r^2=0.59$, $P=0.01$) was observed. Carbapenem consumption was associated with the development of resistance in A. baumannii ($r=0.756$, $P=0.049$), whereas no such association was observed for other antimicrobials among non-fermenters.

Conclusions: Our study highlights the growing problem of high antimicrobial consumption. The increasing prevalence of non-fermenters and the emergence of multidrug-resistant A. baumannii are associated with the consumption of carbapenems. The data cannot prove cause and effect.

Keywords: Pseudomonas aeruginosa, Acinetobacter baumannii, carbapenems, DDDs/100 bed-days, bacteraemia
Does broad-spectrum β-lactam resistance due to NDM-1 herald the end of the antibiotic era for treatment of infections caused by Gram-negative bacteria?

Patrice Nordmann¹*, Laurent Poirel¹, Mark A. Toleman² and Timothy R. Walsh²

¹Service de Bactériologie-Virologie, INSERM U914 ‘Emerging Resistance to Antibiotics’, Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine et Université Paris-Sud, K.-Bicêtre, France; ²Department of Medical Microbiology, School of Medicine, Cardiff University, Cardiff, UK
Candida - Annual Number of Blood Isolates by Species
Non-\textit{albicans} \textit{Candida} species in blood stream infections in a tertiary care hospital at New Delhi, India

Jaswinder Kaur Oberoi, Chand Wattal, Neeraj Goel, Reena Raveendran, S. Datta & Kamaljeet Prasad

\textit{Department of Clinical Microbiology \& Immunology, Sir Ganga Ram Hospital, New Delhi, India}

Received October 18, 2010

\textit{Background \& objectives:} During recent decades, there has been a change in the epidemiology of \textit{Candida} infections, characterized by a progressive shift from a predominance of \textit{Candida albicans} to non-\textit{albicans} \textit{Candida} species. This study was undertaken to analyze the change in the epidemiology of candidaemia and antifungal use at tertiary care hospital in New Delhi, India, over a period of 10 years.

\textit{Methods:} A retrospective review of candidaemia between 1999 and 2008 and antifungal use from 2000 to 2008 was performed at Sir Ganga Ram Hospital, New Delhi. Initially (1999-2005), isolates were differentiated as \textit{C. albicans} and non-\textit{albicans} \textit{Candida} species. Between 2006-2008, these were identified to the species level and antifungal susceptibility was performed.

\textit{Results:} The occurrence of candidaemia and total antifungal use increased significantly. Candidaemia due to non-\textit{albicans} species increased and this was correlated with an increasing use of fluconazole. There
### % Sensitivity in Yeasts Fungi* (Blood Isolates 2012)

<table>
<thead>
<tr>
<th>Species (no. of isolates Tested)</th>
<th>Amphotericin B**</th>
<th>Flucytosine</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Caspofungin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. tropicalis (40)</em></td>
<td>100</td>
<td>97.5</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><em>C. albicans (33)</em></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><em>C. pelliculosa (33)</em></td>
<td>96.9</td>
<td>51.7</td>
<td>84.8</td>
<td>96.9</td>
<td>100</td>
</tr>
<tr>
<td><em>C. parapsilosis (32)</em></td>
<td>100</td>
<td>72</td>
<td>90.62</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td><em>C. haemulonii (23)</em></td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>91.3</td>
<td>100</td>
</tr>
<tr>
<td><em>C. glabrata (17)</em></td>
<td>100</td>
<td>100</td>
<td>52.9</td>
<td>94.1</td>
<td>100</td>
</tr>
<tr>
<td><em>C. krusei (8)</em></td>
<td>100</td>
<td>25</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><em>C. lusitaniae (4)</em></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><em>C. utilis (3)</em></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><em>C. rugosa (3)</em></td>
<td>100</td>
<td>100</td>
<td>66.6</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><em>C. guilliermondii (2)</em></td>
<td>100</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td><em>Kodamea ohmeri (2)</em></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans (2)</em></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td><em>Trichosporon spp. (4)</em></td>
<td>75</td>
<td>50</td>
<td>75</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Antifungal Susceptibility Results Interpreted as per CLSI M27S4 Document (Dec 2012)**

<table>
<thead>
<tr>
<th>Species (no. of isolates Tested)</th>
<th>Amphotericin B**</th>
<th>Flucytosine</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Caspofungin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. tropicalis (40)</em></td>
<td>100</td>
<td>97.5</td>
<td>97.5</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><em>C. albicans (33)</em></td>
<td>100</td>
<td>100</td>
<td>93.9</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><em>C. parapsilosis (32)</em></td>
<td>100</td>
<td>62.5</td>
<td>68.75</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Figures in parenthesis indicate the number of isolates tested.

*Figures in parenthesis indicate the number of isolates tested. ( - = Not done). Antifungal susceptibility results have been interpreted as per CLSI M27A3 document.*

**YST-AST Cards Vitek 2 (bioMerieux, France), E Test (Rpt isolates excluded), CLSI M-39A, Vol. 22, No. 8; 2002 (global consensus guidelines).**

*Isolates with MIC of <1 μg/ml.*

36.6% yeasts isolated from blood samples were non-*C. albicans* Candida spp. in line with the trend noticed previous year (84%). Overall, *C. tropicalis* was the most common species (41 cases; 20.2%), followed by *C. albicans* (33 cases each; 15.8%), *C. parapsilosis* (32 cases; 15.3%), *C. haemulonii* (23 cases; 11.05%) and *C. glabrata* (18 cases; 8.6%). *C. pelliculosa* was the most common cause of candidaemia in neonates consistent with the previous year. Nearly all the isolates were completely sensitive to amphotericin B, the notable exception being *C. haemulonii*. 