

## World Health Day 2011: Antimicrobial Resistance and Practical Solutions

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On 7 April 2011, World Health Organisation (WHO) marked World Health Day 2011. This year's theme is antimicrobial resistance. It is timely given the global emergence and spread of New Delhi metallo-beta-lactamase-1 (NDM-1) in 2010, adding to an increasing list of resistance mutations that may spell the end of "last-line" carbapenems as antibiotics.<sup>1</sup> Extensively drug-resistant *Mycobacterium tuberculosis*,<sup>2</sup> antiretroviral drug resistance in Human Immunodeficiency Virus (HIV),<sup>3</sup> and antimalarial drug resistance<sup>4</sup> add to this alarming pandemic of antimicrobial resistance.

In Singapore, antimicrobial resistance is an under-recognised public health problem with high levels of methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL) in *Escherichia coli* and *Klebsiella pneumoniae*, and carbapenem resistance in *Acinetobacter baumannii* in our hospitals.<sup>5</sup> The question that must be asked is: Can we reverse this tsunami of antibacterial resistance?

The answer lies in the often-forgotten principles of antibiotic use.<sup>6</sup> The approach to implement these principles is called Antimicrobial Stewardship<sup>7</sup> The principles of antibiotic use can be summarised: (i) microbiology guides therapy where possible, (ii) indications should be evidence-based, (iii) the narrowest spectrum effective antibiotic is preferred, (iv) the dosage should be appropriate for the site and type of infections, (v) minimise duration of therapy, and (vi) ensure monotherapy in most cases.

Antimicrobial resistance is not restricted to hospitals. Overuse of antibiotic in primary care can be challenging. However, strong evidence is available to guide the use of antibiotics in common primary care infections. A meta-analysis of 9 randomised trials involving 2547 adults documented the limited benefit of antibiotics for acute bacterial rhino-sinusitis.<sup>8</sup> A meta-analysis of 9 randomised trials with 750 patients on antibiotic for acute bronchitis found the benefits of antibiotic were matched by antibiotic-related adverse events.<sup>9</sup> Antibiotic was found to have no clinical benefit and increase adverse events and stool carriage in non-typhoidal *Salmonella* gastroenteritis in healthy

patients in a meta-analysis of 12 randomised and quasi-randomised trials involving 778 patients.<sup>10</sup> The challenge lies in getting doctors not to prescribe and patients not to request for antibiotics in these common primary care infections. Empowering patients and doctors in saying no to unnecessary antibiotics should be an urgent and ongoing public educational campaign.

In hospitals, antibiotic overuse can be dealt with effectively by Antimicrobial Stewardship Programme (ASP).<sup>11</sup> Procalcitonin can be a very effective strategy to reduce empiric use of antibiotic for the treatment of fever, rather than actual bacterial infections.<sup>12</sup> Randomised controlled trials have documented the safety of shorter course of antibiotic for nosocomial pneumonia (3 to 8 days).<sup>13,14</sup>

Therefore, the solution to the problem of antimicrobial resistance lies in abandoning spiraling empiricism, and returning to the basic principles of antibiotic use. For a long time, the medical community believes broad-spectrum antibiotics will cover most bacteria responsible for many common infections. This led to call to re-examine the cost-effectiveness of microbiological evaluation in common infections such as community-acquired pneumonia and pyelonephritis. However, in the era of "Bad Bugs No Drugs", this paradigm of spiraling empiricism should be re-examined and abandoned.<sup>15</sup>

For most patients who need hospitalisation for intravenous antibiotics, appropriate microbiological cultures are indicated. Evidence-based medicine should determine indications for antibiotic use and duration of antibiotic therapy. Narrow-spectrum antibiotics should be preferred over broad-spectrum antibiotics in cases of positive clinically significant microbiologic cultures. The continuation of broad-spectrum antibiotic for an antibiotic-susceptible bacterium in a clinically significant culture is a lost opportunity to reduce unnecessary broad-spectrum antibiotic. This lack of de-escalation to narrow-spectrum active antibiotic increases the risk of antibiotic resistance for our patients.

Informal antibiotic resistance and usage surveillance at the majority of public hospitals has been undertaken in

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Singapore since 2006. MRSA has shown a trend to decrease over time at three hospitals with formal ASP. Ceftriaxone-resistant *E coli* significantly increased in one hospital without ASP while ceftriaxone-resistant *K pneumoniae* significantly decreased in 2 hospitals with formal ASP. Carbapenem resistance in *Pseudomonas aeruginosa* significantly decreased at one hospital with formal ASP.

Broad-spectrum cephalosporins decreased significantly in 2 hospitals, and fluoroquinolones decreased in these same hospitals with formal ASP. Carbapenems increased in all hospitals except in one with formal ASP. This increase in carbapenem use is especially troubling as there has been no increase in ESBL *E coli* and *K pneumoniae* that justifies its use, and we have increasing carbapenem-resistant *A baumannii* and the recent emergence of NDM-1. These trends are summarised in Table 1. These observations provide empirical evidence that ASP works in Singaporean hospitals. The challenge lies in funding and implementing ASP as part of a comprehensive programme to address multidrug-resistant organisms in hospitals encompassing an effective infection control programme.

In conclusion, we must heed the call from WHO of “No Action Today, No Cure Tomorrow” and Infectious Diseases Society of America of “Bad Bugs, No Drugs”, as we are on the verge of the post-antibiotic era. However, we have a really good chance of turning back time and reversing antibiotic resistance. We must embrace the principles of antibiotic use. Antimicrobial Stewardship Programme is not new science, but an effective way of implementing these principles.

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Table 1. Trends in Incidence Density of Multidrug-Resistant Organisms and Selected Antibiotic Usage from 2006 To 2010 at Five Adult Public Hospitals with and without Antimicrobial Stewardship Programmes

	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5
Antimicrobial stewardship programme exists	Yes	Yes	Yes	No	No
MRSA	Decreasing trend	Decreasing trend	Decreasing trend	Significant increase	Significant increase
Ceftriaxone-resistant <i>Escherichia coli</i>	Stable trend	Stable trend	Not available	Increasing trend	Significant increase
Ceftriaxone-resistant <i>Klebsiella pneumoniae</i>	Significant decrease	Significant decrease	Not available	Decreasing trend	Decreasing trend
Imipenem-resistant <i>Acinetobacter baumannii</i>	Increasing trend	Stable trend	Not available	Increasing trend	Significant increase
Imipenem-resistant <i>Pseudomonas aeruginosa</i>	Significant decrease	Decreasing trend	Not available	Increasing trend	Stable trend
Third/fourth generation cephalosporins	Significant decrease	Significant decrease	Decreasing trend	Increasing trend	Increasing trend
Fluoroquinolones	Decreasing trend	Decreasing trend	Increasing trend	Increasing trend	Increasing trend
Carbapenems	Significant increase	Stable trend	Significant increase	Significant increase	Significant increase

MRSA : methicillin-resistant *Staphylococcus aureus*

Data from the 2006 to 2010 reports of the Network for Antimicrobial Resistance Surveillance (Singapore)