Feature Article

Paving the Way Forward: The Medical City Antimicrobial Stewardship Program

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Background

The discovery of penicillin in 1928 by Sir Alexander Fleming revolutionized the way physicians treat infections. During his Nobel Lecture in 1945, however, Fleming warned: "The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.[1]" As more antimicrobials were discovered throughout the years, we saw with almost mechanical regularity the appearance of strains resistant to these newly discovered drugs, with rates increasing the more these antibiotics were used. As the drug pipeline dried up and fewer novel molecules were discovered, attention now turned to ensuring that these antimicrobials were used judiciously.

A 2014 report from the United Kingdom on antimicrobial resistance (AMR) estimated that there will be 10 million people dying every year from resistant bacteria by the year 2050 if nothing is done about it today.[2] By then, the worldwide cost related to AMR is projected to be as much as US$100 trillion. The magnitude of AMR's effect on people and economies led the World Health Assembly to endorse a Global Action Plan on AMR. Soon, AMR appeared on the agenda of almost every nation, including the Philippines. The 2018 Antimicrobial Resistance Surveillance Program (ARSP) report presents the sobering reality that AMR is present in the Philippines as well (Figure 1). It is but fitting that all physicians should pay attention to this important crisis.

The main driver of antibiotic resistance is antibiotic consumption, whether appropriately or inappropriately prescribed. Sun et al has demonstrated that the occurrence of resistant Escherichia coli and methicillin-resistant Staphylococcus aureus follows the curve of antibiotic prescriptions for aminopenicillins and fluoroquinolones, respectively, with a lag of about one month (Figures 2A & 2B).[3] In short, physician prescriptions directly affect resistance rates. While there are many different factors that affect AMR,[4] the clearest and most direct one is antimicrobial consumption. It is then incumbent upon all physicians to be careful about how they use antibiotics and should consider these medicines a precious resource. This need to rationalize the use of antimicrobials is what antimicrobial stewardship (AMS) is all about.

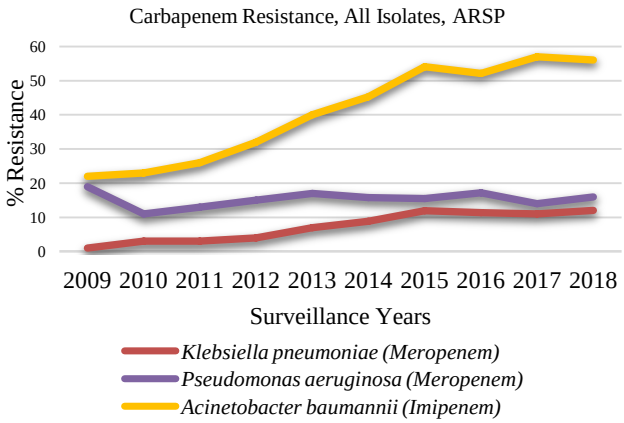

Figure 1. Carbapenem resistance of *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (all isolates) as reported in the Antimicrobial Resistance Surveillance Program (ARSP) from 2009 to 2018. The reported carbapenem for *A. baumannii* is imipenem due to unavailability of meropenem susceptibility in the earlier reports

The Medical City (TMC) started restricting access to very broad-spectrum antimicrobials in the late 1990s. This early attempt at improving antimicrobial use is evidence of TMC's pioneering leadership role in AMS in the country. In response to the global call against AMR, our own government published the Philippine Action Plan to Combat Antimicrobial Resistance: One Health Approach in 2016.[5] Soon thereafter, the Department of Health required all hospitals in the country to create formal Antimicrobial Stewardship Programs (ASPs) as a requirement for licensing and accreditation. Since TMC already had many initiatives in place that promoted antimicrobial stewardship, the creation in 2016 of a formal Antimicrobial Stewardship Committee focused on consolidating and expanding AMS activities was a logical step

Antimicrobial Stewardship: Definition and Rationale

Good AMS is a "practice that ensures the optimal selection, dose, and duration of an antimicrobial therapy that leads to the best clinical outcome for the treatment or prevention of infection while producing the fewest toxic effects and the lowest risk for subsequent resistance.[6]" The fundamental challenge in AMS is the balancing act between providing timely and appropriate empirical broad spectrum antimicrobial therapy for individual patients versus reducing unnecessary use of these same agents and their subsequent collateral damage.[7,8]

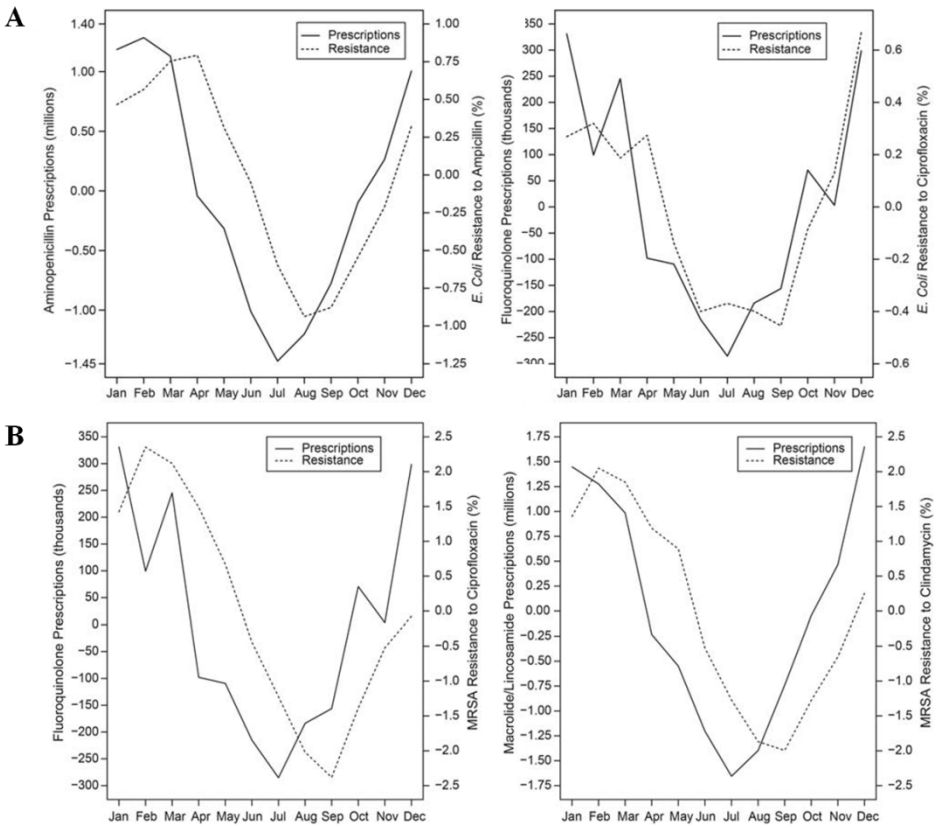

Figure 2. (A) Seasonal pattern of high-usage antibiotic prescriptions and *Escherichia coli* (*E. coli*) resistance, showing 1-month lag; (B) Seasonal pattern of antibiotic prescriptions and Methicillin-Resistant *Staphylococcus aureus* (MRSA), showing 1-month lag. Figures re-printed with permission from Oxford University Press (Sun *et al.*, Seasonality and Temporal Correlation between Community Antibiotic Use and Resistance in the United States, 2012, 55(5): 690-691)

Schuts et al examined the existing evidence for 9 AMS objectives using four pre-defined outcomes: clinical outcomes (mortality and morbidity), adverse events, cost, and resistance rates.[9] While they cite generally low quality of evidence and moderate to high heterogeneity between studies, they found that guidelines-based empirical therapy, de-escalation of therapy, switch from intravenous to oral treatment, therapeutic drug monitoring, antimicrobial restriction, and bedside consultation resulted in significant benefits for one or more of the 4 outcomes.

Honda et al examined inpatient AMS in the Asia Pacific Region.[10] Using 4 outcomes (clinical, antimicrobial prescription, microbiology, and expenditure), the authors reviewed the results of 46 studies from 9 countries. Their meta-analysis demonstrated that ASPs resulted in significant reductions in antimicrobial and carbapenem consumption and trends toward decreased incidence of multidrug-resistant organisms and antimicrobial expenditure. Consistent with the previous reviews, this study showed no significant mortality increase with ASPs.

The most recent Cochrane Review of hospital-based interventions to improve antibiotic prescribing practices[11] showed that enabling and restrictive methods were associated with a 15% increase in compliance with desired practice, a 1.95-day decrease in treatment duration, and a 1.12-day decrease in inpatient length of stay without compromising patient safety.

Components of the TMC Antimicrobial Stewardship Program

In November 2017, the leadership of TMC approved the policy governing all aspects of antimicrobial utilization in our institution. The policy was patterned after the DOH's own Manual of Operations for Antimicrobial Stewardship,[12] with revisions meant to adopt various components to the culture of TMC. Some of the most practical components of the program, as well as its objectives, are described below.

TMC Antimicrobial Use Guidelines (Empiric Recommendations, Surgical Prophylaxis). The hospital's antibiogram is one of the most important tools used in AMS. Aside from informing physicians about which organisms are most common in the hospital, classified by source (blood, urine, respiratory secretions, etc) and by location (outpatient, inpatient wards, and critical care units, (Figure 3A), the antibiogram also reports on susceptibility patterns of these organisms (Figure 3B). The idea is to allow the physicians to make educated decisions about

empiric therapy for individual patients. At TMC, the information from the local antibiogram is synthesized with the recommendations from the National Antibiotic Guidelines Committee (NAGCOM), a multidisciplinary group of experts tasked to review existing local and international guidelines and formulate a unified document to be used by healthcare institutions in the country.[13] The resulting document, TMC's Antimicrobial Use Guidelines, is reviewed and published annually (Table 1) to guide physicians in the management of the most common infections and in making wise choices for surgical antibiotic prophylaxis.

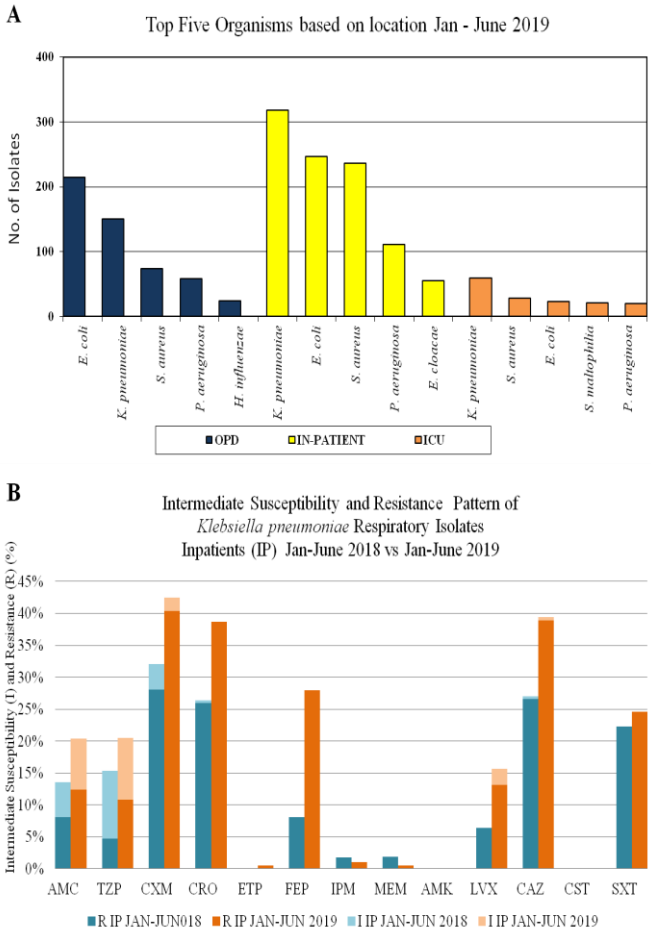

Figure 3. (A) Seasonal TMC Antibiogram January to June 2019, top 5 organisms by hospital location; (B) TMC Antibiogram, intermediate susceptibility and resistance patterns of *Klebsiella pneumoniae* (respiratory isolates obtained from inpatients); AMC- amoxicillin-clavulanic acid, TZP- piperacillin-tazobactam, CXM- cefuroxime; CRO- ceftriaxone, ETP- ertapenem, FEP- cefepime, IPM- imipenem, MEM- meropenem, AMK- amikacin, LVX- levofloxacin, CAZ- ceftazidime, CST- colistin, SXT- trimethoprim-sulfamethoxazole

Drug Duration Audit and Feedback (DDAF or Automatic Stop Order). There is a growing body of evidence that for most infections, a short course of antimicrobials is as effective as the traditional longer courses.[14] Short courses of antimicrobials result in less adverse effects, such as *Clostridioides difficile* infections, lower cost, and better outcomes. The DDAF is our attempt to remind the medical staff to frequently evaluate the need for continued antibiotics in individual patients. DDAF is currently in effect only in critical care units but will soon be implemented hospital-wide in accordance with directives from the DOH.

Prospective Audit of Monitored Antimicrobials with Direct Feedback. TMC was one of a handful of Philippine hospitals participating in the Global Point Prevalence Survey on Antimicrobial Consumption and Resistance.[15] In this survey, we found that 53% of inpatients at our institution are on antimicrobials at any given time.[16] This is a staggering figure since worldwide average is only around 31%.[17] In addition, 43% of our antimicrobial usage did not adhere to NAGCOM guidelines. In an attempt to optimize utilization of antimicrobials at the point of care, the HICEC Executive Committee created a list of 8 "monitored" antimicrobials derived from the most commonly used antibiotics based on the results of our prevalence survey. Prescription of these monitored antimicrobials will trigger the AMS Team (composed of the AMS Committee Chair or ID fellow and AMS clinical pharmacists) to review the patient's chart and to make one or more of the following recommendations: intravenous-to-oral therapy switch, dose optimization, and streamlining or de-escalation. Implementation of this initiative will be in phases and will begin with one or more medical floors with plans for hospital-wide expansion.

Prior Approval of Restricted Antimicrobials (PARA). This stewardship initiative has been in place in one form or another since the late 1990s. In its current form, the list of restricted antimicrobials include: amphotericin B, anidulafungin, cefepime, colistin (polymyxin E), daptomycin, ertapenem, ganciclovir, imipenem, linezolid, meropenem, polymyxin B, tigecycline, valganciclovir, and vancomycin. Prescription of these medications by a non-ID physician must be accompanied by documentation of approval from an ID consultant. This will ensure that the broadest spectrum antimicrobials (and hence the most precious) are used appropriately and judiciously. This stewardship initiative is implemented hospital-wide.

Table 1. The Medical City Empiric Antimicrobial Recommendations 2019

Pneumonia
Community-acquired pneumonia- MODERATE RISK - Ampicillin-sulbactam 1.5g IV every 6 hours OR - Ceftriaxone 2g IV once a day PLUS • Azithromycin 500mg PO once a day OR • Clarithromycin 500mg PO twice a day OR • Levofloxacin 750mg PO once a day
Community-acquired pneumonia- HIGH RISK, without risk factors for *P. aeruginosa* - Ceftriaxone 2g IV once a day OR - Ertapenem 1 g IV once a day PLUS • Azithromycin dehydrate 500mg IV once a day OR • Levofloxacin 750mg IV once a day
Community-acquired pneumonia- HIGH RISK, WITH risk factors for *P. aeruginosa* - Piperacillin-tazobactam 4.5g IV every 6hours OR - Cefepime 2 g IV every 8-12h PLUS • Azithromycin 500mg IV once a day PLUS • Amikacin 15mg/kg IV once a day
Community-acquire pneumonia- HIGH RISK with suspicion of MRSA, ADD: - Vancomycin 25-30 mg/kg IV loading dose then 15-20 mg/kg every 8-12 hours OR - Linezolid 600mg IV every 12 hours OR - Clindamycin 600mg IV every 8 hours
HAP/ VAP- inpatient, no risk factors for MDR organisms (e.g. *A. baumannii*) - Piperacillin-tazobactam OR Cefepime OR Meropenem ± - Amikacin 15mg/kg IV once a day
Pneumonia other than CAP- inpatient with risk factors for MDROs (e.g. *A. baumannii*) - Immediate referral to ID recommended
Pneumonia other than CAP- inpatient, non-ICU, with risk factors for MRSA or aspiration - Add Clindamycin
Pneumonia other than CAP- inpatient, ICU with risk factors for MRSA - Add Vancomycin OR Linezolid
Urinary Tract Infections
Acute cystitis - Nitrofurantoin
Acute uncomplicated pyelonephritis - Ceftriaxone
In-patients (hospital acquired): - Without risk factors for ESBL producing organisms: • Piperacillin-tazobactam OR Amikacin - With risk fac tors for ESBL producing organisms: • Ertapenem OR Amikacin
Skin and Soft Tissue Infections
Caveat: the vast majority of non-purulent SSTI (i.e. no microbiologic data available) is due to Streptococci Community acquired, localized, without signs of sepsis: - Clindamycin OR - Doxycycline OR - Cotrimoxazole (no good Streptococcal coverage) Nosocomial and/ or with signs of sepsis: - Vancomycin OR - Linezolid PLUS • Piperacillin-tazobactam
Azithromycin FDA Drug Safety Communication
1. FDA warns about increased risk of cancer relapse with long term use of azithromycin after donor stem cell transplant (8/3/2018) 2. Azithromycin and the risk of potentially fatal heart rhythms (3/12/2013)
Levofloxacin FDA Drug Safety Communication
1. FDA warns about increased risk of ruptures or tears in the aorta blood vessel in certain patients (12/20/2018) 2. FDA is strenghthening the current warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decrease in blood sugar and certain mental health side effects (7/10/2018)

Future Direction

Except for the PARA initiative, implementation of the components of the AMS program are in place only in selected areas of the hospital. In order to ensure that TMC remains a good steward of these precious antimicrobials and maintain its leadership in this field, the program components have to be implemented hospital-wide. For this to occur, hospital leadership needs to invest in the hiring and training of additional staff (both clinical pharmacists and nurses) with a heart for AMS. Transitioning to a new electronic record with the capacity to automatically generate AMS-related reports should also allow the AMS team to streamline its workflow and devote more time to interacting with the medical teams (i.e. audit and feedback) rather than tedious data collection.

With a national government bent on ensuring implementation of an AMS program nationwide in the next few years, there is a flurry of activity in both the public and private sectors to ensure compliance with newly established policies. For many healthcare institutions, especially the smaller hospitals unfamiliar with the concepts of AMS, this means sending staff to training seminars and multiple strategic planning sessions. Because our institution has invested in AMS for many years, we find ourselves in a somewhat mentorship role in the midst of all this activity. Beginning in 2016, some of our leaders in the Section of Infectious Diseases have been heavily involved in the DOH-sponsored training of hospitals in AMS. In 2016, we hosted two clinical pharmacists in the maiden run of a clinical pharmacy fellowship for AMS. It is evident that our commitment to building the national AMS program is resolute and our role in the national AMS program is an embodiment of our hospital's mission to take a leadership role in shaping how the nation thinks, feels, and behaves about health.

More than all the AMS-related programs and policies in place, the core need of a good antimicrobial stewardship campaign is behavioral change and a paradigm shift among antibiotic prescribers. AMR has been called a "slow moving catastrophe[4]" because it is less acute and less glamorous than ebola or epidemic influenza. But AMR is just as deadly. The families of patients affected by infections caused by multidrug resistant organisms (MDROs) know all too well how lethal these bacteria can be. There is a mountain of evidence showing that antibiotics are overprescribed and abused, despite well-written, evidence-based guidelines. Unless antibiotic prescribers stop thinking small (i.e. just their own patients) and start thinking with a global mindset, antibiotics will continue to be overused. There are many different things physicians can do to reduce inappropriate antibiotic use.[4] The common theme in all these should be a basic understanding of why things need to change.

Antibiotics are one of the most commonly prescribed types of medication and their use cuts across all specialties. If we lose this precious resource to over-prescription and abuse, we may bring the world back to an era when penicillin was unavailable, and patients died from the simplest of infections. All physicians must recognize their critical role as stewards of antibiotics and should work to ensure that these drugs are used properly and judiciously.

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