Multidrug-Resistant Pulmonary Pathogens: Controlling a Major Public Health Risk

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Multidrug-resistant lung infections are increasingly common in vulnerable patient populations, including patients with tuberculosis and cystic fibrosis and the critically ill. In this session, chaired by Samuel M. Moskowitz, MD, Massachusetts General Hospital, Boston, MA, USA and Keertan Dheda, MBChB, PhD, University of Cape Town, Cape Town, South Africa, presenters discussed new approaches to the diagnosis and management of antibiotic-resistant pulmonary pathogens, including the use of first-line combination antibiotic therapy and novel drug delivery.

Emerging Multidrug-Resistant Pathogens

Gram-negative bacteria are increasingly resistant to conventional antibiotics, including beta-lactams, fluoroquinolones, and aminoglycosides. Multidrug-resistant gram-negative bacteria thrive in part because of mobile genes on plasmids that spread readily through bacterial populations. The widespread and inappropriate use of nonprescription antibiotics, particularly the carbapenems, increases the numbers of drug-resistant bacterial clones through selective pressure.

One recent example is the bla_{NDM-1} gene, which encodes New Delhi metallo-beta-lactamase-1 (NDM-1), an enzyme that is expressed by *Enterobacteriaceae* and confers resistance to a broad range of beta-lactam antibiotics. *Enterobacteriaceae*, particularly *Escherichia coli* and *Klebsiella pneumoniae*, are among the most common causes of serious nosocomial and community-associated bacterial infections. NDM-1 was first detected in 2008 in a *K. pneumoniae* isolate that was recovered from a Swedish patient in a hospital in New Delhi, India, and has since been detected in *E. coli* and *K. pneumoniae* isolates in India, Pakistan, Bangladesh, and the United Kingdom [Kumarasamy KK et al. *Lancet Infect Dis* 2010].

The sudden and widespread presence of NDM-1-encoding plasmids suggests an alarming new mechanism for antimicrobial resistance. Without aggressive infection control measures, the medical community may face multidrug-resistant *Enterobacteriaceae* that cause common respiratory infections, resulting in treatment failures and substantial increases in health care costs.

Extensively drug-resistant tuberculosis (XDR-TB) is another multidrug-resistant pathogen that has thrived as a result of inappropriate antibiotic use. XDR-TB is resistant to established first-line drugs (isoniazid and rifampin) as well as second-line therapy with fluoroquinolones and at least one injectable agent (amikacin, kanamycin, or capreomycin). Super XDR-TB is a subtype of XDR-TB that is resistant to all known classes of anti-TB medications. In a study of South African patients with XDR-TB, 68% had isolates that were resistant to all available drugs, leaving no effective treatment options for these patients [Shah NS et al. *Emerging Infect Dis* 2011]. These findings highlight the importance of expanded drug susceptibility testing for second- and third-line drugs to improve diagnosis and guide treatment for patients with multidrug-resistant TB.

Highlights from the
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Management of Multidrug-Resistant Infections

Experience in managing well-characterized respiratory infections may provide insight on the optimal management of emerging multidrug-resistant pathogens. *Pseudomonas aeruginosa* is a major cause of ventilator-associated pneumonia (VAP). In a multicenter, retrospective study of 183 patients with VAP and positive respiratory cultures for *P. aeruginosa*, initial treatment with antibiotic monotherapy provided poor protection against resistance

compared with combination therapy with meropenem/levofloxacin. Moreover, patients who received inappropriate antibiotic therapy had a significantly higher risk of in-hospital mortality compared with patients who received at least one antibiotic with in vitro activity against *P. aeruginosa* (72.5% vs 23.1%; p<0.05) [Garnacho-Montero J et al. *Crit Care Med* 2007]. These findings underscore the importance of initial combination therapy to increase the likelihood of effective therapy and reduce the risk of death, at least until antimicrobial susceptibility can be confirmed and patients can be switched safely to monotherapy.

The Procalcitonin to Reduce Patients' Exposure to Antibiotics in Intensive Care Units (PRORATA) trial was designed to evaluate the effects of reduced antibiotic exposure, through improved diagnosis or shorter treatment duration, on the risk of antimicrobial resistance [Bouadma L et al. *Lancet* 2010]. The PRORATA trial included 620 adult patients with bacterial infections who were expected to be in the intensive care unit (ICU) for at least 3 days. Patients were randomly assigned to antibiotic therapy that was guided by standard clinical parameters (n=319) or by serum procalcitonin (PCT) levels (n=311). In the PCT group, patients discontinued antibiotic therapy when PCT level reached an absolute value of <0.5 µg/L or a relative value of <80% of peak pretreatment level. The primary endpoints were mortality at 28 and 60 days and number of days without antibiotics by Day 28.

Overall mortality was similar in the PCT and control groups at Day 28 and at Day 60 (Table 1). However, patients in the PCT group had significantly more days without antibiotics than those in the control group (14.3 vs 11.6 days; p<0.0001). Thus, PCT-guided treatment reduced mean antibiotic use in critically ill patients, with no apparent adverse outcomes on survival. Reducing cumulative antibiotic exposure through biomarker-directed therapy is a promising option for easing selective pressure toward antibiotic resistance in this highly vulnerable patient population. Additional prospective studies are needed to confirm the safety and efficacy findings of the PRORATA trial before this practice is widely implemented.

Table 1. PRORATA Trial: Biomarker-Directed Therapy in Critically Ill Patients.

Outcomes	PCT-Guided Antibiotic Therapy (n=307)	Standard Care (n=314)	p Value
28-day mortality, %	21.2	20.4	NS
60-day mortality, %	30.0	26.1	NS
Days without antibiotic use	14.3	11.6	<0.0001

NS=nonsignificant; PCT=procalcitonin; PRORATA=Procalcitonin to Reduce Patient Exposure to Antibiotics in Intensive Care Units.

Better delivery of antibiotics to the deep lung may also reduce the risk of multidrug resistance. In a Phase 3 trial, 100 patients with gram-negative VAP were randomly assigned to receive adjunctive nebulized colistimethate sodium (CMS) or nebulized placebo every 12 hours in addition to systemic antibiotic therapy. Patients who received adjunctive CMS had significantly more favorable microbiological outcomes than those in the control group (60.9% vs 38.2%; p=0.03) [Rattanaumpawan P et al. *J Antimicrob Chemother* 2010].

In summary, multidrug resistance, especially among gram-negative bacilli, has emerged as a major factor that affects outcomes in patients with respiratory infections. To combat this looming public health crisis, there is an urgent need for health care providers to apply evidence-based strategies to improve infection control and reduce selective antibiotic pressure in patients with suspected bacterial infections.