New antibacterials?

Kevin B Laupland MD MSc FRCPC¹, David N Fisman MD MPH FRCPC²

The worldwide emergence of multidrug-resistant bacteria is among the most important contemporary health care problems. With few exceptions such as the continued universal susceptibility of *Streptococcus pyogenes* to penicillin despite more than half a century of use, resistance to antimicrobial agents is a generalized phenomenon across all medically important pathogens that has paralleled the introduction and use of antibacterial agents. A relatively short list of particularly notorious, resistant bacterial agents exist and include vancomycin-resistant *Enterococcus faecium* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum-beta-lactamase (ESBL)-producing *Escherichia coli*, ESBL and carbapenemase-producing *Klebsiella pneumoniae*, and multidrug-resistant strains of *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species (1). Multidrug-resistant strains of *Neisseria gonorrhoeae* threaten recent gains in the control of this sexually transmitted infection (2); extensively, drug-resistant tuberculosis is a major emerging global threat (3). Resistant organisms have challenged our ability to manage patients at increased risk for adverse outcomes related to inadequacy of empirical therapies, and directed therapies that often require use of toxic agents or suboptimal routes of administration or efficacy.

Resistance is not a new problem. Only shortly after the clinical use of penicillin did penicillin-resistant strains of *S aureus* emerge that later became ubiquitous. However, the pharmaceutical industry responded with a plethora of new agents across a range of classes to combat this and provide a range of safe and effective treatment options over the subsequent decades. In recent years, this has most certainly changed. There have only been a small number of new systemic antibacterial drugs for treating serious infections approved for use in Canada (Table 1). The determinants as to why so few new agents are coming to market are complex and are not limited to discovery of new agents but, rather to, alternative economic prospects and increasingly stringent regulatory and legal requirements (4).

While these new agents have been important additions to our therapeutic armamentarium against resistant bacteria, they certainly have not been a panacea. The newer quinolone agents have added only a relatively modest enhanced spectrum of activity and have not been generally effective against ciprofloxacin-resistant organisms. Linezolid has been a major advance against resistant Gram-positive infections, most notably VRE and as an alternative to vancomycin for MRSA. While there are some clinical niches for ertapenem and doripenem, these agents do not offer a significant new spectrum

of activity over the existing carbapenem agents against multidrug-resistant organisms. Daptomycin is an important alternative agent for treating serious extrapulmonary infections due to MRSA; however, the emergence of resistance at low doses and concern regarding the side effects at high doses has limited its widespread use. Ceftobiprole, the first cephalosporin agent with activity against MRSA and some enterococci, has certain appeal given its bactericidal mechanism of action and long track record of success with the class of cephalosporins in general. However, data are needed to document its efficacy in serious infections. Tigecycline has activity against a number of resistant organisms including ESBL-producing Enterobacteriaceae, MRSA and glycopeptide-resistant enterococci. However, its bacteriostatic mode of activity limits its ability to be used in many severe infections.

Will the agents coming down the pipeline in the near future solve our problems? Agents in mature stages of development include, but are not limited to, iclaprim (a diaminopyrimidine dihydrofolate reductase inhibitor with bactericidal anti-MRSA activity), ceftaroline (an anti-MRSA cephalosporin), garenoxacin (a broad-spectrum quinolone with activity against many other quinolone-resistant strains) and the cyclic glycopeptides – dalbavancin, oritavancin and telavancin – that have enhanced activity against MRSA and *S aureus* strains with reduced susceptibility to vancomycin but variable activity against VRE (5,6). While these agents offer alternatives to existing therapies, particularly for Gram-positive infections, they offer little for multidrug-resistant Gram-negative infections. Indeed, the situation with multiresistant Gram-negative microbes has become so desperate that some clinicians have begun to use parenteral formulations of antimicrobials (such as colistin and polymyxin B) that had been largely abandoned for systemic use due to toxicity in the 1960s (7).

The future is not bright for the management of severe multidrug-resistant bacterial infections. Historically, rates of resistance have been shown to rise, and agents and mechanisms of resistance have continued to emerge. Mechanistically, this makes sense. As the pool of available agents to which a given pathogen is susceptible shrinks, the concentrated exposure of that pathogen to the few remaining active agents becomes more intense – speeding the loss of the remaining drug classes. The aging population makes it inevitable that an increasing proportion of the population will have age-associated comorbidities that increase the risk of both infection and antimicrobial exposure. However, unlike in the past when pharmaceutical companies readily responded with a vast array of new agents,

¹Departments of Medicine, Critical Care Medicine, Pathology and Laboratory Medicine, Centre for Antimicrobial Resistance, University of Calgary, Calgary Laboratory Services, Calgary Health Region, Calgary, Alberta; ²The Research Institute of the Hospital for Sick Children, University of Toronto, Ontario Agency for Health Protection and Promotion, Toronto, Ontario

Correspondence: Dr Kevin B Laupland, Room 719, North Tower, Foothills Medical Centre, 1403–29th Street Northwest, Calgary, Alberta T2N 2T9. Telephone 403-944-5808, fax 403-944-3199, e-mail Kevin.Laupland@albertahealthservices.ca

TABLE 1
Systemic antibacterial agents approved in Canada (date of notice of compliance) since the turn of the millennium

Generic name	Brand name (company, country)	Date of notice of compliance
Moxifloxacin	Avelox (Bayer HealthCare, USA)	October 19, 2000
Gatifloxacin	Tequin (Bristol-Myers Squibb Canada)	January 9, 2001
Linezolid	Zyvoxam (Pfizer Inc, Canada)	April 2, 2001
Ertapenem	Invanz (Merck & Co Inc, USA)	May 12, 2003
Telithromycin	Ketek (sanofi-aventis, USA)	May 28, 2003
Gemifloxacin	Factive (Oscient Pharmaceuticals, USA)	March 9, 2004
Daptomycin	Cubicin (Cubist Pharmaceuticals, USA)	September 24, 2007
Ceftobiprole	Zeftera (Janssen Ortho Inc, Canada)	June 26, 2008
Tigecycline	Tygaril (Wyeth, Canada)	October 23, 2008
Doripenem	Doribax (Ortho-McNeil-Janssen Pharmaceuticals, USA)	September 2, 2009

the drug pipeline looks quite dry. The possibility that our patients will become infected with organisms resistant to all available agents is a real concern and may become commonplace. What will we do then? A look at the history of infectious diseases may help to direct us in the future and guide us in devising means to better manage resistant infections.

Clinicians often forget the importance of the role of the surgeon or interventional radiologist in source control. Anecdotally, we regularly are referred patients who are often treated with long courses of antibiotics for infections (such as dental and skin and soft tissue abscesses) that promptly resolve with surgical intervention. Before the widespread use of antibiotics, source control was the primary means of infection treatment. In recent years, source control has been relegated to a second-line consideration, and the body of literature optimizing such source control is remarkably limited (8). While the importance of early and appropriate antimicrobial therapy is unquestionably important (9), enhanced efforts, research and a move to the forefront for source control are needed.

Our focus on antibiotic therapy has frequently caused us to neglect the importance of the host immune response and potential for its therapeutic manipulation. Many infectious diseases physicians and medical microbiologists may be unaware of the importance that serum therapy had in the preantibiotic era (10). Indeed, the first Nobel Prize for medicine was awarded in 1901 to the German physiologist Emil Adolf von Behring

for his work on serum therapy. In addition, one of the first 'true' clinical trials demonstrated a mortality reduction with serum therapy for diphtheria compared with standard therapy (eight of 239 [3%] versus 30 of 245 [12%]; $P < 0.001$) (11,12). Serum therapy for pneumococcal pneumonia was also found to reduce mortality to 21% from 31% (RR 0.67; 95% CI 0.60 to 0.75) (13), and intrathecal serum therapy was found to be effective for pneumococcal meningitis (14). However, this therapy was associated with a 10% rate of serum sickness, which led to its abandonment once penicillin became available. In recent decades, highly purified polyclonal intravenous immunoglobulin has become available, and is rarely associated with this side effect. While primarily used as an agent to prevent infection, it has shown promise in the management of severe infections (15).

Because we may lose the ability to manage severe infections due to antimicrobial-resistant bacteria, preventive efforts will become increasingly important. Strict adherence to hygiene and infection prevention and control practices will be of the utmost importance (16). Vaccines must also be recognized as a major tool to reduce the impact of resistant infections. While perhaps not usually considered in this context, the implementation of conjugate vaccines against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* have likely had a far greater impact on reducing mortality rates due to these organisms than any new antimicrobial agent in the recent decades (17). While some vaccines against important resistant bacteria have yielded only modest benefit (18), bacterial vaccines are an increasingly active area of research and development, and we hope for major advances in the coming years (19).

SUMMARY

Resistance in bacterial human pathogens is a major concern. While we can look forward to new antibacterial agents to add to our treatment arsenal, we must not rely on this approach to serve us indefinitely in the future. The diminished availability of effective antimicrobial agents for the treatment of serious infections, and especially those acquired via contact with the health care system, demands a renewed emphasis on infection prevention and control efforts to prevent transmission of these pathogens to vulnerable individuals with complex medical problems. A look to the preantibiotic era can remind us of our past successes in managing bacterial infection and serve as a foundation for developing new and more effective nonantibiotic approaches to the prevention and management and, hopefully, ultimately a reduction in the impact of these infections.

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