

JOURNAL OF SCIENTIFIC & INNOVATIVE RESEARCH**Antibiotics- new tools in current and future drug therapy**Brijesh Gupta^{*1}, Swapnil Singh¹

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Abstract: Over 50 years ago, the golden age of antibiotics dawned with considerable achievements in the discovery and development of the sulfonamides, penicillin and streptomycin. This success was followed by the characterization of the tetracyclines, macrolides, glycopeptides, cephalosporins and nalidixic acid. Most of these compounds are either derived from natural products or are produced by the synthetic modification of natural products. The from this time period have provided the basic scaffold for medicinal chemistry modifications to expand the spectrum and/or potency of improved analogs in subsequent years.

Keywords: Pakad, Alkaloids, Flavonoids and Phytochemical.

Introduction: Historically, the pharmaceutical industry capitalized on the discovery that many microbial secondary metabolites act as antibiotics.¹⁻³The research and development of antibacterial agents during the past 50 years has been an immense success story. The rate of mortality caused by bacterial infections has dropped

precipitously since the pre-penicillin days of the 1930s.^{4, 5}As more antibiotics were discovered, manufacturing processes were simplified, and newer formulations developed, access to antibiotics eased considerably and their use became widespread. Antibiotics had truly become the “panacea” of medicine and were being used to treat even the most common and

trivial types of infections, many of these non-bacterial in nature. Based on the work that he had done in his research laboratory, in an interview with The New York Times in 1945, Sir Alexander Fleming warned that the inappropriate use of penicillin could lead to the selection of resistant “mutant forms” of *Staphylococcus aureus* that could cause more serious infections in the host or in other people that the host was in contact with and thus could pass the resistant microbe. He was right and within 1 year of the widespread use of this drug a significant number of strains of this bacterium had become resistant to penicillin. Only a few years later over 50% were no longer susceptible to this new drug.⁶

Antibiotic Resistance:

In order to be fit to survive, all living organisms strive to adapt to their environment. Part of this adaptation process includes adjusting to weather conditions, to food, water and in many cases to oxygen availability and also to the presence of potentially dangerous or even lethal external agents. It is no secret that many insects have adapted remarkably well to their environment and so have microorganisms. Thus it should not be surprising to us that

bacteria have shown a remarkable ability to endure and adapt to their environment including the development of different mechanisms of resistance to most old and new antimicrobial agents.

The end result of this phenomenon is that many strains bacteria have become resistant, and in many cases multi-resistant to these therapeutic agents, thus rendering these drugs ineffective as treatments of choice for severe infections caused by this pathogens.⁷⁻¹¹

The list of bacteria developing resistance is impressive, from sulfonamide and penicillin-resistant *Staphylococcus aureus* in the 1930s and 1940s^{11, 12} to penicillin-resistant *Neisseria gonorrhoeae* (PPNG), and b-lactamase-producing *Haemophilus influenzae* in the 1970s¹³⁻¹⁶ methicillin-resistant *Staphylococcus aureus* (MRSA) and the resurgence of multi-drug resistant (MDR) *Mycobacterium tuberculosis* in the late 1970s and 1980s.¹⁷⁻²²

Mechanisms of Antibiotic Resistance:

At least 17 different classes of antibiotics have been produced to date (Table 1). Unfortunately, for each one of these classes at least one mechanism of resistance (and

many times more than one) has developed over the years. In fact, in some cases these bacteria have been able to develop simultaneous resistance to two or more antibiotic classes, making the treatment of infections caused by these microorganisms extremely difficult, very costly and in many instances associated with high morbidity and mortality.^{23, 24}

TABLE 1:

Major antibiotic classes by mechanism of action	
Mechanism of action	Antibiotic families
Inhibition of cell wall synthesis	Beta-lactams (penicillins, cephalosporins, carbapenems, monobactams); glycopeptides; cyclic lipopeptides (daptomycin)
Inhibition of protein synthesis	Tetracyclines; aminoglycosides; oxazolidonones (linezolid); streptogramins (quinupristin-dalfopristin); ketolides; macrolides; lincosamides,
Inhibition of DNA synthesis	Fluoroquinolones
Inhibition of RNA synthesis	Rifampin
Competitive inhibition of folic acid synthesis Inhibition	Sulfonamides; trimethoprim
Membrane disorganizing agents	Polymyxins (Polymyxin-B, Colistin)
Other mechanisms	Metronidazole

A short view on the antibacterial agents currently available:

Examination of the current status of potential novel antibacterial drugs indicates

that there are only a few compounds in development by the large pharmaceutical companies (Table 2), with the majority of candidates coming from the smaller biotechnology pharmaceutical companies (Table 3).^{25, 26} In the past 30 years, the only truly novel agents that have been launched are linezolid (Pharmacia and Pfizer) and daptomycin (Cubist).^{1, 26} Concomitant with the development of these novel agents, there has been a decrease in the number of analogs generated of the classical antibacterials, predominantly penicillins, carbapenems, cephalosporins, tetracyclines, macrolides and quinolones.^{4, 27-34} Between 1983 and 2001, 47 new antibiotics won approval by the US FDA or the Canada Health Ministry (<http://www.fda.gov/cder/approval/index.htm>; http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf). Only nine new antibiotics have been approved since 1998, of which just two had a novel mechanism of action. In 2002, there were no new antibacterials in the list of almost 90 drugs approved by the FDA and, in 2003, there were just two antibacterials approved (<http://www.fda.gov/cder/approval/index.htm>).

TABLE 2:

Antibacterials currently in clinical development by large pharmaceutical companies			
Drug name or designation (company)	Class	Target	Status
ABT492 (Wakunaga)	Quinolone	DNA gyrase and topo IV	Phase I ^a
WCK771A (Wockhardt)	Quinolone	DNA gyrase and topo IV	Phase I ^a
PNU288034 [Pfizer (Pharmacia)]	Oxazolidinone	Protein synthesis	Phase I ^a
Garenoxacin [BMS284756 (Schering-Plough and Toyoma)]	Quinolone	DNA gyrase and topo IV	Phase III ^{a,b}
Doripenem (Shionogi and Pennisula Pharma)	Carbapenem	Cell wall	Phase III ^{a,b}
CS-023 (Sankyo and Roche)	Carbapenem	Cell wall	Phase II ^{a,b}
Tigecycline [GAR936 (Wyeth)]	Tetracycline	Protein synthesis	Phase III ^{a,b}

Information acquired from:

^aInvestigational Drugs database; and

^bcompany website, press release or analyst

meeting.

topoisomerase.

Abbreviation:

Topo,

TABLE 3:

Antibacterials currently in clinical development by biotechnology companies			
Drug name or designation (company)	Class	Target	Status
MC02479 [RWJ54428, RWJ442831 ^a (Trine and J&J)]	Cephalosporin	Cell wall and transpeptidation	Phase I ^b
MC04546 [RWJ333441, RWJ333442 ^a (Trine and J&J)]	Cephalosporin	Cell wall and transpeptidation	Phase I ^b
VRC4887 [LBM415 (Vicuron and Novartis)]	Hydroxamate	Peptide deformylase	Phase I ^b
BB83698 (Vernalis, Genesoft and Oscient)	Hydroxamate	Peptide deformylase	Phase I ^{b,d}
Ramoplanin [GTC (Oscient) and Vicuron]	Glycolipodepsipeptide	Transglycosylation and lipid II	Phase II-III ^{b,c}
Oritavancin [LY333328 (Intermune and Lilly)]	Glycopeptide	Cell wall	Phase III ^{b,c}
Rifalazil (Activbiotics)	Benzoxazinorifamycin	RNA polymerase	Phase II ^{b,c}
BAL5788 (Basilea and Roche)	Cephalosporin	Cell wall	Phase II ^{b,c}

MC04,124 (Mpex Pharm, Trine and Daiichi)	Peptide	Efflux pump inhibitor	Preclinical ^{b,c}
MP601,205 (Mpex Pharm and Daiichi)	Peptide	Efflux pump inhibitor	Preclinical ^c
Dalbavancin (Vicuron and Aventis)	Glycopeptide	Cell wall	Phase III ^{b,c}
TD6424 (Theravance)	Lipoglycopeptide	Cell wall	Phase II ^{b,c}

^aProdrug of active component. **Information acquired from:** ^bInvestigational Drugs database; and ^ccompany website, press release or analyst meeting. ^dDiscontinued development. Abbreviation: J&J, Johnson & Johnson.

The essentials of antibiotic and antibacterial discovery:

As with any other therapeutic area, antibiotics requires a novel starting point to spark interest, the perception of do-ability and a sustained commercial value potential in pursuing antibacterial R&D. A key distinction between antibacterials and antibiotics and chronic disease therapy has

been the reliance on natural products for a chemotype starting point^{2, 30, 35} with several important exceptions such as the natural product-based statins, multiple cancer agents and some immunosuppressive drugs.³⁶

Changed in the 'value' of antibiotics and antibacterials:

There are numerous factors that have an impact on the 'value' of antibiotics in the marketplace, including: (i) increase in antibacterial sales (both percentage increase and overall dollars); (ii) generics; (iii) segmentation (specialization of the market); (iv) increased regulatory hurdles and postlaunch commitments; (v) total R&D cost versus 'return on investment' (ROI); and (vi) the competition for resources within the pharmaceutical industry for R&D areas

limited by capital available (i.e. should constrained resources be used to develop antibacterials versus chronic drugs?).^{26, 29, 37, 38}

There is also a lack of appreciation for the untold cost of bacterial resistance development in the microbial community and its effect on clinical efficacy of antibiotics. Resistance, which is inherent in the mode-of-action of all antibiotics and antibacterials, poses challenges in the development of new antimicrobial agents by large pharmaceutical companies, as well as biotechnology companies. The majority of antibiotics and antibacterials have an ‘inherent obsolescence’ because of the emergence of resistance by virtue of the target they attack.^{5, 39-51}

Agricultural and Animal Use of Antibiotics:

Antibiotics are frequently used in animals as part of the process used to manufacture food, especially meats. This is a non-therapeutic use of very valuable drugs and for this reason they should be preserved for use under very special circumstance only.

Recent interactions between regulatory authorities and the food-producing industry

in the U.S. are resulting in commitments to reduce and eventually eliminate the use of common antibiotics for non-therapeutic use.^{52, 53}

Looking at the Future: Is This the Post-Antibiotic Era?

The problem of the explosive growth in the development of antimicrobial resistance in the last two decades has only been made worse by a significant and steady decrease in the number of approvals of new antibacterials in the last 10–15 years (**Figure 1**).^{54, 55}

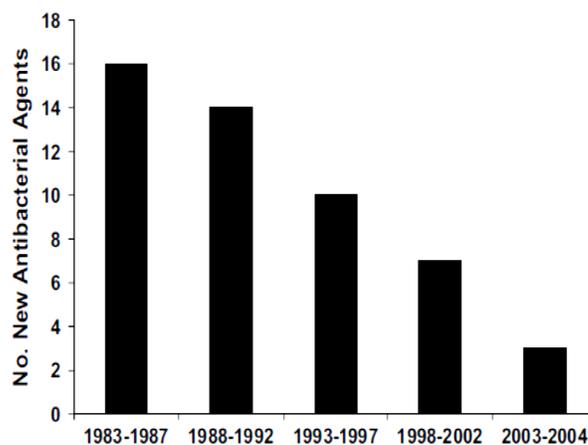


Figure 1: New antibacterial agents approved by the FDA in the U.S from 1983 to 2004.

The different forces contributing to this major paucity in the pace of antibiotic

innovation are multiple, very complex and interlinked, and much has been written about these in recent times. When analyzed individually, these forces seem to have merit on their own weight but they do not appear to be insurmountable.^{56, 57}

Conclusions:

There is a serious unmet medical need for new antibacterial agents to treat drug-resistant infections.⁵⁸ The underlying resistance to antibiotics in emerging pathogens might be selected for by drug exposure in prior rounds of antibiotic therapy; this latent resistance is potentially a major problem to be addressed in the near future. Only the successful identification and development of novel, potent, efficacious antibacterial agents will solve this problem.

In summary, the post-antibiotic era is far from over. Investment in newer anti-infective platforms is essential and urgent as it is a seamless collaboration among industry, academia and government that results in a revolution in our understanding of bacterial resistance and new approaches to control it. However, the era where acute or chronic bacterial infections used to be

treated with “antibiotics-only” appears to have come to an abrupt end.

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