The rapid and ongoing spread of antibiotic resistance poses a serious threat to global public health. The indiscriminant use of antibiotics in agriculture and human medicine along with increasingly connected societies has fueled the distribution of antibiotic-resistant bacteria. These factors together have led to rising numbers of infections caused by multidrug-resistant and pan-resistant bacteria, with increases in morbidity and mortality. This article summarizes the trends in antibiotic resistance, discusses the impact of antibiotic resistance on society, and reviews the use of antibiotics in agriculture. Feasible ways to tackle antibiotic resistance to avert a post-antibiotic era are suggested.

The evolution of resistance in Gram-negatives has challenged the clinical microbiology laboratory to implement new methods for their detection. Multidrug-resistant strains present major challenges to conventional and new detection methods. More rapid pathogen identification and antimicrobial susceptibility testing have been developed for use directly on specimens, including fluorescence in situ hybridization tests, automated polymerase chain reaction systems, microarrays, mass spectroscopy, next-generation sequencing, and microfluidics. Review of these methods shows the advances that have been made in rapid detection of resistance in cultures, but limited progress in direct detection from specimens.

Antimicrobial resistance is a common iatrogenic complication of modern life and medical care. One of the most demonstrative examples is the exponential increase in the incidence of extended-spectrum \( \beta \)-lactamases (ESBLs) production among Enterobacteriaceae, which are the most common human pathogens outside of the hospital setting. Infections resulting from ESBL-producing bacteria are associated with devastating outcomes, now affecting even previously healthy individuals. This development poses an enormous burden and threat to public health. This paper aims to narrate the evolving epidemiology of ESBL infections, and highlight current challenges in terms of management and prevention of these common infections.
Multidrug-Resistant Bacteria in the Community: Trends and Lessons Learned

David van Duin and David L. Paterson

Multidrug resistant (MDR) bacteria are one of the most important threats to public health. Typically, MDR bacteria are associated with nosocomial infections. However, some MDR bacteria have become prevalent causes of community-acquired infections. The spread of MDR bacteria into the community is a crucial development, and is associated with increased morbidity, mortality, health care costs, and antibiotic use. Factors associated with community dissemination of MDR bacteria overlap but are distinct from those associated with nosocomial spread. Prevention of further community spread of MDR bacteria is of the utmost importance, and requires a multidisciplinary approach involving all stakeholders.

Agents of Last Resort: Polymyxin Resistance

Keith S. Kaye, Jason M. Pogue, Thien B. Tran, Roger L. Nation, and Jian Li

Polymyxin resistance is a major public health threat, as the polymyxins represent “last-line” therapeutics for Gram-negative pathogens resistant to essentially all other antibiotics. Improved understanding of mechanisms of, and risk factors for, polymyxin resistance, as well as infection prevention and stewardship strategies, together with optimization of dosing of polymyxins including in combination regimens, can help to limit the emergence and dissemination of polymyxin resistance.

Vancomycin-Resistant Enterococci: Therapeutic Challenges in the 21st Century

William R. Miller, Barbara E. Murray, Louis B. Rice, and Cesar A. Arias

Vancomycin-resistant enterococci are serious health threats due in part to their ability to persist in rugged environments and their propensity to acquire antibiotic resistance determinants. Enterococci have now established a home in our hospitals and possess mechanisms to defeat most currently available antimicrobials. This article reviews the history of the struggle with this pathogen, what is known about the traits associated with its rise in the modern medical environment, and the current understanding of therapeutic approaches in severe infections caused by these microorganisms. As the 21st century progresses, vancomycin-resistant enterococci continue to pose a daunting clinical challenge.

New β-Lactamase Inhibitors in the Clinic

Krisztina M. Papp-Wallace and Robert A. Bonomo

Given the serious medical burden of β-lactamases, many approaches are being used to identify candidate agents for β-lactamase inhibition. Here, we review two β-lactam-β-lactamase inhibitor (BL-BLI) combinations, ceftolozane-tazobactam and ceftazidime-avibactam that recently entered the clinic. In addition, we focus on BL-BLI combinations in preclinical development that have demonstrated activity in clinical isolates via susceptibility testing and/or in vivo models of infection. We highlight only the BLIs that are able to reduce the Clinical Laboratory Standards Institute (CLSI) breakpoints for the BL partner into the susceptible range. Our analysis includes the primary literature, meeting abstracts, as well as the patent literature.
Antibiotic-Resistant Infections and Treatment Challenges in the Immunocompromised Host

Donald M. Dumford III and Marion Skalweit

This article reviews antibiotic resistance and treatment of bacterial infections in the growing number of patients who are immunocompromised: solid organ transplant recipients, the neutropenic host, and persons with human immunodeficiency virus and AIDS. Specific mechanisms of resistance in both gram-negative and gram-positive bacteria, as well as newer treatment options are addressed elsewhere, and are only briefly discussed in the context of the immunocompromised host.

Bacteremia due to Methicillin-Resistant Staphylococcus aureus: New Therapeutic Approaches

Marisa Holubar, Lina Meng, and Stan Deresinski

This article reviews recent clinical evidence for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) bacteremia. Vancomycin remains the initial antibiotic of choice for the treatment of patients with MRSA bacteremia and endocarditis due to isolates with vancomycin minimum inhibitory concentration ≤2 μg/mL, whereas daptomycin is an effective alternative, and ceftaroline seems promising. Treatment options for persistent MRSA bacteremia or bacteremia due to vancomycin-intermediate or vancomycin-resistant strains include daptomycin, ceftaroline, and combination therapies. There is a critical need for high-level evidence from clinical trials to allow optimally informed decisions in the treatment of MRSA bacteremia and endocarditis.

Drug-Resistant Tuberculosis: Challenges and Progress

Sebastian G. Kurz, Jennifer J. Furin, and Charles M. Bark

Antimicrobial resistance is a natural evolutionary process, which in the case of Mycobacterium tuberculosis is based on spontaneous chromosomal mutations, meaning that well-designed combination drug regimens provided under supervised therapy will prevent the emergence of drug-resistant strains. Unfortunately, limited resources, poverty, and neglect have led to the emergence of drug-resistant tuberculosis throughout the world. The international community has responded with financial and scientific support, leading to new rapid diagnostics, new drugs and regimens in advanced clinical development, and an increasingly sophisticated understanding of resistance mechanisms and their application to all aspects of TB control and treatment.

Aminoglycoside Resistance: The Emergence of Acquired 16S Ribosomal RNA Methyltransferases

Yohei Doi, Jun-ichi Wachino, and Yoshichika Arakawa

Aminoglycoside-producing Actinobacteria are known to protect themselves from their own aminoglycoside metabolites by producing 16S ribosomal RNA methyltransferase (16S-RMTase), which prevents them from binding to the 16S rRNA targets. Ten acquired 16S-RMTases have been reported from gram-negative pathogens. Most of them posttranscriptionally methylate residue G1405 of 16S rRNA resulting in high-level resistance...
to gentamicin, tobramycin, amikacin, and plazomicin. Strains that produce
16S-RMTase are frequently multidrug-resistant or even extensively drug-
resistant. Although the direct clinical impact of high-level aminoglycoside
resistance resulting from production of 16S-RMTase is yet to be deter-
mined, ongoing spread of this mechanism will further limit treatment
options for multidrug-resistant and extensively drug-resistant gram-nega-
tive infections.

The Evolving Role of Antimicrobial Stewardship in Management of Multidrug
Resistant Infections

Debra A. Goff and Thomas M. File Jr

This article summarizes the current literature describing how antimicrobial
stewardship interventions impact antimicrobial resistance. Discussion in-
cludes why we need stewardship, how to collaborate with team members,
and the evidence of stewardship’s impact on resistance.