The Emerging Threat of Antibiotic Resistance

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Antibiotic Resistance:

- Two major ways that modern medicine saves lives are through antibiotic treatment of severe infections and the performance of medical and surgical procedures under the protection of advanced anesthesia and antibiotics.
- Though Dr. Flemming discovered penicillin in 1928, it was not introduced to the public until the 1940's during WW II and not to general public until the 1950's.
- He predicted the emergence of resistance at that time!!

Antibiotic Resistance:

- “Golden Age” of antibiotics lasted more than 50 years but has been under attack since the 1990’s as more and more resistance emerged.

- April 2014 WHO declared: “antibiotic resistance threatens the achievements of modern medicine. A post-antibiotic era -- in which common infections and minor injuries can kill -- is a very real possibility for the 21st century."

- Bacteria on earth for ~3.5 Billion years, continuously adapting
- Reproductive cycle for most is approx. 30 minutes
- Adaption along with inappropriate use of antibiotics has led to proliferation and dominance of the none sensitive strains of bacteria which have developed ways also to share resistance
- WW-II was first war in human history where more combatants died of injuries than died of infectious disease!! Danger of return to previous era.

Antibiotic Resistance Facts: NCBI August 2014

- **30%** – All deaths that were bacterial infection related in pre-antibiotic America (tuberculosis, pneumonia, and gastrointestinal infections)
- **$2.0B / 1.6€ billion** – Excess healthcare costs of resistant infections in the US/EU
- **$1.1 billion** – Cost of unnecessarily prescribed antibiotics in the US
- **24.6 million** – Pounds of antibiotics used non-therapeutically on animals in the US per year in early 2000's—and has grown even in light of information

Antibiotic Resistance Facts: NCBI August 2014

- *4 – ONLY FOUR–Multinational pharmaceutical companies with antibiotics divisions remaining*

- **30%** – Antimicrobial component of pharmaceutical budgets in the US

- **1.6%** – Antibiotic allotment of all drugs in development by major pharmaceutical companies

The U.S. President's Council of Advisors on Science and Technology

- September 2014, an executive order from President Barack Obama directed the National Security Council to work with a governmental task force and a nongovernmental advisory council to develop a national action plan by February 2015.

The U.S. President's Council of Advisors on Science and Technology

- Goals include:
  - implementation of antibiotic stewardship in health care facilities and the community
  - development of rapid, point-of-care diagnostics
  - recruitment of academic and industry partners to increase the pipeline of antibiotics, vaccines, and alternative approaches
  - international collaboration for prevention, surveillance, and control of antibiotic resistance.

The U.S. President's Council of Advisors on Science and Technology

- On June 2, 2015, a White House Forum on Antibiotic Stewardship engaged stakeholders, including leaders of healthcare institutions, professional organizations, agribusiness and industry, in improving the use of antimicrobials in human and animal health.

- Federal regulations were announced against human antibiotics in food and the *movement away* from antibiotic use for promoting animal growth.

The U.S. President's Council of Advisors on Science and Technology

- Increased funding to both NIH and CDC was committed to combat antimicrobial resistance.
- Hospitals were and are currently mandated to have antimicrobial stewardship programs.

Issue #1: The retreat of most major pharmaceutical companies from antibiotic research for the development of novel antibiotics

- In a market worth more than $40 billion annually and drugs that are progressively failing since 2013 there are only four multinational pharmaceutical companies with antibiotics divisions left.

- Most compounds and ingredients are produced in China and far east countries with questionable quality control, adding to resistance concerns.

Issue #1: The retreat of most major pharmaceutical companies from antibiotic research for the development of novel antibiotics

- Since 1998 only AstraZeneca, GlaxoSmithKline, Merck, Johnson & Johnson, and Pfizer/Wyeth have developed an antibiotic past phase I clinical trials.
- Why in this market?
- Corporate Profit and ROI is why!
  - Net present value (NPV) is a risk-adjusted measure of the projected future revenues of a drug.
  - A characteristic NPV for an injectable antibiotic may be around 100; unattractive compared to a typical cancer drug, around 300, or a neuroscience drug around 720.

- #2-Major disincentives include the difficulty of conducting large clinical trials in patients with resistant infections.

- #3-Massive over usage and inappropriate application of antibiotics in the treatment of patients across the globe.
  - Center for Disease Control and Prevention (CDC) recently estimated that approximately 50% of antibiotics are prescribed unnecessarily in the US at a yearly cost of $1.1 billion.

- #4-Rampant profiteering through drug dilution, substandard manufacture, and counterfeiting, which foster resistance and undermine treatment, are common across the globe.

- #5-The use of antibiotics in animal feed stocks has also exacerbated the spread of resistance.
  - Especially egregious is their use for non-curative reasons such as prophylaxis, metaphylaxis, and growth promotion which by one estimate accounted for 25-50% of all antibiotic consumption in the early 2000s
    - Governments imposed restraints in the European Union in 2003 and in US in 2012 but not a ban on none therapeutic utilization.

Potential Solutions:

- Technological advances in point-of-care diagnostics enable prescribers to avoid dispensing antibiotics for viral infections and allow prescriptions to be tailored narrowly to a pathogen's susceptibilities.
- Reduce inappropriate use fostered by inaccurate diagnosis, misaligned financial incentives for utilization of agents by providers and by over-the-counter access in many regions of the globe.
- Patient/consumer education to role of antibiotics
- Control utilization in animal and feed products

Antibiotic Resistance:

- Human use (and misuse) of antibiotics has clearly put unnatural selective pressure on bacteria, which has accelerated their natural evolutionary process to the detriment of everyone.

- Estimates based on the genetic divergence of antibiotic biosynthetic genes have suggested that some antibiotics could have evolved hundreds of millions of years ago.
  - Resistance elements have even been found in bacterial DNA that was isolated for 30,000 years in permafrost.

Antibiotic Resistance Facts:

- Estimated that by 2050 10 million deaths per year will be due to antibiotic resistance and uncontrolled infections.
- **20%** of people currently are persistent carriers of *S. aureus*
- **1.3 million** – Worldwide deaths caused by TB per year currently, expected to double by 2024
  - **$483,000** – Average cost of XDR-TB treatment

Bacterial Threat Facts:

- **$3 billion** – Annual healthcare costs associated with MRSA in US (2018)
- **19,000** – Deaths per year caused by MRSA in the US 2018
- **61%** – Vancomycin (**52**) resistance rate of *E. faecium* in the US
- **40%** – *S. pneumoniae* strains resistant to penicillin
- **50%** – Chance of contracting C. difficile with > 4 week hospital stay

Bacterial Threat Facts:

- **30%** – Increase in carbapenem resistant A. baumannii strains from 1995-2004
- **30%** – Quinolone resistance rate for *Enterobacter 2015 and expected to reach > 50% by 2024*
- **700,000** – *N. gonnorhoeae* infections in the US per year

Emergence of Resistance:

- In the 1990s resistant gram positive bacteria materialized as a major threat:
  - Methicillin (MRSA) and Vancomycin (VRSA) resistant *Staphylococcus aureus*
  - VRE (vancomycin resistant enterococci)
  - Penicillin resistant *Streptococcus pneumonia*,
  - Multi-drug resistant (MDR) *Clostridium difficile.*

Mechanisms of Drug Resistance:

- RND (resistance-nodulation-division)- Chromosomally encoded drug efflux mechanisms found in gram negative organisms which are major contributors to antibiotic resistance.
  - Multidrug pumps, particularly those represented by the resistance-nodulation-division (RND) superfamily, mediate intrinsic and acquired multidrug resistance (MDR) and are involved in other functions, including the bacterial stress response and pathogenicity.
  - Efflux pumps interact synergistically with other resistance mechanisms (e.g., alterations with outer membrane permeability barrier, ESBL, thick buffy coats, etc.) to increase resistance levels.

Mechanisms of Drug Resistance: RND

- Plasmid-borne efflux pump genes (including those for RND pumps) have increasingly been identified in microorganisms and shown to spread rapidly among genesis and species of m/o.
- The development of clinically useful efflux pump inhibitors and/or new antibiotics that can bypass pump effects continues to be a challenge.
- Especially important in the ESKAPE pathogens : *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, P. aeruginosa, and Enterobacter sp.* as well as *E. Coli*.

Mechanisms of Drug Resistance:

- Membrane permeability barrier resistance
  - Very small porin cannels, OM proteins producing Ph and electro catatonic charges in the cannel which make penetration difficult for lipophyllic drugs and larger molecules are present in most gram negative m/o today.
    - B-lactams, fluoroquinolones, aminoglycosides, cyclosterine, chloramphenicol penetrate better but not in all cases!!

- Antibiotic target changes: Ex. the alteration in Penicillin Binding Proteins like those noted with many strains of Streptococci or the ribosomal alternation seen with resistance to tetracycline or aminoglycosides.

Mechanisms of Drug Resistance:

- Enzymatic inactivation/modification of drugs
  - Penicillinase, beta-lactamase and extended spectrum beta-lactamases such as carbapenemase or cephalasporinase et.al hydrolyize these agents rapidly and render them ineffective

Emergent Bacterial Threats

BACTERIUM	GRAM STAIN	RESPIRATION	PROBLEMATIC RESISTANCES
Staphylococcus aureus	+	Facultative anaerobe	β-lactams, glycopeptides
Enterococci	+	Facultative anaerobe	β-lactams, glycopeptides, aminoglycosides
Streptococcus pneumoniae	+	Aerotolerant anaerobe	β-lactams, macrolides, quinolones
Clostridium difficile	+	Obligate anaerobe	β-lactams, quinolones
Mycobacterium tuberculosis	+	Aerobe	Rifamycins, quinolones, aminoglycosides
Escherichia coli	−	Facultative anaerobe	β-lactams, quinolones, aminoglycosides
Pseudomonas aeruginosa	−	Facultative anaerobe	All classes except polymyxins
Acinetobacter	−	Facultative anaerobe	All classes

Emergent Bacterial Threats

BACTERIUM	GRAM STAIN	RESPIRATION	PROBLEMATIC RESISTANCES
Klebsiella pneumoniae	–	Facultative anaerobe	β-lactams, quinolones, aminoglycosides
Enterobacter	–	Facultative anaerobe	β-lactams, quinolones
Neisseria gonorrhoeae	–	Aerobe	β-lactams, quinolones, tetracyclines, macrolides

Staphylococcus aureus (MRSA, VISA, and VRSA)

- *S. aureus* is a gram positive, facultative anaerobic pathogen with both hospital and community acquired strains.
- Traditionally opportunistic, many *S. aureus* strains are now aggressively pathogenic.
  - It is the most common skin bacterium with 60% of humans being intermittent carriers and 20% being persistent carriers.

S. Aureus:

- Methicillin resistance is highly prevalent and the single most commonly observed drug resistance in both the US and Europe.
  - MRSA estimated to be responsible for 60–89% of nosocomial infections leading to 19,000 deaths and over $3 billion in health care costs per year in the United States.
  - In 2009 MRSA infections killed more people in US hospitals than HIV/AIDS and tuberculosis combined.

S. Aureus:

- β-lactam resistance noted with MRSA is primarily due to expression of the *mecA* gene which encodes for the low affinity penicillin binding protein.
- The glycopeptides, vancomycin and teicoplanin, previously common treatments for MRSA, are seeing resistance develop towards them rapidly.
  - Vancomycin intermediate *S. aureus* (VISA), which is also usually insensitive to teicoplanin evolved a less permeable cell wall that traps these antibiotics

Resistant *Enterococci* including VRE

- Primarily two species, *E. faecalis* and *E. faecium,* which are gram-positive, facultative anaerobic, opportunistic pathogens.
- VRE isolates express enterococcal surface protein, which allows for the production of thick drug resistant biofilms.
- VRE is known to produce several resistance genes, the most common form of vancomycin resistance, as with VRSA, is *vanA.*

Streptococcus pneumonia

- *S. pneumoniae* is the leading cause of bacterial pneumonia, but it can also cause otitis media, sinusitis, and meningitis among other pathologies.
- Approximately 40% of strains are no longer susceptible to penicillin, (secondary to B-lactamase) and its penicillin resistance often correlates with resistances to macrolides, sulfamides, older tetracyclines, and early generation cephalosporins.
- Macrolide resistances caused by upregulated efflux encoded by *mef* or *erm* genes is increasing in *S. pneumoniae.*

Clostridium difficile

- *C. difficile* is a gram-positive, obligate anaerobic, spore forming opportunistic pathogen.

- *C. difficle* overgrowths spread and produces an enterotoxin (toxin A) and a cytotoxin (toxin B) which play a role in resultant colitis as well as life threatening complications.

- Develops commonly with both fluoroquinolone and cephalosporin utilizations.

Gram Negative Resistance:

- Difficulty in penetration of outer membranes and higher prevalence of efflux pumps make these m/o naturally resistant to many antibiotics.
- Extended Spectrum Beta Lactam resistance is common and spreading
- Carbapenem resistant gram negative strains, particularly *Enterobacteriaceae* (CRE), are becoming increasingly common place.
- The main gram-negative threats are multi- (MDR) and pan- (PDR) drug resistant *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter*, *Klebsiella pneumoniae*, *Enterobacter*, and most recently *Neisseria gonorrhoeae.*

Mycobacterium tuberculosis (MDR-TB and XDR-TB)

- TB is second only to HIV/AIDS as the greatest killer worldwide secondary to a single infectious agent with 1.3 million deaths from 8.6 million new infections in 2012.
- MDR-TB, resistant to the first line combination therapy of rifamycin, isoniazid, and pyrazinamide is commonplace with about 450,000 people in the world developing resistant T.B. in 2012.
- 9.6% are estimated to be extensively drug resistant (XDR-TB), which is further resistant to at least one second-line fluoroquinolone and aminoglycoside.
  - XDR-TB sometimes requires a two-year course of antibiotics at an average cost of $483,000 and can be fatal even with proper treatment.

E. Coli

- Recently, horizontal gene transfer has allowed for the rise of highly resistant strains.
- Strains with extended spectrum β-lactamases (ESBLs) conferring resistance to third generation cephalosporins has been steadily rising in Europe as well as high cross resistance to fluoroquinolones (>80%) and gentamicin (>40%).

- *Rare yet, E. coli* on multiple continents have also acquired the New Delhi Metallo-β-lactamase-1 (NDM-1) enzyme from *K. pneumoniae*, which confers a broad resistance to all β-lactams including carbapenems with the exception of the monobactam, aztreonam.

MDR Pseudomonas Aeruginosa

- Discriminating outer membrane porins make outer membrane impermeable and naturally resistant to many antibiotics, especially lipophyillic.
- A high propensity to form biofilms increases resistances to antibiotics 100 to 1000 fold.
- Further antibiotic resistance occurs thorough a variety of β-lactamases including ESBLs, *K. pneumoniae* carbapenemase (KPC), and metallo-β-lactamases (MBLs).
- *P. aeruginosa* also has an extremely comprehensive efflux pump systems
- Fluoroquinolone resistance can also occur through mutations in target DNA gyrase and topoisomerase IV.

MDR and Pan-drug-resistant *Klebsiella pneumoniae*

- This species commonly acquires MDR determinants, and an impressive array of β-lactamases.
- Resistance mechanisms commonly include AAC AME gene mutations and ribosomal methylases for aminoglycoside resistance, and fluoroquinolone resistant topoisomerase mutations along with thick polysaccharide coats.
- Though NDM-1 producing strains have so far remained rare, rapid globalization coupled with extreme resistance profiles warrants close monitoring.

β-lactam and Quinolone Resistant *Enterobacter*

- *Enterobacter* is a genus of gram-negative, facultative anaerobic, opportunistic pathogens known to exhibit antibiotic resistance through expression of an extensive variety of ESBLs and carbapenemases.

Resistant Neisseria Gonorrhoeae

- Penicillin and ciprofloxacin resistances acquired by plasmid exchange, are now widespread, with resistances to the commonly used macrolide azithromycin and some cephalosporin becoming increasingly common.
- TetM efflux proteins are common.
- Most recently a MDR *N. gonorrhoeae* strain with high level resistances to the third-generation cephalosporins cefixime and ceftriaxone has been identified.

MDR Acinetobacter: A. baumannii or Iraqibacter

- A gram-negative, facultative anaerobic, opportunistic pathogen, its nick-name comes from its rapid emergence as a problem pathogen in wounded soldiers during the Iraq war.
- *A. baumannii* is naturally resistant to many antibiotics due to both poor membrane penetration and active efflux pumps.
- *A. baumannii* isolates also produce an exopolysaccharide capable of forming biofilms.

MDR Acinetobacter: A. baumannii or Iraqibacter

- Two main forms of resistance:
- First is the highly effective efflux pumps, which also impart resistance to ammonia based disinfectants.
- The second is a wide variety of β-lactamases including ESBLs and carbapenemases including imipenem MBLs and oxacillinases (OXAs).
- These antibiotic resistances factors coupled with *Acinetobacter* natural resistances have combined to produce *A. baumannii* strains with resistance to all known antibiotics.
- MDR *Acinetobacter* and *Klebsiella* are so dangerous that their outbreaks have resulted in hospital ward closures on multiple occasions

Table 3 Antimicrobial Drugs of Choice for Various Infections in Adults

	Causative Organism	Drug of Choice	Alternative Drugs
Gram-Positive Cocci	*Staphylococcus aureus*		
	Methicillin susceptible	Penicillinase-resistant penicillin*	A cephalosporin,†‡ clindamycin, vancomycin, amoxicillin-clavulanate, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, a carbapenem,§ a fluoroquinolone‖
	Methicillin resistant¶	Vancomycin	Linezolid, daptomycin; quinupristin-dalfopristin, clindamycin,# trimethoprim-sulfamethoxazole (TMP-SMX), minocycline/ doxycycline**
	Coagulase-negative staphylococci††	Vancomycin	Linezolid, daptomycin, quinupristin-dalfopristin
	Anaerobic streptococcus (*Peptostreptococcus*)	Penicillin G‡‡	Clindamycin, a cephalosporin,†‡ vancomycin
	Streptococcus bovis	Penicillin G‡‡	A cephalosporin,†‡ vancomycin
	Beta-hemolytic streptococci (groups A, B, C, F, and G)	Penicillin G,‡‡ penicillin V, ampicillin, or amoxicillin	A cephalosporin,†‡ a macrolide,§§ clindamycin,# vancomycin
	Streptococcus pneumoniae		
	Penicillin susceptible	Penicillin G‡‡ or penicillin V, ampicillin, or amoxicillin	A cephalosporin,†‡ a macrolide,§§ a fluoroquinolone,‖ a carbapenem,§ vancomycin
	Non–penicillin susceptible	Vancomycin, ceftriaxone or cefotaxime, a fluoroquinolone,‖ a carbapenem§	Linezolid, quinupristin-dalfopristin
	Viridans streptococcci	Penicillin G,‡‡ with or without gentamicin	A cephalosporin,†‡ vancomycin
	Enterococcus		
	Penicillin-susceptible endocarditis or other serious infection	Penicillin G‡‡ or ampicillin plus gentamicin‖‖ or streptomycin	Vancomycin plus gentamicin‖‖ or streptomycin
	Uncomplicated urinary tract infection	Ampicillin or amoxicillin	Nitrofurantoin, a fluoroquinolone,‖ fosfomycin
	Vancomycin resistant	Linezolid, daptomycin, quinupristin-dalfopristin	Chlorampenicol, doxycycline**

Gram-Positive Bacilli	*Bacillus anthracis*	Ciprofloxacin[‖] or amoxicillin (if susceptible)	Doxycycline,** clindamycin
	Bacillus cereus, Bacillus subtilis	Vancomycin	Clindamycin, imipenem[§]
	Clostridium difficile	Metronidazole	Vancomycin (oral)[¶¶]
	Clostridium perfringens	Penicillin G[‡‡] or clindamycin	Metronidazole, a carbapenem,[§] chloramphenicol
	Clostridium tetani	Metronidazole	Penicillin G,[‡‡] doxycycline**
	Corynebacterium diphtheriae	Erythromycin	Clindamycin, penicillin G[‡‡]
	Corynebacterium jeikeium	Vancomycin	Penicillin G[‡‡] plus gentamicin
	Erysipelothrix rhusiopathiae	Penicillin G[‡‡]	A cephalosporin,[†‡] a fluoroquinolone[‖]
	Listeria monocytogenes	Ampicillin, with or without gentamicin	TMP-SMX
	Propionibacterium	Penicillin G[‡‡]	Vancomycin
	Rhodococcus equi	Imipenem,[§] aminoglycosides, erythromycin, or vancomycin, with or without rifampin	Ciprofloxacin,[‖] TMP-SMX, tetracycline,** clindamycin
Gram-Negative Cocci	*Moraxella catarrhalis*	Amoxicillin-clavulanate, second- or third-generation cephalosporin[†‡]	TMP-SMX, a fluoroquinolone,[‖] a macrolide, doxycycline**
	Neisseria gonorrhoeae	Ceftriaxone or cefixime	Cefpodoxime or fluoroquinolone[‖]
	Neisseria meningitidis		
	Meningitis, bacteremia	Penicillin G[‡‡]	Ceftriaxone, cefotaxime, TMP-SMX, a fluoroquinolone, chloramphenicol
	Carrier state	Rifampin	Ciprofloxacin[‖]

Table 3 Continued

	Causative Organism	Drug of Choice	Alternative Drugs
Enteric Gram-Negative Bacilli	*Bacteroides fragilis*	Metronidazole	A carbapenem,§ ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam,
	Campylobacter jejuni	Erythromycin or azithromycin	A fluoroquinolone,‖ doxycycline,** clindamycin
	Citrobacter	A carbapenem§	A third- or fourth-generation cephalosporin,†‡ a fluoroquinolone,‖ ticarcillin-clavulanate, piperacillin-tazobactam, aztreonam, an aminoglycoside
	Enterobacter	A carbapenem§	A third- or fourth-generation cephalosporin,†‡ a fluoroquinolone,‖ ticarcillin-clavulanate, piperacillin-tazobactam, aztreonam, an aminoglycoside
	Escherichia coli		
	Serious infection	A third- or fourth-generation cephalosporin†‡	A carbapenem,§ ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam, a fluoroquinolone,‖ an aminoglycoside, aztreonam
	Uncomplicated cystitis	TMP-SMX or a fluoroquinolone‖	Ampicillin or amoxicillin
	Helicobacter pylori	Omeprazole + amoxicillin + clarithromycin	Tetracycline** + metronidazole + omeprazole + bismuth subsalicylate
	Klebsiella	A third- or fourth-generation cephalosporin†‡	A carbapenem,§ ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam, a fluoroquinolone,‖ an aminoglycoside, aztreonam
	Proteus mirabilis	Ampicillin or amoxicillin	A cephalosporin,†‡ a fluoroquinolone,‖ TMP-SMX, ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam, a carbapenem,§ an aminoglycoside, aztreonam

	Non-*mirabilis*, including *Proteus vulgaris*, *Morganella morganii*, and *Providencia rettgeri*	A third- or fourth-generation cephalosporin[‡‡]	A carbapenem,[§] ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam, a fluoroquinolone,[‖] an aminoglycoside, aztreonam
	Providencia stuartii	A third- or fourth-generation cephalosporin[‡‡]	A carbapenem,[§] ticarcillin-clavulanate, piperacillin-tazobactam, a fluoroquinolone,[‖] TMP-SMX, an aminoglycoside, aztreonam
	Salmonella species (including *typhi*)	Ceftriaxone or a fluoroquinolone[‖]	Chloramphenicol, TMP-SMX, amoxicillin
	Serratia	A carbapenem[§]	A third- or fourth-generation cephalosporin,[‡‡] ticarcillin-clavulanate, piperacillin-tazobactam, a fluoroquinolone,[‖] an aminoglycoside, aztreonam
	Shigella	A fluoroquinolone[‖]	TMP-SMX, ampicillin, azithromycin
	Yersinia enterocolitica	TMP-SMX, a fluoroquinolone[‖]	Cefotaxime, ceftriaxone, an aminoglycoside
Other Gram-Negative Bacilli	*Acinetobacter*	Imipenem, doripenem, or meropenem[§]	An aminoglycoside, sulbactam (available as ampicillin-sulbactam), tigecylcine, minocycline, colistin
	Aeromonas hydrophila	A fluoroquinolone[‖]	TMP-SMX, third- or fourth-generation cephalosporin, a carbapenem[§]
	Bartonella henselae (cat-scratch disease, bacillary angiomatosis) and *Bartonella quintana*	A macrolide	Ciprofloxacin,[‖] doxycycline**
	Bordetella pertussis (whooping cough)	A macrolide	TMP-SMX

Table 3 Continued

Causative Organism	Drug of Choice	Alternative Drugs
Brucella	Doxycycline** with gentamicin or streptomycin	Doxycycline** plus rifampin, TMP-SMX plus gentamicin, a fluoroquinolone[11] plus rifampin
Burkholderia cepacia	TMP-SMX, meropenem, or ciprofloxacin	Minocycline** or chloramphenicol
Burkholderia pseudomallei (melioidosis)	Ceftazidime or imipenem	Doxycycline** plus TMP-SMX, chloramphenicol
Capnocytophaga canimorsus	Amoxicillin-clavulanate	Penicillin G,[‡] ciprofloxacin, cefotaxime or ceftriaxone, a carbapenem[§]
Eikenella corrodens	Penicillin G,[‡] ampicillin, amoxicillin-clavulanate	Ceftriaxone, TMP-SMX, a fluoroquinolone[11]
Francisella tularensis (tularemia)	Gentamicin or streptomycin	Doxycycline** or ciprofloxacin[11]
Fusobacterium	Penicillin G[‡]	Metronidazole, clindamycin
Gardnerella vaginalis (bacterial vaginosis)	Metronidazole (oral)	Intravaginal metronidazole, intravaginal or oral clindamycin
Haemophilus ducreyi (chancroid)	Azithromycin or ceftriaxone	Ciprofloxacin[11] or erythromycin
Haemophilus influenzae	Ceftriaxone, cefotaxime, ampicillin-sulbactam, amoxicillin-clavulante	A fluoroquinolone,[11] a macrolide, TMP-SMX
Legionella species	Fluoroquinolone[11] or azithromycin, with or without rifampin	Clarithromycin, erythromycin, doxycycline,** TMP-SMX
Leptotricia buccalis	Penicillin G[‡]	A tetracycline,** clindamycin, erythromycin
Klebsiella granulomatis (granuloma inguinale)	Doxycycline**	Azithromycin, erythromycin, ciprofloxacin, TMP-SMX
Pasteurella multocida	Amoxicillin-clavulanate, ampicillin-sulbactam	Doxycycline,** a fluoroquinolone[11]
Pseudomonas aeruginosa	Imipenem, meropenem, doripenem, cefepime, ciprofloxacin[11]	Piperacillin-tazobactam, ticarcillin-clavulanate, ceftazidime, levofloxacin,[11] an aminoglycoside, aztreonam
Stenotrophomonas maltophila	TMP-SMX	Minocycline,** moxifloxacin,[11] ticarcillin-clavulanate
Streptobacillus moniliformis (rat-bite fever)	Penicillin G[‡] or doxycycline	Erythromycin or clindamycin
Vibrio cholerae	Doxycycline or a fluoroquinolone[11]	TMP-SMX

	Vibrio vulnificus	Doxycycline**plus ceftazidime	Cefotaxime
	Yersinia pestis (plague)	Gentamicin or streptomycin with or without a doxycycline**	Ciprofloxacin,[11] chloramphenicol
Acid-Fast Bacilli	*Mycobacterium avium* complex	Clarithromycin or azithromycin with ethambutol, with or without rifabutin	Amikacin, moxifloxacin[11]
	Mycobacterium fortuitum/chelonae/ abscessus complex	Amikacin plus cefoxitin, clarithromycin	TMP-SMX, doxycycline, azithromycin, a fluoroquinolone,[11] linezolid
	Mycobacterium kansasii	Isoniazid plus rifampin plus ethambutol	Clarithromycin or azithromycin
	Mycobacterium leprae	Dapsone with rifampin, with or without clofazimine	Minocycline,** ofloxacin or sparfloxacin, clarithromycin
	Mycobacterium marinum	Clarithromycin or minocycline**	TMP-SMX, doxycycline**
	Mycobacterium tuberculosis	Isoniazid plus rifampin plus pyrazinamide plus ethambutol	Streptomycin, a fluoroquinolone,[11] cycloserine, ethionamide, para-aminosalicylic acid, capreomycin, kanamycin, amikacin
Actinomycetes	*Actinomyces israelii*	Penicillin G‡‡ or ampicillin	Doxycycline,** ceftriaxone, erythromycin, clindamycin
	Nocardia	TMP-SMX	Minocycline,** imipenem, amikacin, ceftriaxone, linezolid

Table 3 Continued

	Causative Organism	*Drug of Choice*	*Alternative Drugs*
Chlamydia	*Chlamydia trachomatis*		
	Inclusion conjunctivitis	Erythromycin	Doxycycline**
	Lymphogranuloma venereum	Doxycycline**	Erythromycin
	Pneumonia	Erythromycin	A sulfonamide
	Trachoma	Azithromycin	A tetracycline**
	Urethritis or pelvic inflammatory disease	Doxycycline** or azithromycin	Erythromycin, ofloxacin, levofloxacin
	Chlamydophila pneumoniae	A macrolide or doxycycline**	A fluoroquinolone[11]
	Chlamydophila psittaci	Doxycycline**	Erythromycin
Ehrlichia	*Anaplasma phagocytophila* *Erhlichia chaffeensis*	Doxycycline**	A fluoroquinolone,[11] rifampin, chloramphenicol
Mycoplasma	*Mycoplasma pneumoniae*	A macrolide or doxycycline**	A fluoroquinolone[11]
Rickettsia	*Rickettsia rickettsii* (Rocky Mountain spotted fever) *Rickettsia prowazekii* (louse-borne typhus) *Rickettsia typhi* (murine typhus)	Doxycycline**	Chloramphenicol
	Coxiella burnetii (Q fever)	Doxycycline**	Erythromycin, a fluoroquinolone[11]
Spirochetes	*Borrelia burgdorferi* (Lyme disease)	Doxycycline,** amoxicillin, ceftriaxone	Penicillin G,‡‡ azithromycin, erythromycin
	Borrelia recurrentis (relapsing fever)	Doxycycline**	Erythromycin
	Leptospira	Penicillin G‡‡	Doxycycline**
	Treponema pallidum (syphilis)	Penicillin G‡‡	Doxycycline,** ceftriaxone

The Search for New Antibacterial Agents

- Between 1981 and 2005 cephalosporin's, penicillin's, quinolones, and macrolides accounted for 73% of all new antibiotics.
- Almost all clinically used antibiotics effect one of only 6 targets currently: They either inhibit DNA or RNA replication, protein reproduction, or are one of the > 50% inhibiting cell wall synthesis.

The Search for New Antibacterial Agents

- In total there are less than twenty-five molecular targets that account for current antimicrobial activity.
  - Comparative analysis of bacterial genomes has indicated that there are around 300 essential, highly conserved proteins that could potentially be new, broad spectrum drug targets
- It is necessary to develop new antibiotic classes due to cross resistance.
  - There have only been six first in class antibiotics with totally novel scaffolds approved since the 1960s and all of these have been introduced in the past fifteen years.
    - All have targeted gram positive infections, none for gram negative>

CLASS OR SUBCLASS	PRIMARY TARGET	CURRENT WHO CLINICLLY IMPORTANT MEMBERS
Penicillins	Penicillin binding proteins	Penicillin G and V, ampicillin ampicillin / sulbactam, amoxicillin, amoxicillin/ clavulanate, piperacillin, piperacillin / tazobactam , azlocillin, carbenacillin, mezlocillin, ticarcillin, ticarcillin / clavulanate
Cephalosporins	Penicillin binding proteins	Cefixime, cefotaxime, cefpodoxime, ceftazidime, ceftizoxime, cefoperazone, cefoperazone / sulbactam, ceftriaxone, cefepime, cefpirome, cefoselis
Carbapenems	Penicillin binding proteins	Ertapenem, faropenem, imipenem, meropenem
Aminoglycosides	30S ribosomal subunit	Amikacin, arbekacin, gentamicin, netilmicin, tobramycin, streptomycin
Macrolides	50S ribosomal subunit	Azithromycin, clarithromycin, erythromycin, midecamycin, roxithromycin, spiramycin, telithromycin

CLASS OR SUBCLASS	PRIMARY TARGET	WHO CRITICALLY IMPORTANT MEMBERS
Tetracyclines	30S ribosomal subunit	Tigecycline
Rifamycins	RNA Polymerase	Rifabutin , rifampin, rifaximin
Glycopeptides	Peptidoglycan Units	Teicoplanin, vancomycin
Quinolones	Topoisomerase II and IV	Cinoxacin, nalidixic acid, pipemidic acid, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin,levofloxacin , lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin
Streptogramins	50S ribosomal subunit	Quinupristin / dalfopristin, pristinamycin
Oxazolidinones	50S ribosomal subunit	Linezolid
Lipopeptides	Cell membrane	Daptomycin

New Antibiotics: Only 15 new agents since 2000!!

- B-Lactams-Biapenem, doripenem, ertapenem, and ceftaroline
- The streptogramin combination quinupristin/dalfopristin in 1999
- The oxazolidinone linezolid in 2000
- The lipopeptide daptomycin in 2003
- The pleuromutilin retapmulin in 2007

New Antibiotics:

- The macrolactone fidaxomicin in 2011
- The diarylquiniline bedaquilinein 2012
- Teixobactum 2019—a new macrolide designed in UK in cooperation with ROC released for limited indication this past month in U.S. for treatment of resistant gram + agents.
- Linezolid and bedaquiline are fully synthetic molecules while the others are semi-synthetic or natural products.

Antibiotics of the 21st Century

CLASS	CLINICALLY INTRODUCED SINCE 2000	IN PHASE II OR III TRIALS
Sulfonamides	None	None
β-lactams	Biapenem, ceftaroline , doripenem, ertapenem	Ceftobiprole, ceftolozane, razupenem
Aminoglycosides	None	Plazomicin
Amphenicols	None	None
Macrolides	Telithromycin	Cethromycin, solithromycin
Tetracyclines	Tigecycline	Eravacycline, omadacycline
Rifamycins	Rifaximin	None
Glycopeptides	Telavancin	Dalbavancin, oritavancin, ramoplanin
Quinolones	Balafoxacin, gemifloxacin, pazufloxacin, prulifloxacin	Avarofloxacin, delafloxacin, finafoxacin, JNJ-Q2, levonadifloxacin, nemonoxacin
Streptogramins	None	None
Polymyxins	None	None
Oxazolidinones	Linezolid	AZD5847, radezolid, sutezolid, tedizolid
Lipopeptides	Daptomycin	Surotomycin
Pleuromutilins	Retapmulin	BC-3781
Macrolactones	Fidaxomicin	None
Diarylquinolines	Bedaquiline	None

New Antibiotics

- As of October, 2021, 43 new antibiotic compounds were in development stages.
- 13 in phase 3, where historically 60% will emerge for market.
- Most exert activity against gram positive agents, including S. Aures, MRSA, TB, etc.

Natural Product Development:

- Recently estimated that with current technology 10^7 actinomycete strains would have to be screened to discover the next novel antibiotics class.
- Exploration of bacteria from other ecological niches has recently yielded many promising new lead compounds.
  - The producers of these include deep sea sediment actinomycetes, marine sponges and seaweeds, bacterial symbionts of insects, ascidians, fungi and myxobacteria.
- Genomic prospecting has also begun.

Semi-Synthetic Approaches

- Information about cellular targets and binding modes of established antibiotics have made the rational design of semi-synthetic analogs of natural products fruitful.
  - Precursor directed biosynthesis, mutasynthesis, and chemoenzymatic approaches are being investigated to diversify certain established scaffolds.
- These include the β-lactams meropenem and tazobactam, the aminoglycoside amikacin, the macrolide azithromycin, the tetracycline tigecycline, the rifamycin rifampicin, the glycopeptide telavancin, and the streptogramin combination quinupristin/dalfoprisitin.

Synthetic Development:

- To date rarely occurring: the sulfa drugs, quinolones, oxazolidinones, and diarylquinolines being only examples.
- Historically, synthetic classes were originally discovered outside of traditional antibiotic discovery programs.
  - Sulfa drugs were originally developed as dyes, the first quinolone was an intermediate in the synthesis of chloroquine, and oxazolidinones were originally developed to treat foliage diseases in plants.

Challenges to Development of Synthetics:

- The greatest challenges to developing new synthetic scaffolds is bacterial cell penetration.
- Especially true of gram-negatives, which are naturally resistant to many antibiotics because of outer membranes that keep many amphipathic drugs out as well as inner membranes and highly active efflux pumps that often recognize highly hydrophilic agents.

Combination Therapy

- Taking success with highly active anti-retroviral therapy (HAART) and combating *M. tuberculosis*, the use of antibiotics in combination therapies is becoming an increasingly attractive approach to combat resistance.

New Antibacterial Targets

- Symmetric bis-indoles have been identified that function as groove binders of double stranded nucleic acids to inhibit DNA and RNA synthesis
- Promising new targets are antibacterial enzymes and one of the most extensively discussed is undoubtedly FtsZ, a highly conserved, GTPase, tubulin homolog.
- A new class of antibiotics has been focused on biosynthetic enzymes, an example of which is spirotetronate-polyketides, abyssomycin C.
- Fatty acid biosynthesis inhibitors also are generating interest.

Resources:

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