

BIOL UN3404: Syllabus for the Seminar on the Global Threat of Antimicrobial Resistance
Fall Semester, 2018

Instructor:

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Prerequisite: BIOL UN2005/6 or BIOL UN2401/2

Credits: 3

Seminar size: 20

Introduction

Course Overview: The goal of this seminar is to provide an in-depth analysis of the ongoing worldwide threat of antimicrobial resistance. The seminar will cover the: 1) molecular mechanisms of antimicrobial resistance; 2) diverse epidemiology of pathogen transmission; 3) consequences of antimicrobial resistance; and 4) efforts to reduce the further emergence and spread of these pathogens both in the community and in healthcare settings. As a result of these discussions, students will also be exposed to selected topics in medical microbiology.

Course Objectives – Students will be able to:

- Interpret the international, national, regional and local statistics on antimicrobial resistance
- Understand the molecular mechanisms of antimicrobial resistance and its clinical relevance
- Discuss different approaches to investigate the spread of microbial pathogens in the healthcare setting or in the community
- Effectively analyze original medical literature
- Possibly develop a group research project related to antimicrobial resistance

Expectations: Students are expected to attend class and to have read the assignments prior to each class. There will be a brief quiz on the assigned reading at the start of each session. Students will be assigned to provide introductory remarks for each seminar. This might include providing background information on the microbiology and clinical relevance of the topic or a study guide for the session. Dr. Lowy will be available to help with the preparation for these sessions.

All students will be assigned a paper (15-20 double-spaced pages) to discuss one of the topics covered during the course in greater detail. Students should prepare an outline with relevant references of their research topic by the 5th week of the course. The outline will be reviewed by the instructor.

Method of Evaluation: Grades will be based on performance during each student's presentation for their assigned seminar and their class participation. There will be quizzes on the assigned material. Students will receive a grade for their initial outline of their paper as well as for the final paper. Quizzes will count for 10% of the final grade, the outline 10%, class participation/presentations 40% and the paper 40%.

Reading Assignments: There will be “assigned” and “optional” reading assignments for the seminars. Background reading (e.g., on antibiotics, bacteria or relevant topics) will often be from *Sherris Medical Microbiology* 7th Edition. Students should review these assignments prior to the seminar. The text can be accessed at:

<http://accessmedicine.mhmedical.com/content.aspx?bookid=2268§ionid=176081144>).



General background resources on antimicrobial resistance:

CDC's Antimicrobial Resistance Web Site: <https://www.cdc.gov/drugresistance/>

CDC's Antibiotic Resistance Patient Safety Atlas (Healthcare-associated infections through the National Healthcare Safety Network). Maps of resistance across the country on a statewide basis

Instructions: <https://www.cdc.gov/hai/surveillance/ar-patient-safety-atlas.html>

Maps: <https://gis.cdc.gov/grasp/PSA/MapView.html>

WHO's website on antimicrobial resistance: <http://www.who.int/antimicrobial-resistance/en/>

APUA (Association for the Prudent Use of Antibiotics) - <https://apua.org>

Center for Infectious Disease Research and Policy (CIDRAP): <http://www.cidrap.umn.edu>

Seminar 1 (9/10/2018): Introduction: A discussion of the global threat of antimicrobial resistance.

- a. Overview of the course, some examples of the impact of antimicrobial resistance
- b. Some definitions
- c. Presentation of international, national, regional, institutional data
- d. Discussion of a possible group study on antimicrobial resistance (e.g., Investigation of antimicrobial resistance in the students' environment, or suspected hotspots for resistance).

Background readings and Assignments for Seminar 1:

CDC - Antibiotic Resistance Threats in the United States, 2013

CDDEP – The State of the World's Antibiotics – 2015. Executive Summary (page 8-13)

Marston *et al.*, Antimicrobial resistance. JAMA 316:1193, 2016

Goossens *et al.*, Outpatient antibiotic use in Europe... Lancet 365:579-87, 2005

Optional:

IDSA – Faces of Antimicrobial Resistance -

<http://www.idsociety.org/uploadedFiles/IDSA/FOAR/FOAR%20Report%201-up%20final.pdf>

Antibiotics vs. Bacteria: Fighting the Resistance (NIH):

<https://www.youtube.com/watch?v=oLPAodRN1b0>

Seminar 2 (9/17/2018): Antibiotics 101: An overview of antibiotics and the molecular biology of resistance

- a. Some history
- b. Some basic microbiology
- c. Mechanisms of antimicrobial resistance
- d. Horizontal gene exchange
- e. Illustrations of the clinical relevance of antimicrobial resistance

Assignments:

Sherris – Chapters 21 Bacteria - Basic Concepts and Chapter 23 – Antibacterial agents and resistance (Introduction, Antibacterial agents and therapy up to, but not including, selected antibacterial agents)

Levy – Scientific American. The challenge of antibiotic resistance 46-53; March 1998
Davies and Davies - Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev 74:417, 2010

Optional:

Brief History of antibiotics: <https://www.youtube.com/watch?v=AZ5Vcybl8ws>

Khan academy –

1. Antibiotic Overview: <https://www.khanacademy.org/science/health-and-medicine/current-issues-in-health-and-medicine/antibiotics-and-antibiotic-resistance/a/antibiotics-an-overview>
2. Antibiotic Resistance: <https://www.khanacademy.org/science/health-and-medicine/current-issues-in-health-and-medicine/antibiotics-and-antibiotic-resistance/a/what-is-antibiotic-resistance>

Seminar 3 (9/24/2018): Deciding how to treat infections.

- a. How is antimicrobial susceptibility determined?
- a. Pharmacokinetics/Pharmacodynamics – penetration and persistence of antibiotics in the blood and at different tissue sites
- b. Why does resistance emerge during therapy?
- c. Do antimicrobial combinations help prevent the emergence of resistance?

Assignments:

Sherris – Chapter 23 (Section on Antimicrobial Resistance)

Karchmer *et al.*, Prosthetic valve endocarditis caused by *Staphylococcus epidermidis*. JAMA 253:2867-2868, 1985

Principles of Antibacterial Pharmacokinetics & Pharmacodynamics (Stanford Medicine)(YouTube)
- <https://www.youtube.com/watch?v=01WrflmxK0>

Optional:

Pulido *et al.*, Progress on the development of rapid methods for antimicrobial susceptibility testing. J Antimicrob Chemotherapy 68:2710-2717, 2013

Seminar 4 (10/1/2018): The emergence of Community-Associated Methicillin-resistant *Staphylococcus aureus* (MRSA)

- a. The emergence of a single methicillin-resistant *S. aureus* (MRSA) epidemic clone (USA300) in the community
- b. How was this single clone able to spread?

Assignments:

Sherris Chapter – 24

Chambers - The Changing Epidemiology of *Staphylococcus aureus*. Emerg Infect Dis 7:178, 2001

Moran - Methicillin-resistant *S. aureus* infections among patients in the emergency department. NEJM 355:666, 2006

Baggett *et al.*, Community-onset methicillin-resistant *Staphylococcus aureus* associated with antibiotic use and the cytotoxin Panton-Valentine leukocidin during a furunculosis outbreak in rural Alaska. J Infect Dis 189:1565-1573, 2004

Optional:

Herold *et al.*, Community-acquired methicillin-resistant *staphylococcus aureus* in children with no identified predisposing risk. JAMA 279:593-598

Seminar 5 (10/8/2018): Multidrug resistant *Mycobacterium tuberculosis*

- a. History of therapy for MTB – why does resistance occur with this pathogen?
- b. Tugela Ferry and XDR-TBC
- c. AIDS and MDR-TBC

Assignments:

Sherris Chapter 27 (only *Mycobacterium tuberculosis* section)

Gandhi *et al.*, Nosocomial transmission of extensively drug-resistant tuberculosis in a rural hospital in South Africa. J Infect Dis 207:9-17, 2013; Editorial: Dharmadhikari J Infect Dis 207:1-3, 2013

Gandhi *et al.*, Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 368:1575, 2006

Optional:

Zumla *et al.*, Tuberculosis. NEJM 368:745-755

Seminar 6 (10/15/2018): Sexually Transmitted Diseases – *Neisseria gonorrhoeae*

- a. Identifying settings where resistant *N. gonorrhoeae* outbreaks are likely to occur
- b. What are the current mechanisms of *N. gonorrhoeae* resistance?

Assignments:

Sherris – Chapter 30 (Section on *Neisseria gonorrhoeae* only)

CDC Web site on gonorrhea - <https://www.cdc.gov/std/gonorrhea/arg/>

Katz *et al.*, Cluster of *Neisseria gonorrhoeae* Isolates with high-level azithromycin resistance and decreased ceftriaxone susceptibility, Hawaii, 2016. Clin Infect Dis 65:918-923 2017 Editorial: Hook. Continued evolution of gonococcal antimicrobial resistance. Clin Infect dis 65:924-926, 2017

Optional:

Wi *et al.*, Antimicrobial resistance in *Neisseria gonorrhoeae*: Global surveillance and a call for Int'l collaborative action PLOS Medicine. <https://doi.org/10.1371/journal.pmed.1002344>

Martin *et al.*, Rapid Sequence-Based Identification of Gonococcal Transmission Clusters in a Large Metropolitan Area. J Infect Dis. 189:1497, 2004

Seminar 7 (10/22/2018): *Clostridium difficile*

- a. How does antibiotic use affect the emergence of the nosocomial pathogen *Clostridium difficile*?
- b. What is the association of fluoroquinolone resistance with the emergence of high virulence strains of *Clostridium difficile*.

Assignments:

Sherris – Chapter 29 Section on *C. difficile*

Pepin *et al.*, Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis 41:154-1260, 2005.

McDonald *et al.*, An epidemic, toxin-gene variant of *C. difficile*. NEJM 353:2433-2441, 2005
Editorial: Bartlett and Perl – The new *C. difficile*... NEJM 353:2503-2505, 2005

Optional:

Loo *et al.*, A predominantly clonal multi-institutional outbreak of clostridium difficile–associated diarrhea with high morbidity and mortality NEJM 353:2442-9, 2005

Seminar 8 (10/29/2018): HIV Therapy and Resistance

- a. The critical role “resistance thresholds” in the emergence of antiviral resistance
- b. Rationale for combination therapy
- c. The critical role of adherence to antiretroviral therapy in preventing resistance

Assignments:

Sherris - Chapter 18 Human Immunodeficiency Virus (HIV); Chapter 8 Section on Inhibitors of HIV
Harrigan *et al.*, Predictors of HIV drug-resistance mutations in a large antiretroviral-naïve cohort initiating triple antiretroviral therapy. J Infect Dis 191:339-347, 2005
Jourdain *et al.*, Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. NEJM 351:229-240, 2004

Seminar 9 (11/12/2018): Agriculture and antimicrobial resistance

- a. The continuing debate on the use of antibiotics in animal feed
- b. Evidence for animal to human transmission of antimicrobial resistant bacteria

Assignments:

Levy – Changes in intestinal flora of farm personnel after introduction. NEJM 295:583-588, 1976
Kluytmans *et al.*, Extended-spectrum β -lactamase–producing *Escherichia coli* from retail chicken meat and humans: comparison of strains, plasmids, resistance genes, and virulence factors. Clin Infect Dis 56:478, 2013
Phibro Animal Health Corporation – animal antibiotics - <http://animalantibiotics.org>
Nat Geographic - http://phenomena.nationalgeographic.com/2015/12/14/adufa-2014/?_ga=2.123409675.1651160069.1522180254-1980095523.1499711734

Optional:

Chang *et al.*, Antibiotics in agriculture and the risk to human health: how worried should we be? Evol Applic 8:240-245, 2015
APUA - http://emerald.tufts.edu/med/apua/policy/apua_action_8_670390492.pdf
Cohan – Antibiotics in Meat.... New York Times
<https://www.nytimes.com/2018/05/25/opinion/sunday/meat-antibiotics-organic-farming.html?action=click&module=Opinion&pgtype=Homepage>
Hakim – Hamburger central..... New York Times
<https://www.nytimes.com/2018/03/23/business/cattle-antibiotics.html>

Seminar 10 (11/19/2018): Outbreak investigations – How are antimicrobial pathogens transmitted and how are outbreaks investigated?

- a. What are the molecular epidemiologic techniques used for outbreak investigations

- b. Examples of two outbreak investigations

Assignments:

Sabat *et al.*, Overview of molecular typing methods for outbreak detection and epidemiologic surveillance. EuroSurv 2013

<https://www.eurosurveillance.org/content/10.2807/ese.18.04.20380-en>

Koser *et al.*, Rapid whole-genome sequencing for investigation of a neonatal MRSA outbreak. NEJM 366: 2267-2275, 2012

Ostrowsky *et al.*, *Serratia marcescens* bacteremia traced to an infused narcotic NEJM 346:1529, 2002

Seminar 11 (11/26/2018): The role of the microbiome in the development of antimicrobial resistance

- a. The effect of antibiotics on the susceptibility to infection
- b. Exposure to food
- c. Emergence of antimicrobial resistant bacteria in the GI flora of immunocompromised patients

Assignments:

Cho and Blaser. The human microbiome: at the interface of health and disease. Nature Rev Genetics 13:260-270, 2012

Ubeda *et al.*, Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. J Clin Invest 120:4332-4341, 2010

Li *et al.*, Clonal emergence of invasive multidrug-resistant *Staphylococcus epidermidis* deconvoluted via a combination of whole-genome sequencing and microbiome analyses Clin Infect Dis 2018

Optional:

Leung *et al.*, Antimicrobial resistance gene acquisition and depletion following fecal microbiota transplantation for recurrent *Clostridium difficile* infection. Clin Infect Dis 66:456-459, 2018

Seminar 12 (12/3/2018): Presentation of research on colonization with multidrug resistant bacteria and the risk of infection in liver transplant patients – Anne-Catrin Uhlemann, MD/PhD

- a. How are studies exploring the basis for the development of multidrug resistant bacterial infections designed?
- b. How does colonization with a multidrug resistant pathogen contribute to subsequent infection?
- c. How is whole genome sequencing used to identify possible transmission pathways?

Assignments:

Macesic *et al.*, Genomic surveillance reveals diversity of multidrug-resistant organism colonization and infection: a prospective cohort study in liver transplant recipients. Clin Infect Dis In Press, 2018

Seminar13 (12/10/2018): Interventions to reduce antimicrobial resistance; Possible results of group study

- a. A description of CDC – educational efforts

- b. The role of antibiotic stewardship
- c. Reducing antimicrobial use in animal feeds
- d. Your ideas!

Assignments:

Spellberg *et al.*, The future of antibiotics and resistance NEJM 368:299, 2013

CDC – Antibiotic Resistance Solutions Initiative. <https://www.cdc.gov/drugresistance/solutions-initiative/index.html>

Schooley *et al.*, Development and use of personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated resistant *Acinetobacter baumannii*. Infection Antimicrob Agents Chemotherap 61:10:1-14, 2017

Optional:

NYCDOH Judicious prescribing of antibiotics CHI 36, 25-32, 2017

Lyon - Phage therapy's role in combating antibiotic-resistant pathogens. JAMA E1 2017

Doran and Davidson - Antimicrobial stewardship. Mayo Clin Proc 86:1113-1123, 2011

About the professor: Frank Lowy, MD is the Clyde '56 and Helen Wu Professor of Medicine and Pathology & Cell Biology (in Epidemiology). He went to Columbia College and the College of Physicians & Surgeons. His medical house staff training was at Harlem Hospital and he trained in Infectious Diseases at the Albert Einstein College of Medicine. He remained at Einstein on faculty until he returned to Columbia in 1999. His research has focused on the pathogenesis of staphylococcal infections and the transmission of antimicrobial-resistant *Staphylococcus aureus* in high risk populations. He is also active as a teacher at the medical school and as a clinician at the medical center.

Statement on Academic Integrity: The intellectual venture in which we are all engaged requires of faculty and students alike the highest level of personal and academic integrity. As members of an academic community, each one of us bears the responsibility to participate in scholarly discourse and research in a manner characterized by intellectual honesty and scholarly integrity.

Scholarship, by its very nature, is an iterative process, with ideas and insights building one upon the other. Collaborative scholarship requires the study of other scholars' work, the free discussion of such work, and the explicit acknowledgement of those ideas in any work that inform our own. This exchange of ideas relies upon a mutual trust that sources, opinions, facts, and insights will be properly noted and carefully credited. In practical terms, this means that, as students, you must be responsible for the full citations of others' ideas in all of your research papers and projects; you must be scrupulously honest when taking your examinations; you must always submit your own work and not that of another student, scholar, or internet agent. Any breach of this intellectual responsibility is a breach of faith with the rest of our academic community. It undermines our shared intellectual culture, and it cannot be tolerated. Students failing to meet these responsibilities should anticipate being asked to leave Columbia. (taken from - <http://www.college.columbia.edu/academics/academicintegrity>)

Disability accommodation: Students, instructors, and Disability Services (DS) all have rights and responsibilities in the process of ensuring that students receive the reasonable accommodations necessary for their full participation in their academic program. This page provides a brief oversight of these rights and responsibilities, but for more information you are referred to [Disability Services](#).

Student Rights and Responsibilities

In order to ensure their rights to reasonable accommodations, it is the responsibility of students to report any learning-related disabilities, to do so in a timely fashion, and to do so through the Office of Disability Services. Students who have documented conditions and are determined by DS to need individualized services will be provided a DS-certified 'Accommodation Letter'. It is students' responsibility to provide this letter to all their instructors and in so doing request the stated accommodations.

Disability Services Rights and Responsibilities

DS is responsible for working with students with disabilities to assess their academic needs, for assisting students in communicating with individual instructors regarding reasonable accommodations and, in some cases, for facilitating the implementation of the approved accommodations. DS shares the educational mission of all offices in the University and is therefore also responsible for upholding the academic policies established by the faculty and for the integrity of academic programs. DS therefore has the right to receive current disability documentation and to deny requests for accommodations that are not warranted or are not reasonable.

Instructor Rights and Responsibilities

It is the right of all instructors to establish the academic standards for the courses that they teach and to consult with DS to determine what accommodations are reasonable for a given course. It is therefore the responsibility of an instructor to provide accommodations, as determined by the DS-certified 'Accommodation Letter', as long as they do not undermine the academic integrity of the course. Instructors are also responsible for evaluating the academic work of students with disabilities according to the same criteria of evaluation utilized for all other students in the class.

It is also the responsibility of an instructor to maintain student confidentiality. Instructors are expected to refrain from discussing a student's disability with other students, to file accommodation requests in a

secure location, and to provide opportunities for students to discuss privately their accommodation needs.

Lastly, while individual students with documented disabilities are entitled to reasonable and specific accommodations, instructors are responsible for fostering accessible learning environments for all students. Many strategies for teaching students with disabilities are known to benefit all students. These include:

- Clear statement of course goals and objectives;
- Clarity in course syllabus, schedule, and requirements;
- Multiple modes of presentation - lecture, handouts, power points;
- Setting the tone for intellectually rigorous and socially courteous engagement with all students;
- Including in syllabi a statement regarding classroom accommodations

(taken from - <http://www.college.columbia.edu/rightsandresponsibilities>)