UWTASP

tele-antimicrobial stewardship program

July 8th, 2019

Announcements

- TASP Noon Session
- Cases!

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Agenda

- Didactic:

Extended-Spectrum Beta-Lactamases

- Case Discussions

Antimicrobial Drug Resistance

What is it?

Non-specific term indicating that a micro-organism is no longer susceptible to the antimicrobials typically used for that infection.

Associated with worse outcomes, longer LOS and increased costs

Examples…

- MRSA, VISA, VRSA
- VRE
- Extended-spectrum beta-lactamases (ESBLs)
- Carbapenem-resistant enterobacteriaceae, such as *E. coli, Salmonella, Klebsiella,* and *Shigella* spp.
- Multi-drug resistant tuberculosis (MDR-TB)
- Drug-resistant *Neisseria gonorrhea*

Definitions of Common Terms Used to Describe Resistant Gram-Negative Bacilli

β-lactam antibiotics	These antibiotics comprise the penicillins , cephalosporins and carbapenems, which share the common basic chemical structure of a 4-member β-lactam ring.
β-lactamases	These enzymes hydrolyze the β-lactam ring and inactivate the β-lactam class antibiotics.
Ambler classification	This is a classification system for β-lactamases on the basis of their amino acid sequences and their active site residue.
Extended-spectrum β-lactamases (ESBLs)	These are broad-spectrum, Ambler class A β-lactamases, which hydrolyze the penicillins, and first- to fourth-generation cephalosporins, which are cefoxitin susceptible and are inhibited by the β-lactamase inhibitors (eg clavulanate).
Cephalosporinases	ESBLs are technically cephalosporinases but the term cephalosporinase is generally reserved to describe Ambler class C AmpC β-lactamases, which are cefoxitin resistant, hydrolyze the penicillins and first to third-generation cephalosporins, and are not inhibited by the β-lactamase inhibitors, such as clavulanate.
Carbapenemases	These are broad-spectrum β-lactamases (usually Ambler class A, B, or D), which have the ability to hydrolyze carbapenems, in addition to the penicillins and also the first- to fourth-generation cephalosporins, although activity may vary depending on the exact type of carbapenemase.
Carbapenem-resistant gram-negative bacilli and carbapenem-resistant Enterobacteriaceae vs carbapenemase-producing gram-negative bacilli (CPGNB) and carbapenemase-producing Enterobacteriaceae	CPGNB are most often CRGNB (susceptibility testing may yield rare isolates and may have low carbapenem minimum inhibitory concentrations); however, not all CRGNB are carbapenemase producers. Carbapenem resistance may be mediated by ESBL or AmpC production, for example, associated with porin loss.

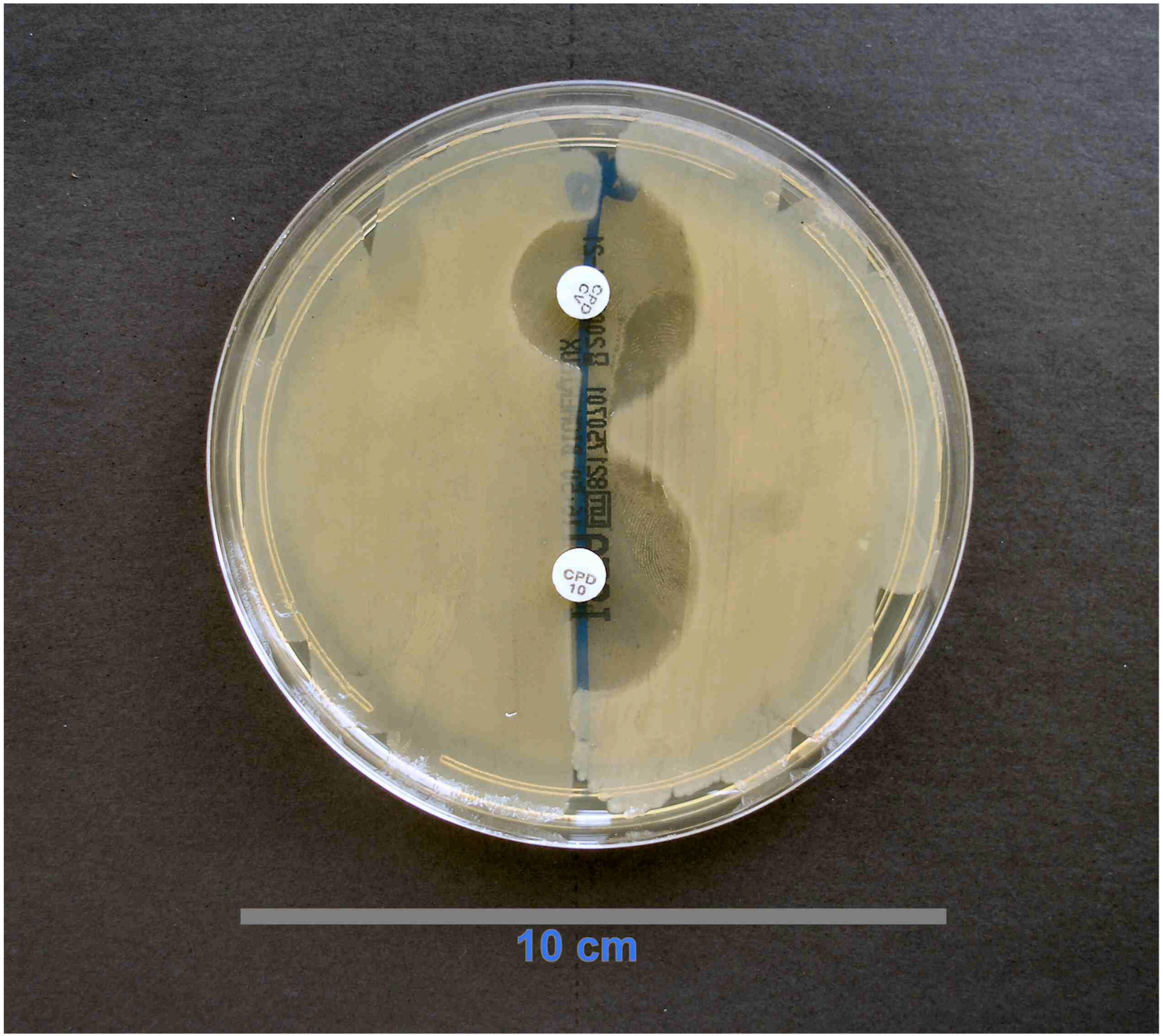
Vasoo, Mayo Clin Proc 2015

ESBLs

- MOST IMPORTANT mechanism of resistance in GNRs
- First identified in Germany in 1983
- A family of enzymes (often on a plasmid) that degrade the beta-lactam ring of most penicillins and cephalosporins
  - Exceptions: carbapenems, cephamycins (cefoxitin), ceftolozane-tazobactam, ceftazidime-avibactam
- Main mechanism of resistance to 3rd generation cephalosporins like ceftriaxone, ceftazidime and cefotaxime

ARS: Which of the following genes encodes an ESBL?

A. CTX-M
B. SHV
C. TEM
D. OXA
E. AmpC
F. None of the above
G. A through C


CPD 10
CPD 10
10 cm

GNR Resistance Detection: ESBLS

MOA		ESBL	
Location		Plasmid	
Bugs		*E.coli, Klebsiella*	
1 gen Ceph		R	
2 gen Ceph		S	
3 gen Ceph		R	
4 gen Ceph		R / S	
Cefotax + Clav		S	
Carbapenem		S	

ESBLs

- Organisms with ESBL genes often have other mechanisms of resistance (plasmids, transposons, etc)
- Incidence in the U.S. is rising

Rate of ESBL Phenotype in Escherichia coli and Klebsiella Species in 2009 and 2011

	2009	2011
E. coli in United States	11.9%	17.4%
E. coli in Europe	17.8%	20.3%
Klebsiella species in United States	16.2%	18.6%
Klebsiella species in Europe	27.5%	41.8%

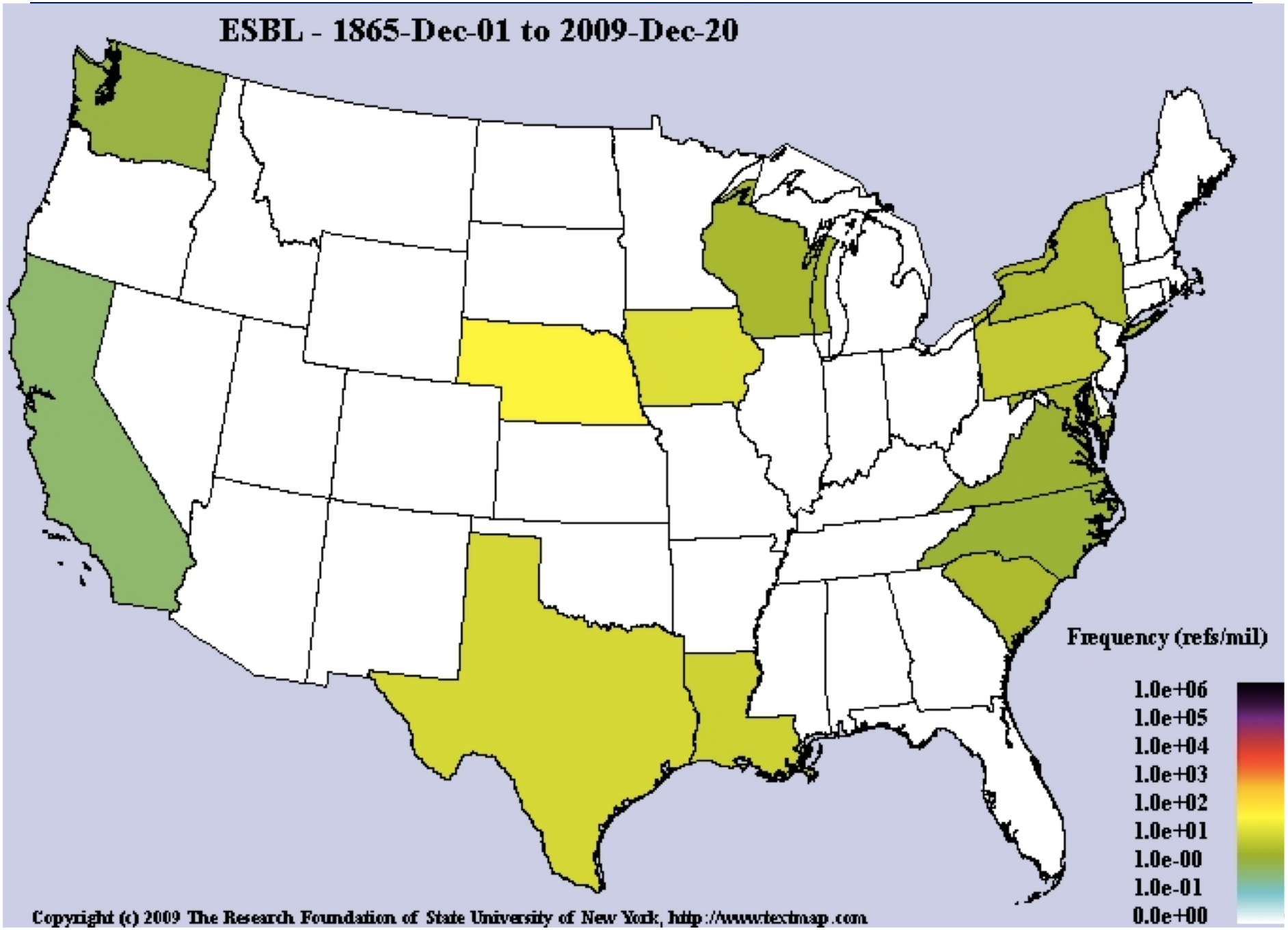
Dynamed, 2016

ESBLs: Epidemiology

- Global epidemic
- Initially all/most were healthcare-acquired
- More recently, infections also coming from community
- Risk factors:
  - recurrent UTI
  - SNF/LTACH residence
  - Exposure to cephalosporins/fluoroquinolones
  - Older age

Comparison of the antimicrobial usage during the last 60 days prior to inclusion in the study population with and without ESBL-producing Enterobacteriaceae infection.

Antimicrobials	ESBL (n = 212)	Non-ESBL (n = 2089)	*p* Value
Aminoglycoside	18 (8.5)	25 (1.2)	<0.0001
Carbapenem	50 (23.6)	239 (11.4)	<0.0001
Cephalosporin			
First generation	11 (5.2)	161 (7.7)	0.184
Second generation	42 (19.8)	120 (5.7)	<0.0001
Third generation	19 (9.0)	200 (9.6)	0.7724
Fourth generation	64 (30.19)	61 (2.9)	<0.0001
Chloramphenicol	9 (4.3)	1 (0.1)	<0.0001
Cyclic lipopeptide	1 (0.5)	11 (0.5)	0.6951
Fosfomycin	5 (2.4)	12 (0.6)	0.0156
Fluoroquinolone	48 (22.6)	160 (7.7)	<0.0001
Glycopeptide	18 (8.5)	112 (5.4)	0.0601
Clindamycin	21 (9.9)	67 (3.2)	<0.0001
Macrolide	1 (0.5)	37 (1.8)	0.1213
Oxazolidinone	30 (14.2)	38 (1.8)	<0.0001
Penicillin	6 (2.8)	224 (10.7)	0.0003
Penem	2 (0.9)	9 (0.4)	0.2691
ST[a]	15 (7.1)	61 (2.9)	0.0013
Tetracycline	43 (20.3)	38 (1.8)	<0.0001
Antifungal agent	25 (11.8)	89 (4.3)	<0.0001


ESBL - 1865-Dec-01 to 2009-Dec-20
Frequency (refs/mil)
1.0e+06
1.0e+05
1.0e+04
1.0e+03
1.0e+02
1.0e+01
1.0e-00
1.0e-01
0.0e+00
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Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study

Maris S Arcilla, Jarne M van Hattem*, Manon R Haverkate, Martin C J Bootsma, Perry J J van Genderen, Abraham Goorhuis, Martin P Grobusch, Astrid M Oude Lashof, Nicky Molhoek, Constance Schultsz, Ellen E Stobberingh, Henri A Verbrugh, Menno D de Jong, Damian C Melles, John Penders*

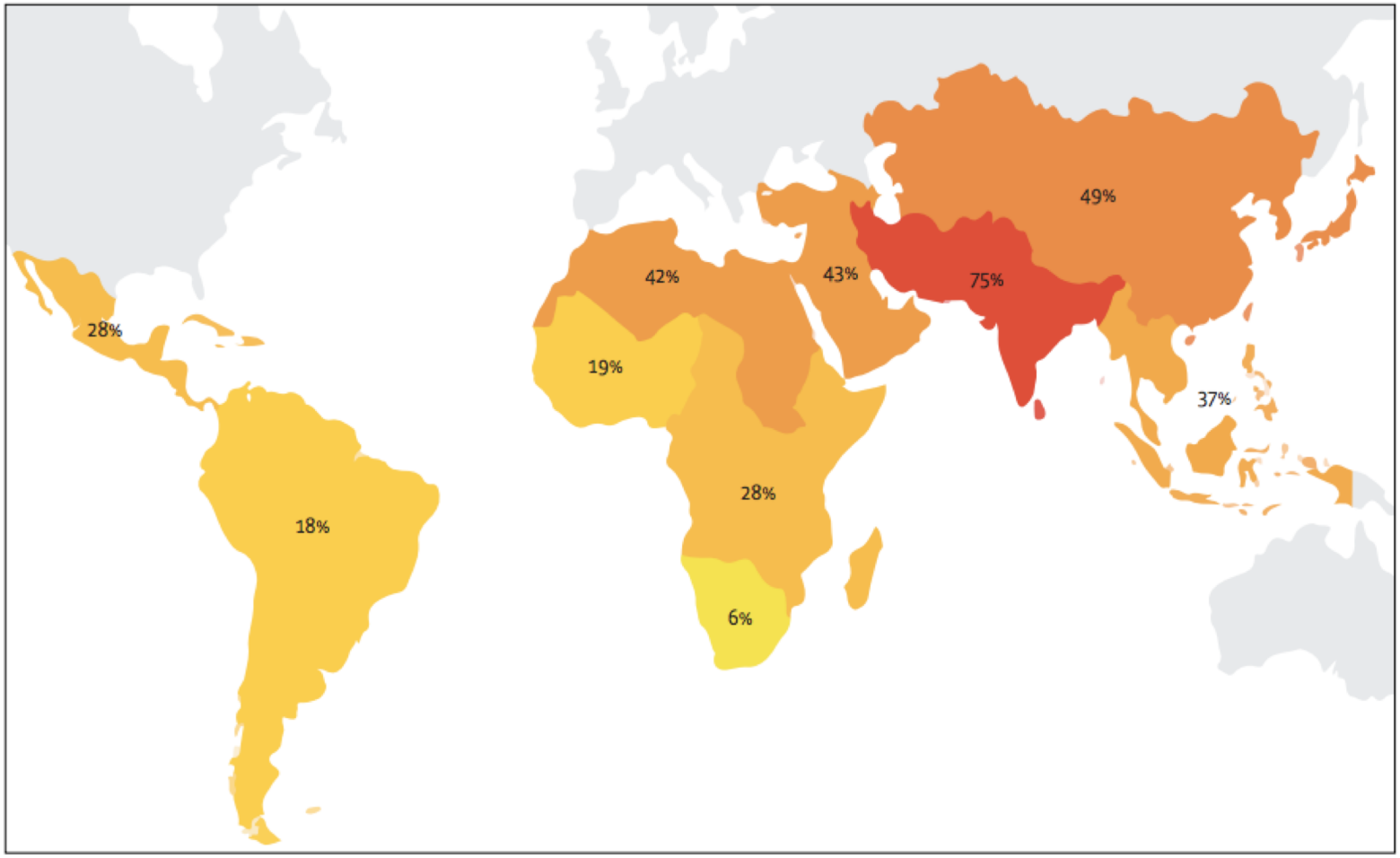
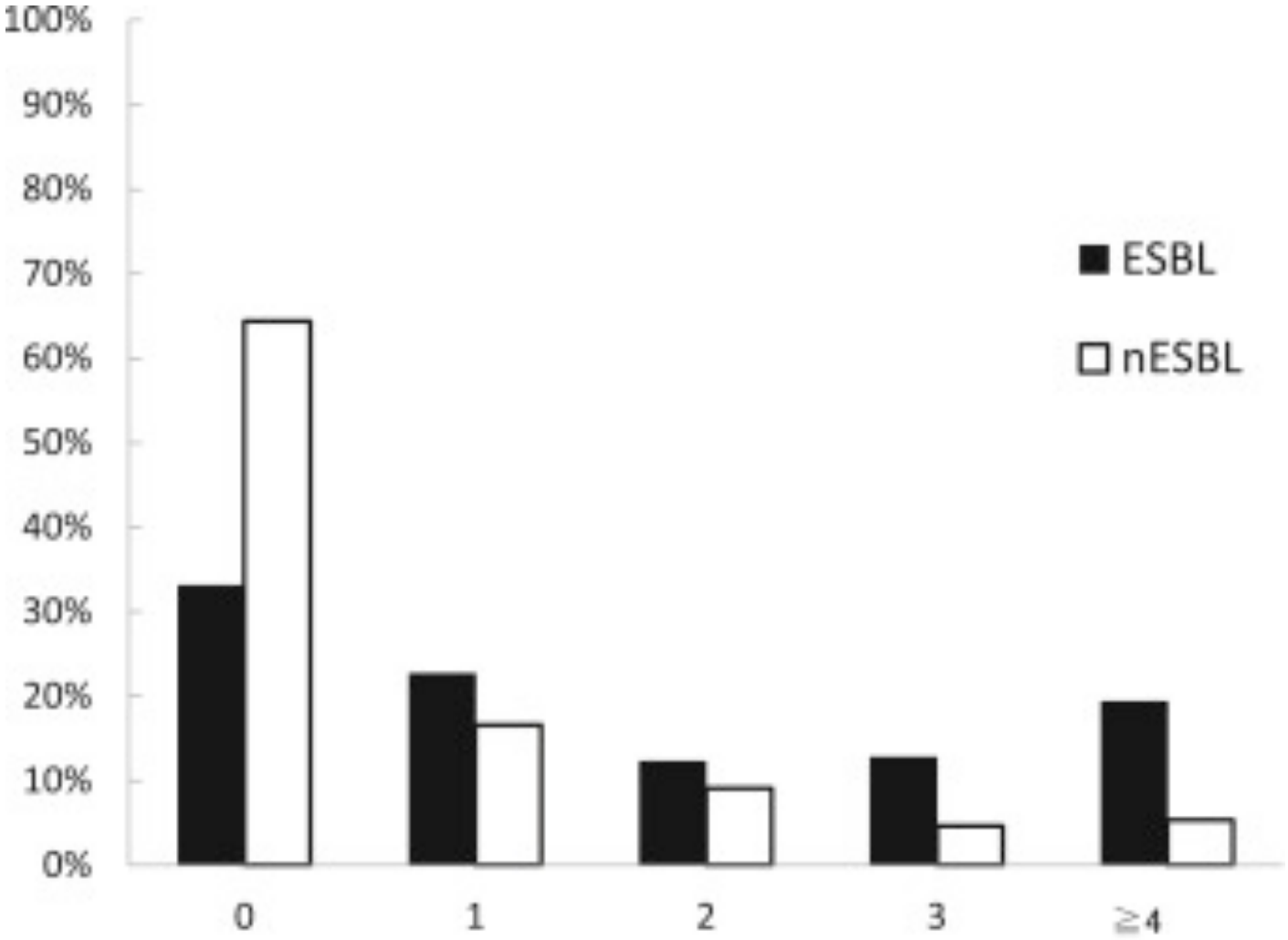


Figure 1: Percentages of travellers that acquired β-lactamase-producing Enterobacteriaceae per subregion, according to the United Nations geoscheme

In the COMBAT Study, what was the median time of colonization?

A. 2-3 months
B. 6 months
C. 12 months
D. 16 months
E. 2-3 years
F. Indefinitely



The number of antimicrobial usage between infectious patients with and without- ESBL-producing Enterobacteriaceae proceeding 60 days. The frequency of antimicrobial usage in infectious patients with ESBL-producing Enterobacteriaceae was higher than tha...

Hazuki Nakai,Journal of Infection and Chemotherapy, Volume 22, Issue 5, 2016, 319–326

Treatment Options

- Carbapenems
- Fosfomycin
- Cetazidime-avibactam or cetolozane-tazobactam
- Nitrofurantoin
- Aminoglycosides
- Tigecycline

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