Discordant Results in the AR Lab Network

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Case 4: *Candida auris*

Drug	MIC (µg/mL)	Interpretation (*Candida albicans*) or Range/MIC_{50}/MIC_{90}
Micafungen	0.12	S
Anidulafungin	0.24	S
Caspofungin	0.5	I
Fluconazole	2	S
Posaconazole	4	Range: <0.015 to 8 MIC_{50}: 0.06 MIC_{90}: 2
Voriconazole	16	R
Intraconazole	2	Range: <0.03 to 2 MIC_{50}: 0.125 MIC_{90}: 0.5
Isavuconazole	4	Range: <0.015 to 4 MIC_{50}: 0.25 MIC_{90}: 2
Amphotericin B	4	Range: <0.125 to 8 MIC_{50}: 1 MIC_{90}: 4

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Three Classes of Antifungals

- **Azoles – Resistance in *Candida auris* usually occurs**
  - Fluconazole
  - Posaconazole
  - Voriconazole
  - Intraconazole
  - Isavuconazole
- **Echinocandins – Resistance is *Candida auris* is infrequent**
  - Micafungen
  - Anidulafungin
  - Caspofungin
- **Polyene – Resistance in *Candida auris* is common**
  - Amphoterocin B

Mechanism of Resistance

Table 1

Summary of molecular mechanisms of fluconazole resistance in *Candida* spp.

Mechanism	Gene(s) involved[a]	Regulator(s) involved[a]	Species
Drug target overexpression	*ERG11*	*UPC2*	*Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*
Drug target alteration	*ERG11*		*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *Candida auris*
Bypass pathways	*ERG3*		*C. albicans*, *C. tropicalis*
Efflux pump overexpression			
ABC transporters	*CDR1*, *CDR2*, *SNQ2*, *ABC1*	*TAC1*, *PDR1*	*C. albicans*, *Candida glabrata*, *C. parapsilosis*, *Candida krusei*
MFS transporters	*MDR1*, *TPO3*	*MRR1*	*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*
Aneuploidy/loss of heterozygosity	*ERG11*	*UPC2*, *TAC1*	*C. albicans*

Berkow & Lockhart, Infect Drug Resist, 2017

Breakpoints vs Epidemiological Cut-off Values

- Breakpoints
  - Requires 3 types of data
  - MIC distribution data
  - PK/PD data
  - Clinical outcomes data
- ECVs
  - Can be set when only MIC data available
- Reporting Results
  - Breakpoint: susceptible, intermediate, susceptible dose-dependent, resistant
  - ECV: MIC is less than wild type or higher than wild type

Troubleshooting

- Confirm the isolate identification
- Repeat the susceptibility
- Send the isolate to CDC if results repeat

Case 6: *Neissseria gonorrhoeae*

Drug	MIC (µg/mL)	Interpretation
Ceftriaxone	1	R
Cefixime	2	R
Ciprofloxacin	32	R
Tetracycline	4	R
Azithromycin	0.5	S

Treatment Guidelines for Gonorrhea

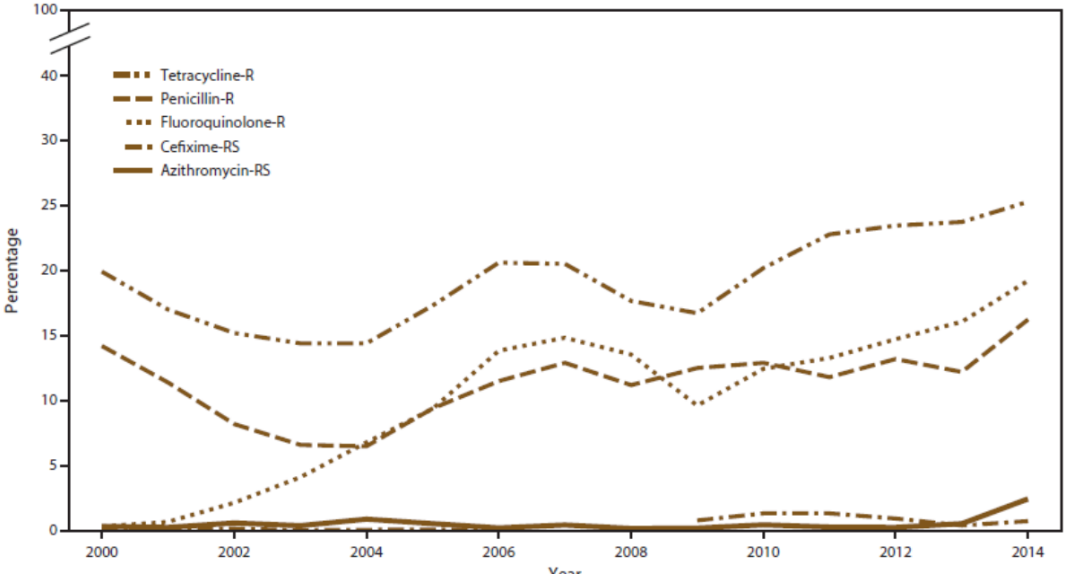
- All treatment is empiric treatment because of culture-independent diagnostics

- CDC treatment guidelines
  - Dual therapy with ceftriaxone and azithromycin

Trends in Resistance

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report

FIGURE 2. Prevalence of tetracycline, penicillin, or fluoroquinolone resistance* or reduced cefixime or azithromycin susceptibility,† by year — Gonococcal Isolate Surveillance Project, United States, 2000–2014



New Resistance in *Neisseria gonorrhoeae*

European Centre for Disease Prevention and Control

Rapid Risk Assessment: Extensively drug-resistant (XDR) Neisseria gonorrhoeae in the United Kingdom and Australia

Troubleshooting

- New resistance – communicate results immediately
- Send an AR Alert – this requires epidemiological intervention
- Confirm resistance
- Send to CDC

Case 5: *Klebsiella pneumoniae*

Drug	MIC (µg/mL)	Interpretation
Ceftazidime	8	R
Ceftazidime-avibactam	8/4	R
Imipenem	16	R
Meropenem	8	R
Colistin	1	Wild type
Tigecycline	16	R
Amikacin	16	R
Gentamicin	32	R
Levofloxacin	8	R

More Info

- Test Results
  - mCIM +; produces a carbapenemase
  - PCR + for NDM; a metallo-beta-lactamase

- Metallo-beta-lactamase
  - Not inhibited by beta-latamase inhibitors
  - Most new CRE drugs using beta-lactamase inhibitors for CRE activity

The Efficacy of Colistin

Clinical Infectious Diseases

MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[6] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2]; for the Antibacterial Resistance Leadership Group

Thirty-eight patients were treated first with ceftazidime-avibactam and 99 with colistin. Most patients received additional anti-CRE agents as part of their treatment. Bloodstream (n = 63; 46%) and respiratory (n = 30; 22%) infections were most common.

In patients treated with ceftazidime-avibactam versus colistin, IPTW-adjusted all-cause hospital mortality 30 days after starting treatment was 9% versus 32%, respectively (difference, 23%; 95% bootstrap confidence interval, 9%–35%; *P* = .001).

If Not Colistin – Then What?

Aztreonam - Avibactam

TABLE 4 Comparative MICs of aztreonam-avibactam and aztreonam against 267 isolates of *Enterobacteriaceae* positive for an MBL gene alone or positive for an MBL gene and one or more additional β-lactamase genes

	MIC[b] (μg/ml) for:					
	Aztreonam-avibactam			Aztreonam		
Group (*n*)[a]	50%	90%	Range	50%	90%	Range
All MBL producers (267)	0.12	1	≤0.015 to 8	64	>128	≤0.015 to >128
MBL only (6)[c]	–	–	≤0.015 to 0.06	–	–	≤0.015 to 1
MBL + OSBL (24)	0.12	0.25	0.03 to 0.5	0.25	2	0.06 to 64
MBL + ESBL (26)	0.25	0.25	0.03 to 0.25	64	>128	0.06 to >128
MBL + ESBL + OSBL (69)	0.12	0.25	≤0.015 to 0.5	128	>128	2 to >128
MBL + AmpC (33)	0.12	2	≤0.015 to 8	0.25	64	≤0.015 to 128
MBL + AmpC + OSBL (28)	0.5	2	≤0.015 to 8	16	128	≤0.015 to >128
MBL + ESBL + AmpC (13)	0.25	0.25	0.03 to 1	64	>128	1 to >128
MBL + ESBL + AmpC + OSBL (30)	0.12	0.5	≤0.015 to 2	128	>128	0.5 to >128
MBL + KPC (1)	–	–	0.5	–	–	>128
MBL + KPC + ESBL (2)	–	–	0.5 to 1	–	–	>128
MBL + KPC + ESBL + OSBL (2)	–	–	0.5 to 2	–	–	>128
MBL + KPC + AmpC + OSBL (1)	–	–	0.5	–	–	>128
MBL + KPC + ESBL + AmpC + OSBL (2)	–	–	0.5	–	–	>128
MBL + OXA-48-like + OSBL (5)[d]	–	–	0.12 to 2	–	–	0.25 to 1
MBL + OXA-48 + ESBL (3)	–	–	0.12 to 0.25	–	–	>128
MBL + OXA-48-like + ESBL + OSBL (13)[d]	0.25	0.5	0.12 to 1	>128	>128	128 to >128
MBL + OXA-48 + AmpC (3)	–	–	0.25 to 1	–	–	0.25 to 16
MBL + OXA-48 + AmpC + OSBL (5)	–	–	0.25	–	–	32
MBL + OXA-48 + ESBL + AmpC + OSBL (1)	–	–	0.25	–	–	128

[a]The MBLs included NDM (142 isolates), VIM (96 isolates), and IMP (29 isolates); the ESBLs included SHV, CTX-M, VEB, and the endogenous ESBL common to *K. oxytoca*. OSBL, original-spectrum β-lactamase. Original-spectrum β-lactamases are enzymes that do not hydrolyze expanded-spectrum cephalosporins or carbapenems and include TEM-1, SHV-1, and SHV-11. *n*, number of isolates tested.

[b]–, MIC_{50}s and MIC_{90}s were not calculated when there were <10 isolates.

[c]Does not include species with endogenous AmpC or ESBL enzymes.

[d]Includes isolates carrying OXA-48 and OXA-232.

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Thank You

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For more information, contact CDC
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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.