

AN ACCREDITED SYMPOSIUM
AT THE 2015 AMMI CANADA-CACMID
ANNUAL CONFERENCE

CHALLENGES AND OPPORTUNITIES IN PREVENTING & MANAGING SERIOUS BACTERIAL INFECTIONS

Multi-drug Resistant Gram-negative Organisms Challenges and Opportunities

Susan M. Poutanen, MD, MPH, FRCPC
Microbiologist/Infectious Disease Specialist, UHN/MSH
Associate Professor, University of Toronto

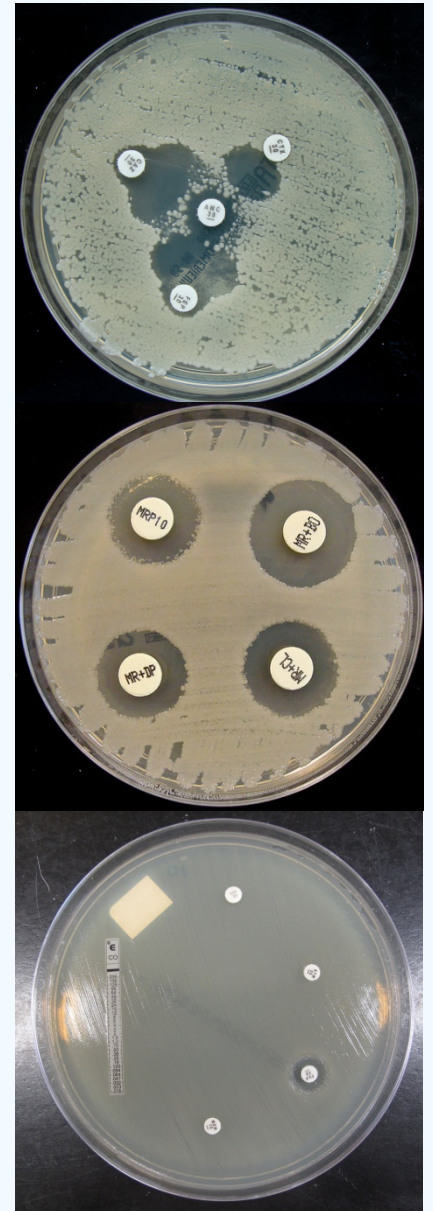
April 16, 2015

Disclosures

- **Advisory Boards/Consultant**
 - Optimer/Cubist
 - Merck
 - Paladin Labs
- **Speakers Bureau**
 - Merck
 - Pathogenica

Objectives

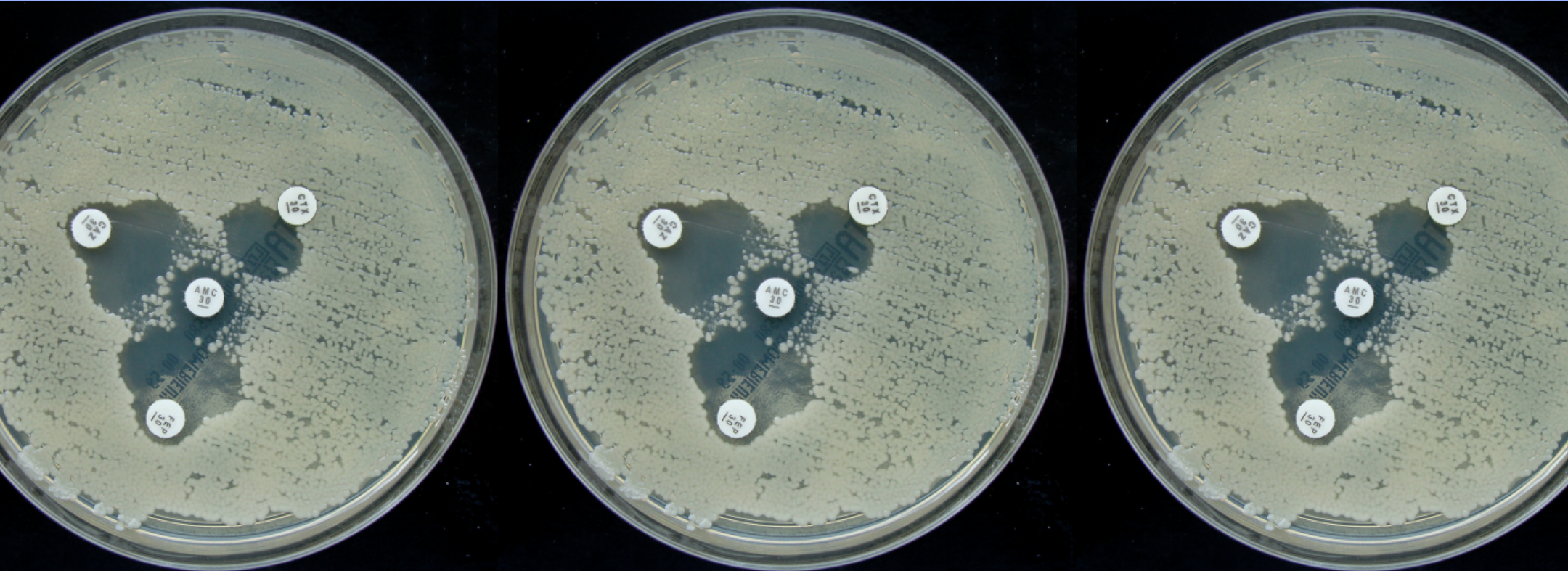
1. To appreciate the impact of the rise in **ESBL resistance** on empiric prophylaxis and treatment
2. To be aware of the challenges related to the management of serious **CPO infections** and detection of **CPO colonization**
3. To recognize the need for new antimicrobials active against **XDR *Pseudomonas aeruginosa***



AN ACCREDITED SYMPOSIUM
AT THE 2015 AMMI CANADA-CACMID
ANNUAL CONFERENCE

CHALLENGES AND OPPORTUNITIES IN PREVENTING & MANAGING SERIOUS BACTERIAL INFECTIONS

Case 1



Case 1

- 71M previously well with elevated PSA, allergic to penicillin “rash”
- May 1 – transrectal prostate biopsy
 - given ciprofloxacin 500 mg po x 1 as prophylaxis
- May 3 – fever, myalgia, chills
- May 4 – goes to ED
 - T 38.9, HR 118, p/e N, WBC 13, CXR N
 - Urine and blood cultures are ordered

Case 1 (cont'd)

- What would you give as empiric antimicrobial therapy to this patient with sepsis?
 - a) defer antibiotics until cultures back
 - b) ciprofloxacin
 - c) TMP-SMX
 - d) ceftriaxone
 - e) piperacillin-tazobactam
 - f) ertapenem
 - g) other

Case 1 (cont'd)

- What would you give as empiric antimicrobial therapy to this patient with sepsis?



- Empirically treated with ertapenem

Case 1 (cont'd)

- **BC *E. coli***
- **Urine *E. coli***
- **Ertapenem continued**

Case 1 (cont'd)

- **BC *E. coli***
 - S amox-clav, ceftriaxone, pip-tazo, ertapenem
 - R cefazolin, cipro, TMP-SMX, gentamcin, tobramycin
- **Urine *E. coli* ESBL Class A**
 - S ertapenem, gentamicin, nitrofurantoin
 - R cipro, TMP-SMX



- Ertapenem continued x 14d

Case 1 (cont'd)

- May 27 – 7 d after completing 14 d course of ertapenem, develops weakness, myalgias
- May 28 – fever, hematuria
- May 30 – goes to ED
 - urine and BC are ordered
 - abdominal ultrasound – normal
- May 31
 - transurethral ultrasound – small prostatic abscess 0.6cm

Case 1 (cont'd)

- What would you give as empiric antimicrobial therapy to this patient with sepsis?
 - a) defer antibiotics until cultures back
 - b) ciprofloxacin
 - c) TMP-SMX
 - d) ceftriaxone
 - e) piperacillin-tazobactam
 - f) ertapenem
 - g) other

Case 1 (cont'd)

- What would you give as empiric antimicrobial therapy to this patient with sepsis?



- Empirically treated with ertapenem

Case 1 (cont'd)

- BC no growth
- Urine *E. coli*
- Ertapenem continued

Case 1 (cont'd)

- **BC no growth**
- **Urine *E. coli***
 - S amox-clav, ceftriaxone, pip-tazo, ertapenem
 - R cefazolin, cipro, TMP-SMX, gentamicin, tobramycin



- **Ertapenem changed to cefixime x 6 weeks**

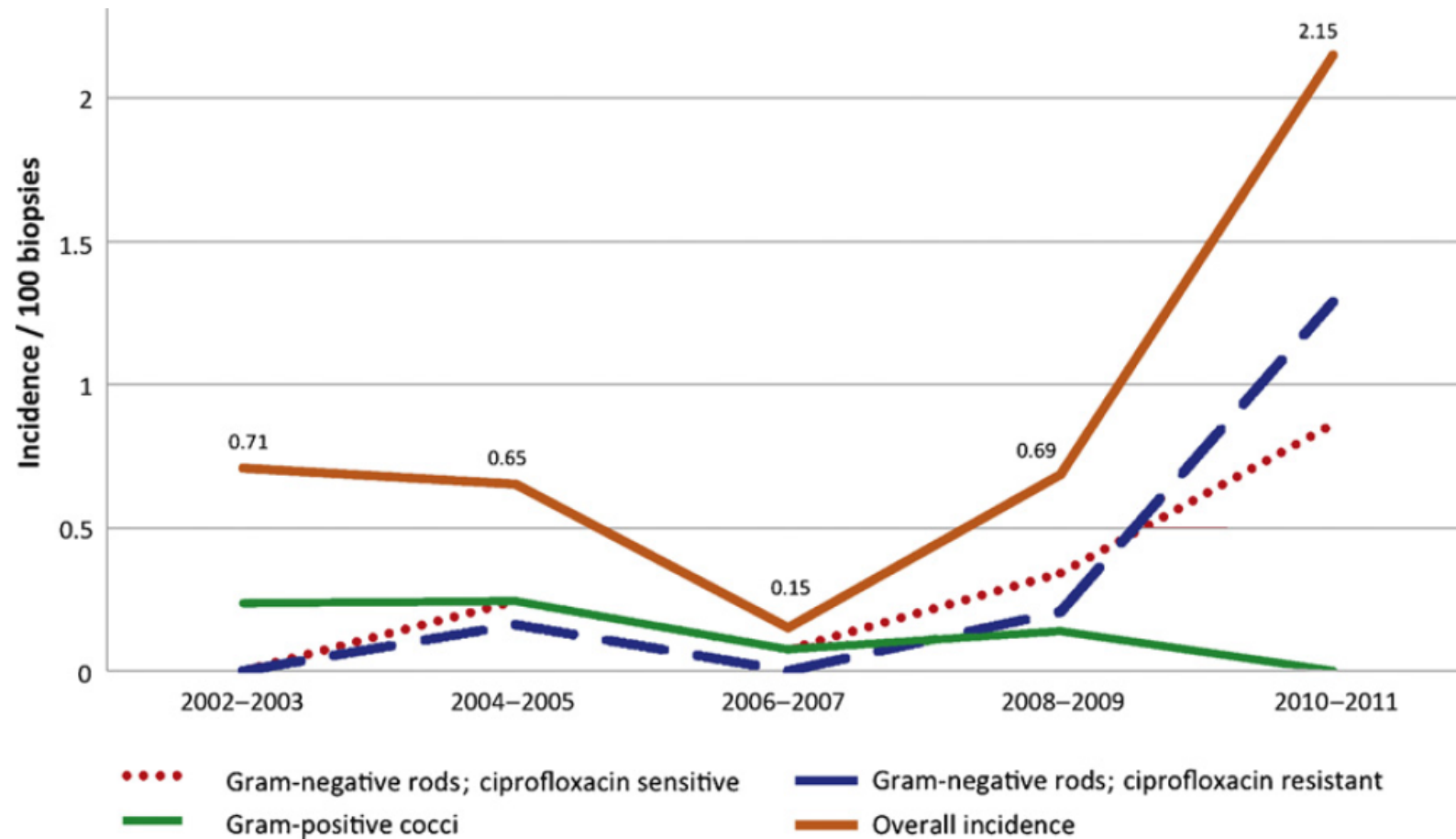
IDSA EIN Survey

Transrectal Prostate Biopsy-Associated Prophylaxis and Infectious Complications:

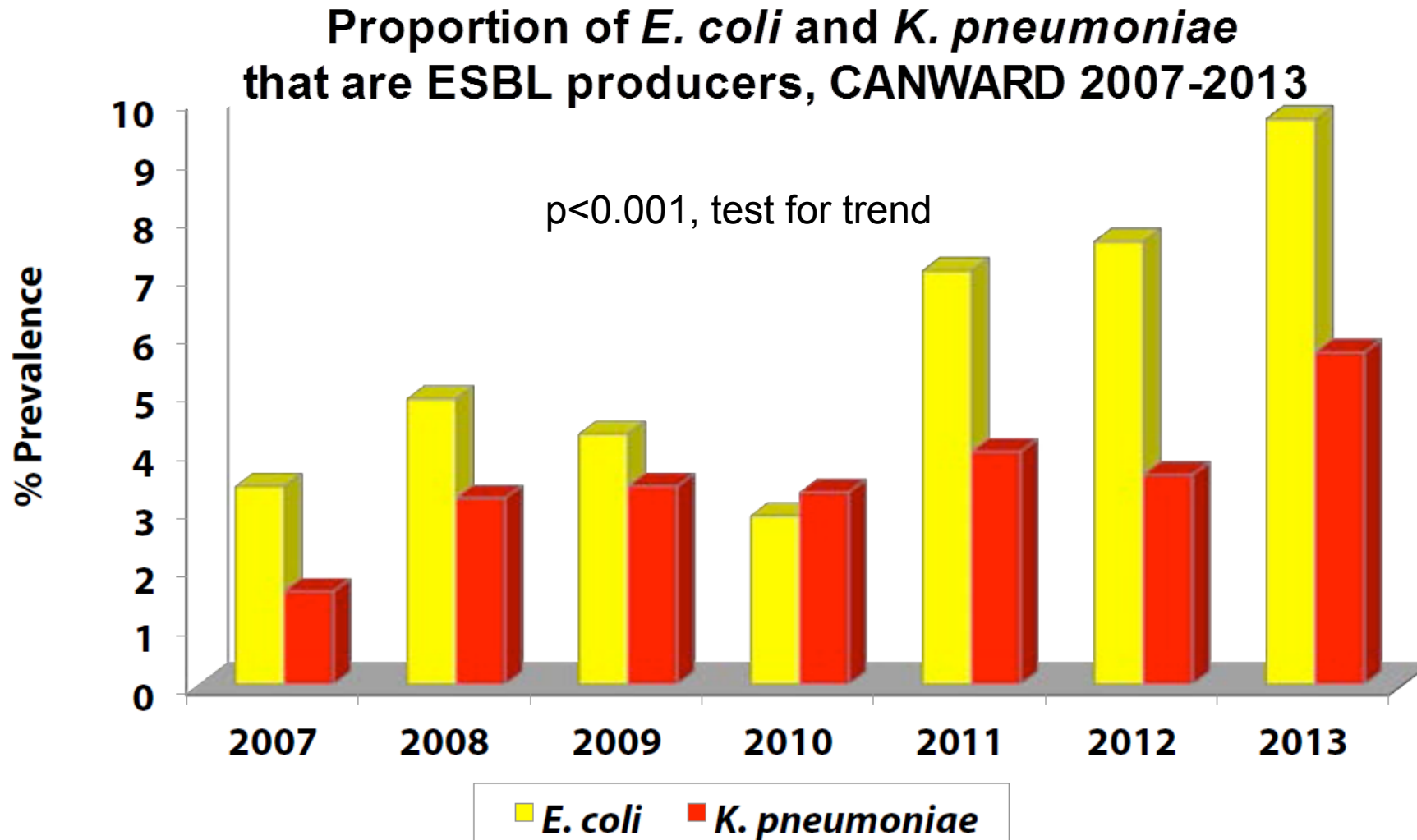
Type of Infection	Frequency, no. (% of 233 Respondents) ^a
Sepsis ^b , pyelonephritis, and/or febrile urinary tract infection (UTI), ±documented bacteremia	207 (89%)
Acute prostatitis	101 (43%)
Acute lower urinary tract infection (UTI, cystitis)	96 (41%)
Recurrent or chronic UTI/prostatitis	29 (12%)
Orchitis and/or epididymitis	20 (9%)
Death	6 (3%)
Other ^c	8 (3%)

Increasing Risk of Infectious Complications After Transrectal Ultrasound-Guided Prostate Biopsies: Time to Reassess Antimicrobial Prophylaxis?

Alex Carignan^{a,*}, Jean-François Roussy^a, Véronique Lapointe^a,
Louis Valiquette^a, Robert Sabbagh^b, Jacques Pépin^a



CANWARD – Canadian Data, All Sources



Risk Factors for ESBLs

- recent hospitalization
- residence in a long-term care facility
- international travel
- prior colonization with an ESBL
- household contact of an ESBL + person
- recent antibiotic use
- age $\geq$ 60 years
- diabetes mellitus

Ben-Ami et al. Clin Infect Dis. (2009) 49 (5): 682-690

Rodríguez-Baño et al. Arch Intern Med. 2008;168(17):1897-1902

Harris et al. EID 2007;13(8):online

Colodner R et al. Eur J Clin Microbiol Infect Dis. 2004 Mar;23(3):163-7

Tängdén et al. AAC 2010;54(9):3564-3568

Hilty M et al. Clin Infect Dis 2012 Oct 1; 55:967

CUA Guidelines on antibiotic prophylaxis for urologic procedures

Guideline recommendations

There is a high risk of adverse infection-related events in patients undergoing TRPB, and prophylactic antibiotics are recommended for these patients (Grade A, Level of Evidence IA). Most studies investigated the use of fluoroquinolones; single dose or short-courses of antibiotics appear to be as effective as the longer course regimens. There was insufficient evidence for efficacy of pre-procedural enemas to recommend their routine use. The choice of specific agent for prophylaxis should be based, in part, on the local epidemiology of drug resistance in potential uropathogens (Grade D, Level of Evidence IV). In patients at increased risk of harboring resistant organisms, perirectal culture swabs prior to TRPB should be considered.

CUA Guidelines on antibiotic prophylaxis for urologic procedures

Guideline recommendations

There is a high risk of adverse infection-related events in patients undergoing TRPB, and prophylactic antibiotics are recommended for these patients (Grade A, Level of Evidence IA). Most studies investigated the use of fluoroquinolones; single dose or short-courses of antibiotics appear to be as effective as the longer course regimens. There was insufficient evidence for efficacy of pre-procedural enemas to recommend their routine use. The choice of specific agent for prophylaxis should be based, in part, on the local epidemiology of drug resistance in potential uropathogens (Grade D, Level of Evidence IV). In patients at increased risk of harboring resistant organisms, perirectal culture swabs prior to TRPB should be considered.

Best Practice Policy Statement on

UROLOGIC SURGERY

ANTIMICROBIAL PROPHYLAXIS

(1/1/14): There are changes for recommended prophylaxis for transrectal prostate biopsy. Oral Trimethoprim-sulfamethoxazole is now allowed as a prophylactic agent, and when using IM/IV Aminoglycoside or Aztreonam as an alternative agent, Metronidazole or Clindamycin are no longer required.

Best Practice Policy Statement on

UROLOGIC SURGERY

ANTIMICROBIAL PROPHYLAXIS

(1/1/14): There are changes for recommended prophylaxis for transrectal prostate biopsy. Oral Trimethoprim-sulfamethoxazole is now allowed as a prophylactic agent, and when using IM/IV Aminoglycoside or Aztreonam as an alternative agent, Metronidazole or Clindamycin are no longer required.

Options for **Prophylaxis**

- Ciprofloxacin
- Review local epidemiology
- TMP-SMX*
- IM/IV aminoglycoside*
- (?Fosfomycin)
- Consider culture-directed prophylaxis

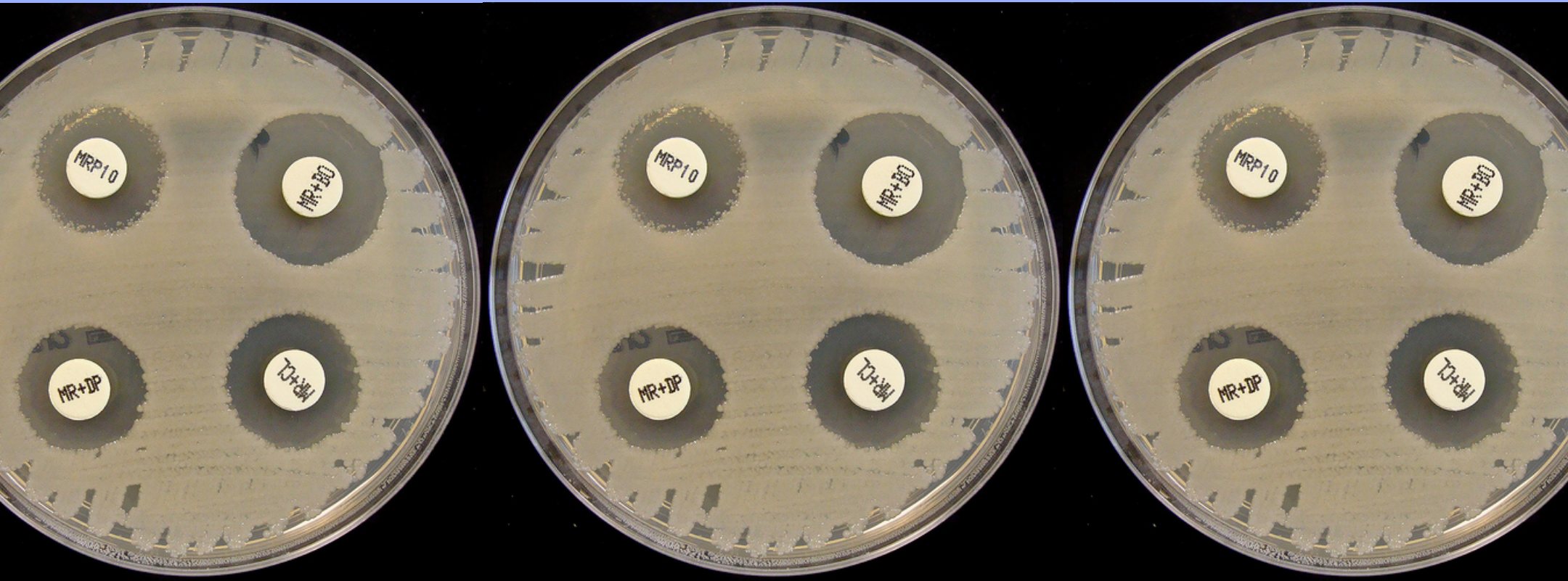
Options for **Empiric Treatment**

- Review local epidemiology
- Carbapenems
- Aminoglycosides
- (?Fosfomycin)

AN ACCREDITED SYMPOSIUM
AT THE 2015 AMMI CANADA-CACMID
ANNUAL CONFERENCE

CHALLENGES AND OPPORTUNITIES IN PREVENTING & MANAGING SERIOUS BACTERIAL INFECTIONS

Case 2



Case 2

- 70M with recent travel to India admitted for induction chemotherapy for newly diagnosed AML
- April 15 - c/b febrile neutropenia
- Blood cultures, urine cultures, CXR ordered

Case 2 (cont'd)

- What would you give as empiric antimicrobial therapy for febrile neutropenia?
 - a) cefazolin + aminoglycoside
 - c) ceftriaxone +/- aminoglycoside
 - d) cefazidime +/- aminoglycoside
 - e) piperacillin-tazobactam
 - f) meropenem
 - g) other

Case 2 (cont'd)

- What would you give as empiric antimicrobial therapy for febrile neutropenia?



Empirically treated with piperacillin-tazobactam
+ gentamicin

Case 2 (cont'd)

- **BC *K. pneumoniae***
- Piperacillin-tazobactam + gentamicin continued

Case 2 (cont'd)

- **BC *K. pneumoniae*, Class D carbapenemase**
 - Pan-resistant including carbapenems
 - *OXA-48 carbapenemase positive*
 - tigecycline MIC=3 mg/L (EUCAST S≤1 mg/L)
 - fosfomycin DD zone=12 mm (CLSI R≤12)
 - **colistin MIC=0.25 mg/L (EUCAST S≤ 2 mg/L)**



- Antimicrobials changed to colistin + tigecycline
April 17

Case 2 (cont'd)

- BCs remained persistently positive (April 15, April 18, April 20)
- Pt's course deteriorated with development of renal failure
- April 20 Pt transferred to ICU
 - Rectal screening swab positive for **OXA-48 and NDM positive *K. pneumoniae***
- April 22 care withdrawn and pt died

IDSA GUIDELINES

11. Modifications to initial empirical therapy may be considered for patients at risk for infection with the following antibiotic-resistant organisms, particularly if the patient's condition is unstable or if the patient has positive blood culture results suspicious for resistant bacteria (B-III). . . .

. Risk factors include previous infection or colonization with the organism and treatment in a hospital with high rates of endemicity.

- i. MRSA: Consider early addition of vancomycin, linezolid, or daptomycin (B-III).
- ii. VRE: Consider early addition of linezolid or daptomycin (B-III).
- iii. ESBLs: Consider early use of a carbapenem (B-III).
- iv. KPCs: Consider early use of polymyxin-colistin or tigecycline (C-III).|

IDSA GUIDELINES

11. Modifications to initial empirical therapy may be considered for patients at risk for infection with the following antibiotic-resistant organisms, particularly if the patient's condition is unstable or if the patient has positive blood culture results suspicious for resistant bacteria (B-III). . . .

..... Risk factors include previous infection or colonization with the organism and treatment in a hospital with high rates of endemicity.

- i. MRSA: Consider early addition of vancomycin, linezolid, or daptomycin (B-III).
- ii. VRE: Consider early addition of linezolid or daptomycin (B-III).
- iii. ESBLs: Consider early use of a carbapenem (B-III).
- iv. KPCs: Consider early use of polymyxin-colistin or tigecycline (C-III).|

Risk Factors for CPOs

- Previously colonized or infected with CPO
- Contact of a known case of CPO
- Receipt of care in a hospital on the U.S. eastern seaboard region (e.g., New York City) in the past 12 months
- Receipt of care in a hospital in Greece, Israel or the Indian subcontinent in the past 12 months
- Receipt of care in any hospital that has reported transmission of CPO

Screening for CPOs

- Based on risk factors
- Primary screening specimens:
 - stool or rectal swabs
- Also consider:
 - urine specimens
 - swabs from open wounds
- In critical care settings, also consider:
 - sputum or endotracheal tube specimens
 - swabs from exit sites

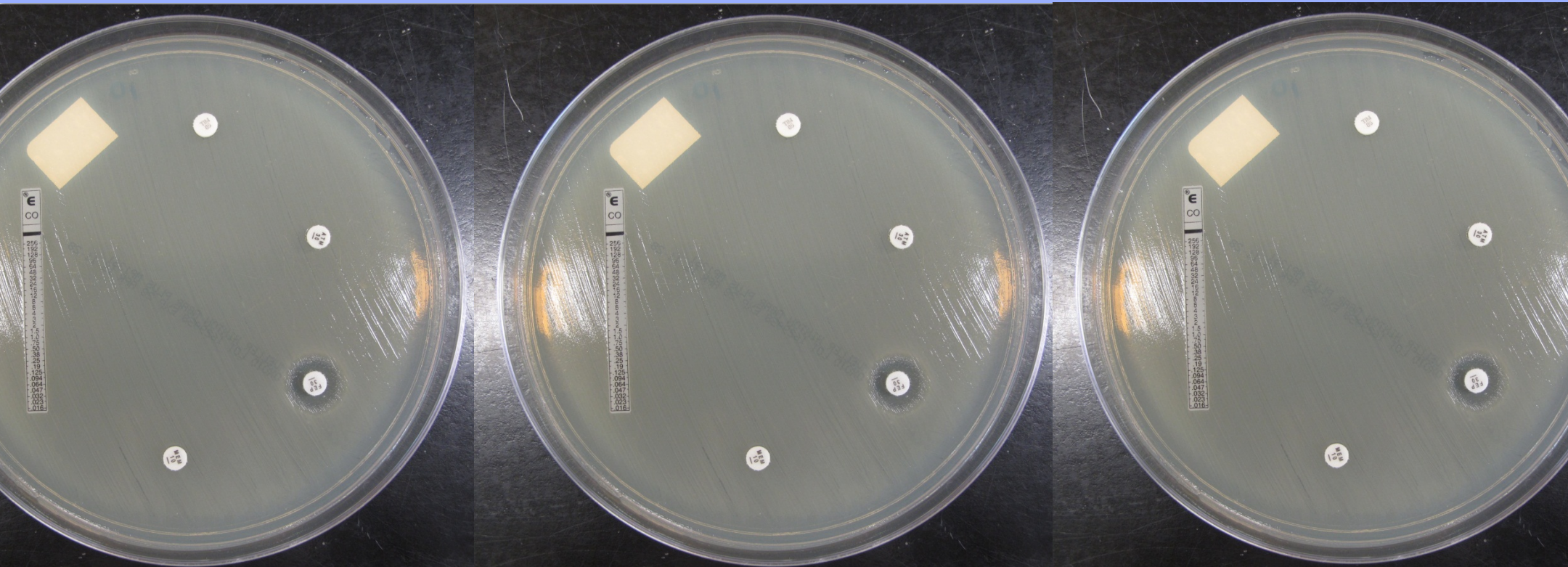
Optimal Screening Specimens?

- Long-term rehabilitation centre patient with past rectal swabs positive for **KPC + *Klebsiella pneumoniae***
- Follow-up routine and broth-enriched surveillance cultures:
 - Rectal swab negative
 - Sputum negative
 - G tube site negative
 - Trach site **positive**
- All broth enriched cultures positive by PCR

AN ACCREDITED SYMPOSIUM
AT THE 2015 AMMI CANADA-CACMID
ANNUAL CONFERENCE

CHALLENGES AND OPPORTUNITIES IN PREVENTING & MANAGING SERIOUS BACTERIAL INFECTIONS

Case 3



Case 3

- 63F with end stage cystic fibrosis colonized with **MDR *Pseudomonas aeruginosa*** awaiting lung transplant
- Treated intermittently with ceftazidime + tobramycin, ciprofloxacin + neb. colistin for exacerbations
- Pre-transplant given suppressive meropenem, ceftazidime, ciprofloxacin, and colistin to reduce the load of *P. aeruginosa*

Case 3 (cont'd)

- Mar 3 – undergoes double lung transplant without complications
- Mar 3 – pre-lung transplant recipient BAL sent for cultures

Source: Bronchial Alveolar Lavage

	P. aerug
Amikacin	R
Aztreonam	R
Cefepime	R
Ceftazidime	R
Ciprofloxacin	R
Colistin	R
Gentamicin	R
Meropenem	R
Piperacillin/Taz	R
Ticarcillin/Clav	R
Tobramycin	R

Case 3 (cont'd)

- Many transplant programs give prophylactic antibiotics x 2-3 weeks to suppress colonizing flora post-transplant
- Would you choose to give prophylactic antibiotics?
 - a) yes
 - b) no

Case 3 (cont'd)

- With what?
 - a) the same combination of antimicrobials as was used for pre-op suppression
 - b) ceftolozane-tazobactam through the Special Access Program
 - c) other
 - d) N/A – I would not give prophylaxis

Welcome to the Cubist Microbiology Voluntary Program (**MVP**)

coordinated by



Questions?

Please call International Health Management Associates (**IHMA, Inc.**)

☎ 1-800-738-3344

Case 3 (cont'd)

- Ceftolozane/tazobactam MIC=64 mg/L
- Ceftolozane/tazobactam DD zone=6 mm
 - FDA approved Cubist Pharmaceuticals product monograph suggests:
 - MIC $\geq$ 16 mg/L and DD $\leq$ 16 mm correlate with **resistance** for *P. aeruginosa*

Case 3 (cont'd)

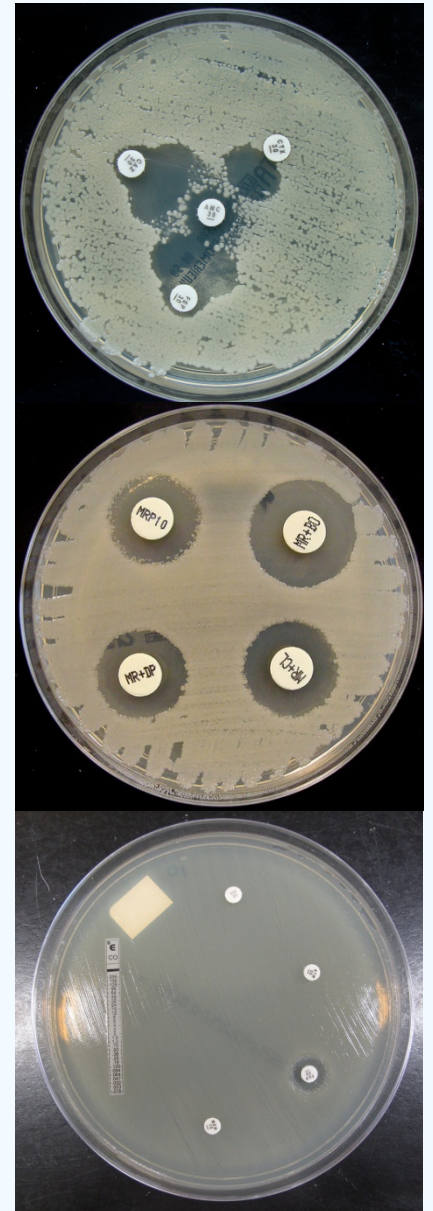
- To date, the patient has been well
- Surveillance BALs Mar 9 and Mar 25 clear (*P. aeruginosa* NOT detected)

Gram-Negative Pipeline

Product	Class (Mechanism of Action)	Novel Mechanism of Action?	Status
Ceftolozane/taxobactam (CXA-201; CXA-101/tazobactam)	Antipseudomonal cephalosporin/ BLI combination (cell wall synthesis inhibitor)	No	Phase 3 (cUTI, cIAI)
Ceftazidime-avibactam (ceftazidime/NXL104)	Antipseudomonal cephalosporin/ BLI combination (cell wall synthesis inhibitor)	No	Phase 3 (cIAI)
Ceftaroline-avibactam (CPT-avibactam; ceftaroline/NXL104)	Anti-MRSA cephalosporin/ BLI combination (cell wall synthesis inhibitor)	No	Phase 2 (cUTI, cIAI)
Imipenem/MK-7655	Carbapenem/BLI combination (cell wall synthesis inhibitor)	No	Phase 2 (cUTI, cIAI)
Plazomicin (ACHN-490)	Aminoglycoside (protein synthesis inhibitor)	No	Phase 2 (cUTI)
Eravacycline (TP-434)	Fluorocycline (protein synthesis inhibitor targeting the ribosome)	No	Phase 2 (cIAI)
Brilacidin (PMX-30063)	Peptide defense protein mimetic (cell membrane disruption)	Yes?	Phase 2 (ABSSSI)

Objectives

1. To appreciate the impact of the rise in **ESBL resistance** on empiric prophylaxis and treatment
2. To be aware of the challenges related to the management of serious **CPO infections** and detection of **CPO colonization**
3. To recognize the need for new antimicrobials active against **XDR *Pseudomonas aeruginosa***



CHALLENGES AND OPPORTUNITIES IN PREVENTING & MANAGING SERIOUS BACTERIAL INFECTIONS

Questions?

