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THE CRISIS IN ANTIBIOTIC RESISTANCE

Science 257: 1064, 1992.

Dr. Harold C. Neu

The synthesis of large numbers of antibiotics over the past three decades has caused complacency about the threat of bacterial resistance. Bacteria have become resistant to antimicrobial agents as a result of chromosomal changes or the exchange of genetic material via plasmids and transposons. Streptococcus pneumoniae, Streptococcus pyogenes, and staphylococci, organisms that cause respiratory and cutaneous infections, and members of the Enterobacteriaceae and Pseudomonas families, organisms that cause diarrhea, urinary infection, and sepsis, are now resistant to virtually all of the older antibiotics. The extensive use of antibiotics in the community and hospitals has fueled this crisis. Mechanisms such as antibiotic control programs, better hygiene, and synthesis of agents with improved antimicrobial activity need to be adopted in order to limit bacterial resistance.

BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates ... A Public Health Crisis Brews





July 2004



A 'slow catastrophe' unfolds as the golden age of antibiotics comes to an end



Research scientist Rosslyn Mayback was part of the team that identified a strain of E. coli bacteria with a gene that could spread antibiotic resistance. (Walter Reed Army Institute of Research)

By Melissa Healy

JULY 11, 2016, 10:05 AM | REPORTING FROM BETHESDA, MD.



\$	The Joint Commission Prepublicatio	n
	·Issued June 22, 2016· Requirement	S
NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT	The Joint Commission has approved the following revisions for prepublication. While revise published in the semiannual updates to the print manuals (as well as in the online E-dition® organizations and paid subscribers can also view them in the monthly periodical <i>The Joint Perspectives</i> [®] . To begin your subscription, call 877-223-6866 or visit http://www.jcrinc.com.	d requirement), accredited Commission
DACIERIA	Joint Commission Regulirement New Antimicrobial Stewardship Stan	dard
	APPLICABLE TO HOSPITALS AND CRITICAL ACCESS HOSPITALS Note: An example of an education for patients and families includes th Control and Prevention's Get Smar or Bacteria—What's got you sick? Medication Management (MM)	al tool that can be le Centers for Dis t document, "Viru at <u>http://www.cdc.</u> tsmart-chart.pdf.
MARCH 2015	4. The [critical access] hospital has an Standard MM.09.01.01 The [critical access] hospital has an antimicrobial stewardship program based on current scientific literature. Elements of Performance for MM.09.01.01 1. Leaders establish antimicrobial stewardship as an organi-	 The [critical access] hospital has an antimicrobial ste ardship multidisciplinary team that includes the follow members, when available in the setting: Infectious disease physician Infection preventionist(s) Pharmacist(s) Prarmacist(s)
	zational priority. (See also LD.01.03.01, EP 5) Note: Examples of leadership commitment to an antimicrobial stewardship program are as follows: Accountability documents Buidete plans	f are acceptable a irdship multidisci- able as members
		nacipiniary team.
Proposed CMS rule on inf	ection control and inappropriate antibiotic use	

advance healthcare quality and equity in our nation's hospitals. In a proposed rule open for public comment, CMS recommends strengthening Conditions of Participation (CoPs) related to infection prevention and antibiotic prescribing in U.S. hospitals and critical-access hospitals (CAHs).

The rule includes provisions for preventing healthcare-associated infections, stopping spread of antibiotic-resistant germs and reducing inappropriate antibiotic prescribing. Hospitals and CAHs would be required to have and demonstrate adherence to facility-wide infection prevention and control programs, as well as antibiotic stewardship programs.

The proposed rule builds on the Department of Health and Human Services (HHS) quality initiatives, including the <u>National Quality</u> <u>Strategy</u>, the Centers for Disease Control's <u>Antibiotic Resistance Solutions Initiative</u> and the <u>Partnership for Patients</u>.

(CMS

National Antibiotic Resistance Trends 2016

Multidrug-resistant organisms -- MDROs

ESCAPE pathogens

- Enterococcus (VRE)
- **Staphylococcus aureus (MRSA and VISA)**
- Carbapenem-resistant Enterobacteriacea (CRE KPC, NDM-1, etc)
- Acinetobacter (MDR strains)
- **P**seudomonas (Fluoroquinolone resistant)
- Extended spectrum beta-lactamase producing GNR (ESBL positive E. coli, Klebsiella, Enterobacter)
- plus Clostridium difficile (**C diff**)

Impact of Antibiotic Resistance

What happens if the patient gets infected with an MDRO?

Organism	Increased risk of <u>death</u> (OR)	Attributable LOS (days)	Attributable cost
MRSA bacteremia	1.9	2.2	\$6,916
MRSA surgical infection	3.4	2.6	\$13,901
VRE infection	2.1	6.2	\$12,766
Resistant Pseudomonas infection	3.0	5.7	\$11,981
Resistant <i>Enterobacter</i> infection	5.0	9	\$29,379

Original Investigation

Prevalence of Antimicrobial Use in US Acute Care Hospitals, May-September 2011

Shelley S. Magill, MD, PhD; Jonathan R. Edwards, MStat; Zintars G. Beldavs, MS; Ghinwa Dumyati, MD; Sarah J. Janelle, MPH; Marion A. Kainer, MBBS, MPH; Ruth Lynfield, MD; Joelle Nadle, MPH; Melinda M. Neuhauser, PharmD, MPH; Susan M. Ray, MD; Katherine Richards, MPH; Richard Rodriguez, MPH; Deborah L. Thompson, MD, MSPH; Scott K. Fridkin, MD; for the Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team

IMPORTANCE Inappropriate antimicrobial drug use is associated with adverse events in hospitalized patients and contributes to the emergence and spread of resistant pathogens. Targeting effective interventions to improve antimicrobial use in the acute care setting requires understanding hospital prescribing practices.

RESULTS Of 11 282 patients in 183 hospitals, 5635 (49.9%) 95% CI, 49.0%-50.9%) were administered at least 1 antimicrobial drug; 77.5% (95% CI, 76.6%-78.3%) of antimicrobial drugs were used to treat infections, most commonly involving the lower respiratory tract, urinary tract, or skin and soft tissues, whereas 12.2% (95% CI, 11.5%-12.8%) were given for surgical and 5.9% (95% CI, 5.5%-6.4%) for medical prophylaxis. Of 7641 drugs to treat infections, the most common were parenteral vancomycin (1103, 14.4%; 95% CI, 13.7%-15.1%), ceftriaxone (825, 10.8%; 95% CI, 10.1%-11.5%), piperacillin-tazobactam (788, 10.3%; 95% CI, 96%-11.0%), and levofloxacin (694, 9.1%; 95% CI, 8.5%-9.7%). Most drugs administered to treat infections were given for community onset infections (69.0%; 95% CI, 68.0%-70.1%) and to patients outside critical care units (81.6%; 95% CI, 80.4%-82.7%). The 4 most common treatment antimicrobial drugs overall were also the most common drugs used for both community-onset and health care facility-onset infections and for infections in patients in critical care and noncritical care locations.

Fluoroquinolone resistance in Pseudomonas (ciprofloxacin)



Fluoroquinolone resistance in Pseudomonas (ciprofloxacin)



Are our work-horse agents eroding in value due to emerging resistance?





"Community-acquired" MRSA

- 1988: first appearance of sporadic cases
- 1993-1995: University of Chicago Children's Hospital -- 25-fold increase in CA-MRSA
 - Different sensitivity pattern noted in some
 - Cellulitis and abscesses
- 1999: Minnesota and North Dakota – 4 pediatric deaths
- 2002–2003: clusters of cases in athletes, IVDU's, gay men
- 2004–2007 prevalent in many communities



Clusters of CA-MRSA in athletes risk factors

- Football, rugby, wrestling
- Towel and soap sharing
- Turf burns, other sites of abrasion
- Body shaving
- Suboptimal hygeine in players, trainers
- BMI (e.g. linemen)
- Prior antibiotic use
- Poor maintenance of equipment (e.g. whirlpools)
- Relatively little nasal carriage



A nasty, drug-resistant staph infection—the kind usually seen in hospitals—is racing across the U.S.

By CHRISTINE GORMAN

EWAUN SMITH, A 9-YEAR-OLD BOY FROM Chicago, is lucky to be alive. A scrape on his left knee that he picked up riding his bike last October turned into a runaway infection that spread in a matter of days through the rest of his body, leaving his lungs riddled with holes. Iewaun managed to survive, but what worries doctors most about his near-death experience is that it's not an isolated case. The bacteria that infected his knee has become resistant to the most common antibiotics and is on the march across the U.S. It has spread rapidly through parts of California, Texas, Illinois and Alaska and is beginning to show up in Pennsylvania and New York.

"This bug has gone from 0 to 60, not in five seconds but in about five years," says Elizabeth Bancroft, a medical epidemiologist at the Los Angeles County Department of Health Services. "It spreads by contact, so if it gets into any community that's fairly close-knit, that's all it needs to be passed."

This is not bird flu or SARS or even the "flesh-eating bacteria" of tabloid fame. But it

is every bit as dangerous, even if it goes by an uncommonly ungainly name: communityacquired methicillin-resistant *Staphylococcus aureus* (MRSA).

Never heard of it? Neither have most doctors. But major new health threats don't usually announce themselves with press releases. A quarter of a century ago, the world learned about the AIDS epidemic because a health bureaucrat noticed an uptick in prescriptions for treatment of a rare pneumonia. In 1912-more than a half-century before the Surgeon General's report-a New York physician chronicled "a decided increase" in lung cancer, which was considered rare at the time, and suggested that eigarettes might be the cause.

Which helps explain why infectiousdisease specialists in the U.S. are so alarmed by the new killer bug. "We're out here waving our arms, trying to get everyone's attention," says Dr. Robert Daum, director of the University of Chicago's pediatric infectiousdisease program, who was one of the first to call attention to the rapid spread of MRSA, back in 1998. "People talk about bird flu, but this is here now."

Hospital workers know all about drug-

TIME, JUNE 26, 2006

resistant bacteria. Several strains have been making the rounds of the biggest hospitals for the past 15 years or so, often posing a greater risk for patients than the condition they were admitted for. But until the late 1990s, epidemiologists assumed that the problem was restricted to large hospitals and nursing homes.

The MRSA strains turning up in the community at large are related to but different from the ones found in medical institutions. The hospital variety usually requires intervention with powerful intravenous antibiotics and is pretty hard to catch. By contrast, the new strains of MRSA respond to a broader range of antibiotics but spread much more easily among otherwise healthy folks. The bugs can be picked up on playgrounds, in gyms and in meeting rooms, carried on anything from a shared towel to a poorly laundered necktie.

One of the difficulties in tracking MRSA is that doctors rarely check for it. The standard test usually takes a couple of days, and hardly any doctors do it anymore because everyone assumes that most skin infections

WHAT

YOU

takes a couple of days, and ors do it anymore because is that most skin infections

Try to avoid cuts and scrapes as much as possible. Wear gloves to protect your hands while gardening, doing repair work or tinkering in the garago.

Thoroughly clean even Wi superficial wounds with soap and water. Do cli not use hydrogen cli peroxide. Cover wounds S with a clean, dry bandage. m

lesion." Bancroft says.

respond to the usual antibiotics. "HMOS aren't

going to be paying for you to do a culture on

what they consider to be a [common] skin

the problem. The germs are part of the

usual microscopic landscape of your outer

and inner skin, including the mucus lin-

ings of the nose. Most of those bacteria

The ubiquity of staph bacteria adds to

Wash your hands regularly and insist that any clinician examining you or a loved one do so too. Soap disrupts many parts of the germ at once, making resistance difficult.

don't cause illness, and in fact their presence is a good thing, since they can crowd out more dangerous pathogens. But every once in a while, the good guys take a beating, and one of the bad guys, like MRSA, takes hold. colonizing the skin.

ALL BETTER NOW

Jewaun was riding a bike last fall near

his Chicago home when he got the

scrape that caused all the trouble

IN THE HOSPITAL

tted, the

By the time Jewaun

Even when that happens, it doesn't necessarily signal an emergency. The skin, after all, is an effective barrier against many kinds

> Don't share towels or other linens. Make sure that all laundry is properly washed at 120°F or higher (unless a low-temperature detergent is used) and dried at 180°F.

of threats. But anytime you get a break in that barrier—even a tiny cut—there's a chance some bacteria will get inside and infect the wound. What makes MRAA germs particularly dangerous is that they excrete a potent toxin that attacks the skin, causing an abscess that's often mistaken for a spider bite. Normally, the body can wall that area off. But if the infection spreads, treatment with antibiotics may be called for.

And that's the problem. Doctors have grown used to prescribing antibiotics like vacailin or cephalexin in that situation. It's not clear if that long-standing habit helpod the bugs grow resistant in the first place. But what is abundantly clear is that those standard treatments are no longer effective.

There's another factor that makes the community-based MRAs so dangerous, one that has been revealed only recently by genetic analysis. In addition to their normal chromosomal NNA, staph and other bacteria like to mix and match genetic information by exchanging short strips of DNA called cassettes. Some of those cassettes carry genetic instructions to do two things at once: confer antibiotic resistance and make the host even more susceptible to infection. "MRSA is where resistance and virulence converge," says Daum.

What epidemiologists still can't explain, however, is how that particular bug manages to get around to so many cities and towns yet has left others relatively unscathed—at least so far. Cases of the new MRSA strain have only just started cropping up in New York City, for example. "We've been waiting for this to happen," says Dr. Betsy Herold of Mt. Sinai. "Now, we're in a unique position to watch it unfold and to find out why it's happening."

Meanwhile, there are things you can do to protect yourself (see box). To prevent more bugs from developing resistance, it's important to remember that not all skin infections need antibiotic treatment, even MRSA. "A garden-variety infection is still a garden-variety infection," says Dr. Philip Graham at New York-Presbyterian's Children's Hospital in New York City. "If your cuts and scrapes are acting like they always do, don't worry."

If, however, you or a loved one is running a high fever, has a lot of redness or shows signs that an abscess is forming, you need to get to a doctor right away. "It never hurts for a patient to say something like, Could this be an MRSA infection?" says Dr. Jack Edwards, chief of infectious disease at Harbor-UCLA Medical Center in Los Angeles. It could make all the difference in the world. —Reported by Wendy Cole/Chicage and Dan CrayLos Angeles



52

53

How should we control MRSA?

- Hand sanitation!
- Isolation of proven / suspect MRSA
- Pre-emptive screening for MRSA
 - Nursing home admissions
 - Transfer from other acute care institutions
 - Admissions from WCC's
- Routine barrier precautions (CCU)
- Antibiotic controls

Emergence of MRSA over 20 years Stamford Hospital Microbiology Lab data

(community and hospital strains)



Stamford MRSA Prevalence is Declining



Stamford Hospital Screening Program for MRSA

- Populations at high risk for screening protocol
 - Nursing home patients
 - Acute care transfers
 - WCC patients
 - ICU admissions
 - SCU admissions
 - Hemodialysis patients
- Preop
 - TJR, Spines, Cardiac
- Methodology
 - PCR (GeneXpert)



ain.

20 Cycles

Hand hygiene





Hand Hygiene Stamford Hospital



Stamford Hospital Screening Program for MRSA

- Populations at high risk for screening protocol
 - Nursing home patients
 - Acute care transfers
 - WCC patients
 - ICU admissions
 - SCU admissions
 - Hemodialysis patients
- Preop
 - TJR, Spines, Cardiac
- Methodology
 - PCR (GeneXpert)



ain.

20 Cycles

CONTACT PRECAUTIONS

<u>VISITORS</u> -- Report to Nurses' Station for instructions before entering room

HANDS – Wash BEFORE and AFTER patient contact

GOWNS and GLOVES – must be worn by all entering the room

UPON LEAVING the room, remove gloves and gown. Wash your hands after leaving the room <u>VISITANTES --</u> Reportense a la Estación de las Enfermeras para recibir instrucciones antes de entrar

MANOS – Hay que lavarse las manos ANTES y DESPUES de contacto con el paciente

BATAS y GUANTES – se deben poner al entrar en la habitación

ANTES DE SALIR de la habitación, quítese los guantes y las batas. Lavese las manos después de salir

Hospital-acquired MRSA Infections Stamford Hospital Overall



Extended Spectrum Beta-lactamases (ESBL)

- Confer resistance to all cephalosporins and penicillins
 - Gram negative bacilli (E coli, Klebsiella, etc)
 - 700 different profiles
- Prevalence of ESBLs is unappreciated
 - Laboratories fail to detect ESBL in 25% of instances depending on the type of enzyme present (Tenover, CDC, 2009)
- Chronic intestinal carriage
- High rate of treatment failure
- Inpatient and community prevalence

ESBL-positive isolates at Stamford



Outpatient urine culture

Procedure	Result	Verified
URINE CULTURE Final Source: URINE CLE SEE M29565 FRO	AN CATCH MIDSTREAM M 07/23/15.	Verified 07/27/15-0835
This organism (**ESBL**) act unreliable. Co	exhibits extendend s ivity. In vitro susc nsider Infectious D	pectrum beta lactamase eptibility testing may be seases consultation.
Organism Colony Count:	ESCHEF >100,0	.ICHIA COLI **ESBL** 000 COL./CC.
	E.COLI ** MIC RX	
TRIMET/SULFA AMPICILLIN CEFAZOLIN CIPROFLOXACIN GENTAMICIN NITROFURANTOIN TETRACYCLINE	>2/38 R >16 R* >16 R* >2 R >8 R <=32 S >8 R	

Emergence of Carbapenem-resistant Enterobacteriaceae (CRE)

- Carbapenems have remained effective against most of the *Enterobacteriaceae*, including ESBL producing strains.
- CRE (KPC most common)
 - Appeared 1996; 2690 cases in NYS, 50% hospital acquired in 2014
 - Klebsiella, E. coli, Enterobacter and others
 - Confer resistance to all β-lactams including extended-spectrum cephalosporins and carbapenems
 - Usually co-resistant to multiple other agents
 - Multiple enzyme profiles (KPC, NDM, VIM, OXA, others)
 - High mortality due to co-morbidities and lack of effective treatment
 - **Plasmid mediated**

Patients with KPC-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of January 2017, by state



File Help

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Procedure	Result			
FLUID CULTURE Preliminary	(continued)	Verified (8/04/16-1228	
Method: MAN Perf	Site: <i>TSH</i>			
3. KLEBSIELLA PNEUMONIAE	**KPC** MSCAN GRAM N	EG MIC45 Ent: 4	08/04-1228 GOCAM	1F0
<u>Target</u> F	loute Dose	<u>RX AB Cost</u>	<u>M.I.C. IQ</u>	<u>NP</u>
TRIMET/SULFA		R	>2/38	
AMOXAC/CLAVUL		R -	>16/8	NP
AMPICILLIN		R	>16	
AMP/SUL		R	>16/8	
AZIREUNAM GERNZOLIN		R	>16	NP
GEFOTININE		R	> 10	ND
GEFONITIN		R	> 32	NP
CEFUALLIN GEETAZIDIME		к D	> 10	NP
CEFTRIATONE		R	>16	NP
CEFERIME		r D	> 16	NP
CEFEDOXIME		r D	>16	NF
CIPROFICYACIN		P	>10	
FRTAPFNEM		R	>1	NP
GENTAMICIN		T	8	141
CEFOTAZCLAV		r R	>4	NP
CEFTAZ/CLAV		R	>2	NP
CFTE SCREEN		ESBL	>1	NP
IMIPENEM		R	>8	NP
LEVOFLOXACIN		R	> 4	NP
MEROPENEM		R	>8	NP
NITROFURANTOIN		R	>64	NP
PIPERACILLIN		R	>64	
TETRACYCLINE		R	>8	
TICAR/K CLAV		R	>64	NP
TIGECYCLINE		R	> 4	
TOBRAMYCIN		R	>8	NP
AMIKACIN		I	32	NP
PIP/TAZO		R	>64	
FLUID CULTURE Preliminary	(changed)	Verified (08/02/16-1506	
Method: MAN Perf	Site: TSH			
Ent: 08/02-1506 GOCAMPO,	Ver: 08/02-1506 GOCAM	'FO		

<u>CDC Action Plan</u> for CRE Control

- Surveillance
- HCW education
- Laboratory detection
 lab education
- Mandatory Reporting
- Strict isolation / contact tracing / screening
- Antibiotic stewardship
- Limited options for treatment
 - colistin, ceftazidime + avibactam (Avycaz), fosfomyçin





Highly resistant MCR-1 'superbug' found in US for first time

Filed Under: MCR-1; Antimicrobial Resistance Jim Wappes | Editorial Director | CIDRAP News | May 26, 2016

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Bacteria carrying the very worrisome MCR-1 resistance gene—which makes the last-line antibiotic colistin useless against them—have been found in human and animal samples for the first time in the United States, according to a report today in *Antimicrobial Agents and Chemotherapy* and a statement by federal health officials.

A Chinese team first described the MCR-1 gene last November, after finding it in pigs, pork, and humans. Since then scientists in several countries have found the gene, sometimes alongside other resistance genes, after examining their sample collections. The gene can be transferred to other organisms, compounding the concern.

Today's findings involve a 49-year-old woman whose urine contained *Escherichia coli* harboring the MCR-1 gene and an *E coli* isolate from a pig intestine that also contained the colistin-resistance gene.

MCR-1 in urine sample

The woman sought care at a Pennsylvania clinic for symptoms of a urinary tract infection 1 month ago



Email

FDA, Michael J. Ermarth / Flickr cc

Infection Prevention Escalation

MRSA, VRE, ESBL

Basic

Infection Control

- Hand Hygiene
- Contact precautions

Intensive

Infection Control

Hand Hygiene

CRE

- Contact precautions
- Cohort patients and staff
- Screening cultures of patient contacts
- Save cultures
- Report to DPH

Antibiotic Resistance is frequently associated with Hospital-acquired Infections



Hospital-acquired infections (HAI)

- Often due to drug-resistant pathogens
- High patient mortality (up to 20% of HAI) and morbidity
- High costs
 - Attributable direct care (\$30-45 billion)
 - Indirect costs (LOS, lost business, isolation)
 - Liability costs
- Infection Prevention = Expense Prevention
- Preventable ("zero infections")
- Public interest
 - Federal initiatives and reimbursement penalties
 - Mandatory reporting of infections
 - National reporting requirements (CMS)
 - Public perception of poor quality of care

Hospital-acquired infection = Medical Mistake



What is antibiotic stewardship?

Antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobial agents, improves patient outcomes, reduces microbial resistance, reduces cost, and decreases the spread of infections caused by multidrug-resistant organisms.

Stamford Hospital

Antibiotic Stewardship Program

- Formulary restrictions
- Prescribing limitations / ID approval required by drug / dose
- Preprinted orders / pathways (e.g. CAP, febrile neutropenia)
- Antibiotic prophylaxis standards
- IV to PO program (pharmacy based)
- Renal dosing (pharmacy based)
- Antibiogram review
- Restricted susceptibility reporting (cascade system thru micro lab)
- Daily Blood culture monitoring for appropriateness of Rx
- Drug:Bug Mismatch detection in micro lab
- De-escalation program in ICU "antibiotic time-out"
- Education for correct duration of rx
- Monitoring MDRO for determining formulary changes and guideline changes
- Spot Drug Use Evaluations (DUEs)
- Escalation of rapid molecular diagnostics
- Increased emphasis on using biomarkers (e.g. procalcitonin) ³⁹

Vancomycin Usage Reduction Program



<u>The most dramatic complication of excess</u> <u>antibiotic use is Clostridium difficile infection</u>

- ≥95% CDI pts have received antibiotic therapy
 - Fluoroquinolones > cephalosporins > penicillins
 - Role of PPIs
- Environmental contamination by *C. difficile* is common (spores are difficult to eradicate)
- Personnel carry *C. difficile* on their hands
- Asymptomatic patients carry C. difficile
 - 3-6% community carriage
- Patients regularly acquire *C. difficile* in health care facilities



Difficulties in controlling the spread of <u>C. difficile</u>

- Difficulty preventing infection in high risk settings "incident density" pressure – carriers + ill
- High community prevalence
- Antibiotic use and overuse (stewardship program)
- Prolonged fecal and skin carriage (isolation for duration of hospitalization)
- Frequent recurrence (longer treatment courses, fidaxomycin, fecal transplant)
- Persistence of spores in the environment (bleach or peracetic acid for disinfection; UV light disinfection)

Stamford Hospital-acquired C difficile



Superbugs in the Headlines

- *Klebsiella pneumoniae* carbapenemase (KPC)
- New Delhi Metallo-beta-lactamase-1 (NDM-1)
- Oxacillinase-48 (OXA-48 and OXA-48-like)
- Verona Integron-Encoded Metallo-betalactamase (VIM)
- Novel Carbapenemases
- Plasmid-mediated Colistin Resistance (mcr -1, mcr-2)

