WHAT'S HOT IN CLINICAL INFECTIOUS DISEASE

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Conflicts of interest- None

Clinical Update: Infectious Diseases

- Recent victories
- Community-acquired pneumonia
- Short course antibiotics
- ID specialists as surgeons
- *F. necrophorum* pharyngitis
- VZV role in Giant Cell Arteritis (GCA)
- *Clostridium difficile* infection
- Stewardship

RECENT VICTORIES

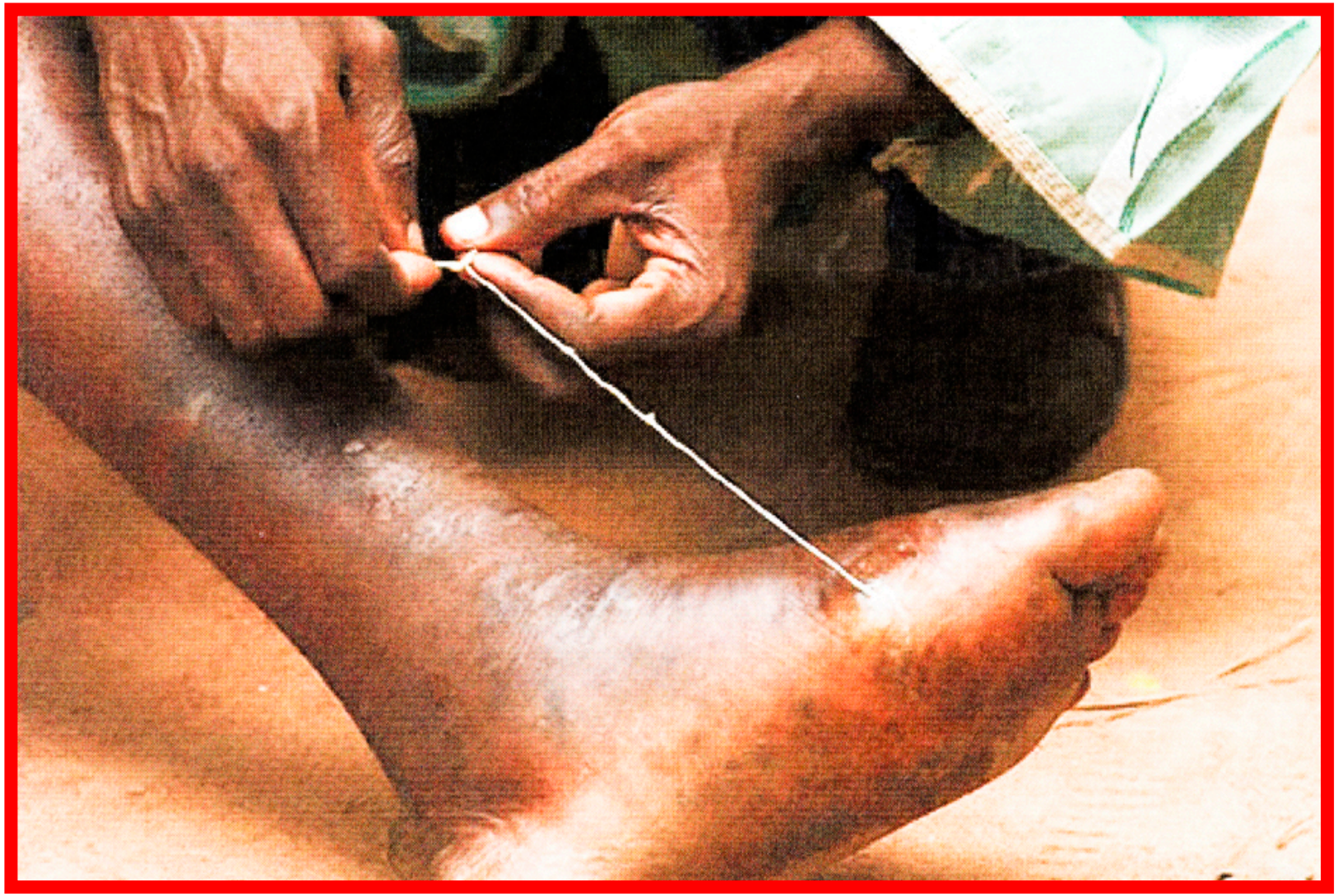
- **Disease eradication: Smallpox (done)**
  #2: Guinea worm vs polio
- **Whitehouse call to action on Antibiotic Stewardship**
- **Antibiotic pipeline: Surging**
- **Hepatitis C & HIV progress report**

President Jimmy Carter,
August 21, 2015:

“My greatest hope is that the last guinea worm will die before I do”

PATHOGEN ERADICATION

Year	Countries	Cases
POLIO		
1988	125	600,000
7/30/15	10	46
DRUNCULIASIS		
2006	20	3,500,000
9/20/15	4	11(-99.97%)



Guinea Worm 2006: 3,500,000 cases

2015: 15 cases to 10/1/2015

The Next Epidemic- Lessons from Ebola

Bill Gates NEJM 3/19/15

Issue: Prepare for epidemic that could kill > 10 mil

Examples: Flu-1918; HIV, SARS

Precedent: War – NATO

Last example of preparing for pandemic: Dark Winter- Smallpox (Inglesby T CID; 2002 34:972)

Recommended components: 1) Health systems; 2)Surveillance; 3)Trained respondants; 4) Good data; 5) Diagnostics, vaccines, drugs

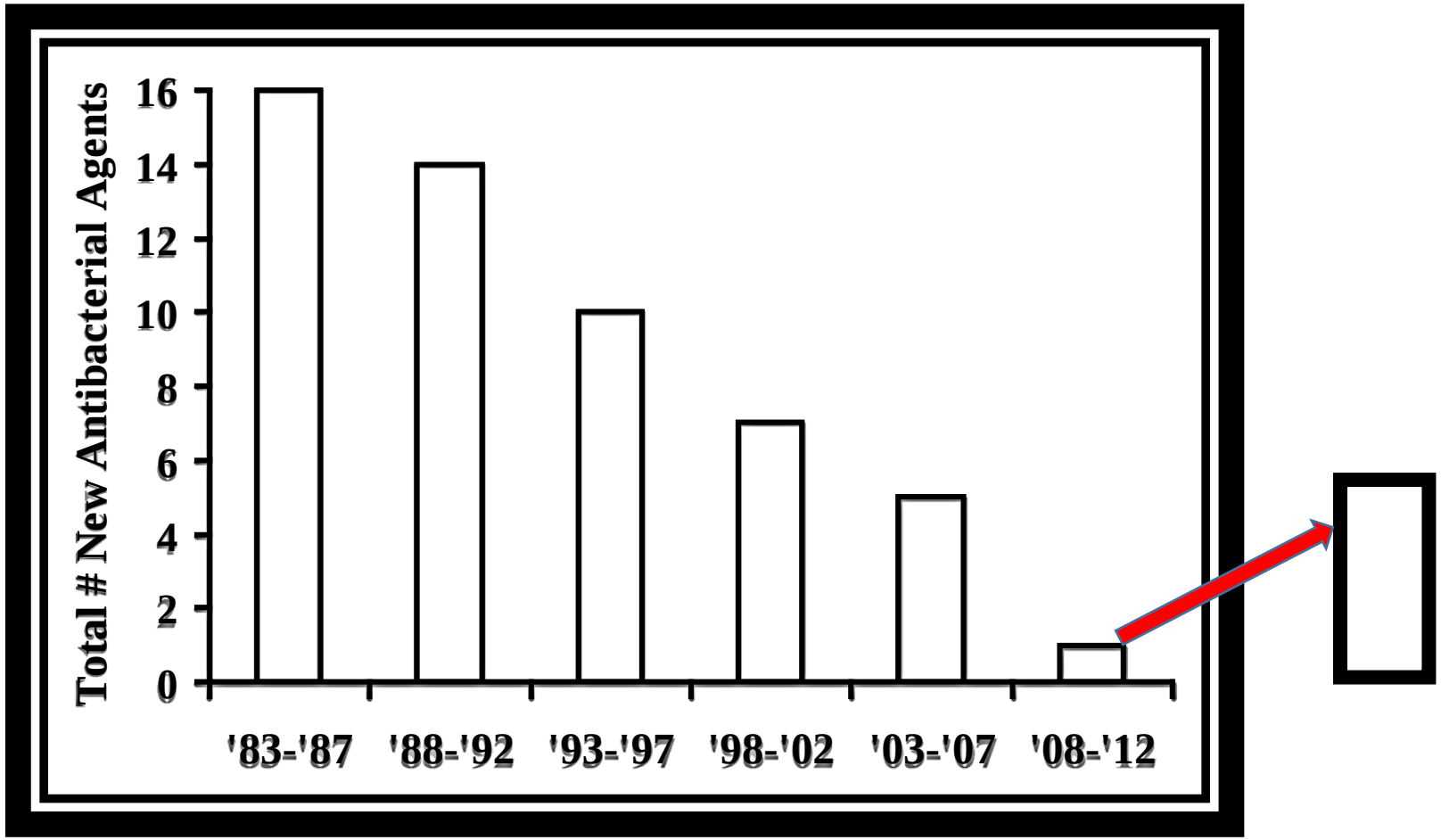
Greatest current threat: Influenza

Call to Action for Human Health Stewardship

FORUM ON ANTIBIOTIC STEWARDSHIP

JUNE 2, 2015

NUMBER OF NEW ANTIBIOTICS BY YEAR



Hepatitis C: Test ➡ Treat ➡ Cure

Pub-Med publications
1/1/14-10/6/15: 8,389

HIV: New WHO Guidelines

ART for all w/HIV; PrEP for all at risk

Community-acquired pneumonia

- Current concepts appear antiquated:
  Needs a re-run for teaching, diagnostics;
  Empiric vs pathogen-directed antibiotics
- ? Management: Can we trump the robust
  Medicare data?

COMMUNITY-ACQUIRED PNEUMONIA

Jain S et al, NEJM 2015;373:415

Micro: Sputum, bronch, urine ag, CDC-PCR

Results: Any pathogen: 38%

***Strep. pneumoniae* : 5%**

Atypicals (all 3): 4%

Bacteria : 11%

Virus / Rhinovirus: 23% / 9%

Conclusion:Despite extensive current tests, no pathogen in 62% cases & viruses dominated

Yield of *S. pneumoniae*

Total yield: 115/2,259 cases (5%)
Blood culture: 26/2070 (1%)
Urine antigen: 56/1923 (3%)
Sputum culture or PCR: 8/267 (3%)
BAL Culture: 3/83 (4%)
More than one specimen source: 21/2259 (1%)

RECOVERY RATES OF *S. PNEUMONIAE* IN SPUTUM FROM ADULTS WITH CAP

Source	Pts	%	Source	Pts	%
Bullowa, ’37	4416	81%	Aubertin ’87	247	12%
Fiala, ‘69	193	55%	Marrie ’87	301	9%
Moore, ’71	144	47%	Levy ’88	116	26%
Fekety, ’71	100	62%	Bates ’89	53	6%
Sullivan, ’72	292	35%	Marrie ’89	719	6%
Dorff, ’73	148	53%	Fang ’90	359	15%
McFarl, ’82	127	76%	Farr ’91	245	18%
Klimek, ’83	204	36%	Oldach ’92	424	16%
Dans, ‘84	147	40%	File 2010*	1240	11%
Brit Tho Soc’87	433	42%			
Holmberg, ’87	147	39%	Medicare 2005-33,000 6%		
Woodhead, ’87	236	36%			

*File T Ceftaroline trial JAC 2011; 66: Suppl 3: iii19

ANTIBIOTIC SELECTION FOR CAP

(Bratzler D, CID 2008;47: Suppl 3; S193)

Method: Retrospective analysis 27,330 patients >65 yrs hospitalized with CAP 1998-9. Analysis based on PSI-adjusted mortality correlated with drug class & reported as OR for 30 day mortality vs 3rd gen ceph

Results Drug	PSI II/III	IV/V	P value
Fluorquinolone	0.9	0.7	0.001
Ceph/macrolide	0.9	0.7	<0.001

Timing: Significant Mortality ⬆ with >4 hr abx delay

Rapid diagnostics & procalcitonin to inform abx decisions (Gilbert D Diag Micro & Inf Dis (in press)

Method: Trial-Non-blinded, cluster randomized of CAP diagnostics at 480 bed hospital.

Standard tests: Blood/sputum culture, urine AG, nasal PCR-SP/S.aureus, FilmArray, procalcitonin

Results: 59 evaluable pts		Procalcitonin
Total w/pathogen:	46/59(78%)	
S. pneumoniae	13(22%)	
Virus only	18(31%)	Virus only-0.2 ng/mL
Bacteria only	14(24%)	Bacteria-6-10ng/mL

FilmArray- RESPIRATORY PANEL

	Sensitivity	Specificity
Influenza	100%	>99%
Paraflu 1-3	87-100%	99.8%
Rhinovirus	96%	100%
Metapneumo	100%	100%
Adenovirus	90%	98%
Coronavirus	96%	99%
RSV	100%	89%
2 “Atypicals”	>99%	>99%
B. pertussis	100%	100%
S. pneumoniae	Not reported-FDA ruling	

Results: <60 minutes; Cost: $300-500/test (?)

Detects: *M pneumo, C pneumo*, pertussis- 12%

Fails: *S pneumo, H flu,* Legionella, *S aureus*,GNB

Procalcitonin for RTI decisions
(Mitsuma SF CID 2013; 56:996)

Messages-Procalcitonin

*RTIs: N=4221

Best use:When to stop

CAP/HAP

Bronchitis,AECB, URI

When to start

*Interpretation:

Start:>0.25 ug/mL

Stop<0.1 ug/mL

When to start or stop

	PROCAL	CONTROL
CAP	90%	99%
VAP	99%	100%
BRON-CHITIS	24%	66%
COPD	48%	73%
URI	15%	48%

PNEUMOCOCCAL VACCINE: CAPiTA Trial (Bonten MJM NEJM 2015;372:1114)

Method: Randomized, placebo controlled trial of Prevnar 13 in 84,496 persons >65 yrs; Netherlands

Results	Placebo	PVC13	Dif
	n=42,256	n=42,240	
S. pneumo CAP	144	100	- 30%
Invasive pneumo	28	7	- 75%
CAP-any pathogen	787	747	- 9%

Problem: Trial in Netherlands where there is no pneumococcal vaccine policy or "herd immunity"

Concerns about CAPiTA as a trial to drive vaccine strategies in the US

The risk for pneumococcal infection- largely driven by vaccine policy with children as major vectors of pneumococcal infections in adults.

PREVNAR 7: great impact on rates of pneumococcal carriage & invasive infection in vaccinated children, and "herd immunity" in adults

Conclusion: 1. PREVNAR 13 makes sense for peds in US & peds & adults in Netherlands (no national ped vaccine policy)

3. PPV23 (only) makes sense for US adults >65 for cost & benefit

What can we conclude about CAP in the US?

CDC (Jain):Most comprehensive US CAP study in decades

Quality: Most specimens for culture- collected post abx; PCR - CDC "home brews" but totality of quality is robust.

Conclusions:

*** We do not know etiology in most US cases**

*** *S. pneumoniae* accounted for 5% & "atypicals"for 4%**

*** We should not base CAP guidance on foreign CAP data due to variations in *S. pneumoniae* vaccine policies.**

*** Viral pneumonia (non-influenza) is likely important.**

*** Treatment guidance largely from Medicare data**

Randomized Trial of Rapid Multiplex PCR-based Blood Culture ID & Susceptibility Banerjee R R CID 2015;61:1071

Method: Comparison of 1) Standard BC; 2) Rapid mPCR (FilmArray); 3) Rapid mPCR + real time abx stewardship.

Results:	Standard N=207	rmPCR N=198	+Stewardship N=212
Time to ID	22.3 hr	1.3 hr*	1.3 hr*
Abx – contaminants	25%	11%*	8%*
Time to path-specific abx	34hr	38hr	21hr*

Conclusion: rmPCR & stewardship achieved reduced abx duration & time to pathogen-specific antibiotic treatment

Editorial comment: A. Caliendo (CID 2015;61:10810)

Review of the Mayo Clinic trial

- **First randomized trial rmPCR to ID blood culture isolates**
- **Trial design- excellent**
- **Demonstrated significant reduction in antibiotic consumption and improved pathogen-specific treatment**

Concerns

- **This technology is very expensive**
- **Mayo Clinic may be atypical- "templated comments", routine MALDI-TOF & required ID stewardship available 24/7**
- **The rmPCR test IDs 80% of BC isolates-also need routine BC**

* **No significant impact on mortality, cost of care or LOS**

CAP: COUNTRY COMPARISONS

Using similar diagnostic methods

Country	US	Norway	Finland	Sweden
No. patients	2,259	267	49	184
Pos-pathogen	38%	63%	92%	67%
S. pneumoniae	5%	30%	57%	38%
Atypical agents	4%	20%	16%	9%
Bacteria-any	9%	49%	82%	63%
Virus-only	21%	15%	9%	29%
Rhinovirus-only	9%	1%	10%	7%

HISTORY OF CAP: US

1937 Bullowa: *S pneumo* in 78% of 165 TTNAs

1970-2000: J Washington-sputum fleck picks/GS

1975-80 Transtracheal aspiration; Bronchoscopic lavage w/protected brush cath & quantitative culture

2000-present: 6 hr CMS "door-to-needle": No micro

2010- present: Molecular methods

British Thoracic Society: CAP Bundle
Lim WS et al Thorax 7/21, 2015

Bundle: *Chest X-ray within 4 hours

*** O2 assessment with appropriate Rx**

*** Assess: CURB-65**

*** Antibiotics within 4 hours**

Evaluation: Bundle started Oct 2012

assessment of 14,962 CAP patients

Results: Bundle use reduced mortality

8.8% vs 13.6%; OR 1.52 (p=0.03)

Duration of antibiotics

Contemporary use of abx is often or usually unjustified by indication and duration. (This is likely to be audited in the future).

Vertebral Osteomyelitis: Treatment- 6 vs 12 weeks (Bernard L Lancet;2015;875)

Issue: Guideline recommend antibiotics for 6 or “at least 12 weeks” without evidence for either

Method: 71 center study – open label, randomized, micro-confirmed osteomyelitis randomized to antibiotics – 6 vs 12 wks w/providers choice of agent. End point-cure rate at one year.

Results:	6 wks (N=176)	12 wks(N=175)
Cured and alive	159 (91%)	151 (92%)
Device infection	2 (1%)	3 (1%)

Conclusion:1) 6 wks- long enough; 2) Consortium -powerful

Messages from the vertebral osteo trial beyond 6 vs 12 weeks.

IV vs PO: Median duration of IV treatment: 14 days; outcome same for comparison of <1 wk IV vs longer.

Note: All PO may be OK and 6 wks may be too long.

Consortium: The trial was done in a French consortium with funding from the French Ministry of Health. The US seriously needs a comparable system to answer important questions in the context of “the resistance crisis”

SHORT COURSE ABX-Cochrane Reviews

Diagnosis	Short	Long	No	Result
CAP	5	7	1,929	ND
CAP	3	8	119	ND
HAP	7	10-15	1,705	ND
VAP	8	15	197	ND
Pyelo	7	14	126	ND
AECB	≤5	≥7	3,532	ND
UTI	1 dose	7	1,622	INF*

*Single dose inferior for pregnant women

Fusobacterium nucleatum pharyngitis

New cause of pharyngitis ? (as well as Lemierre Disease)

Fusobacterium necrophorum Pharyngitis (Centor RM Ann Intern Med 2015;162:241)

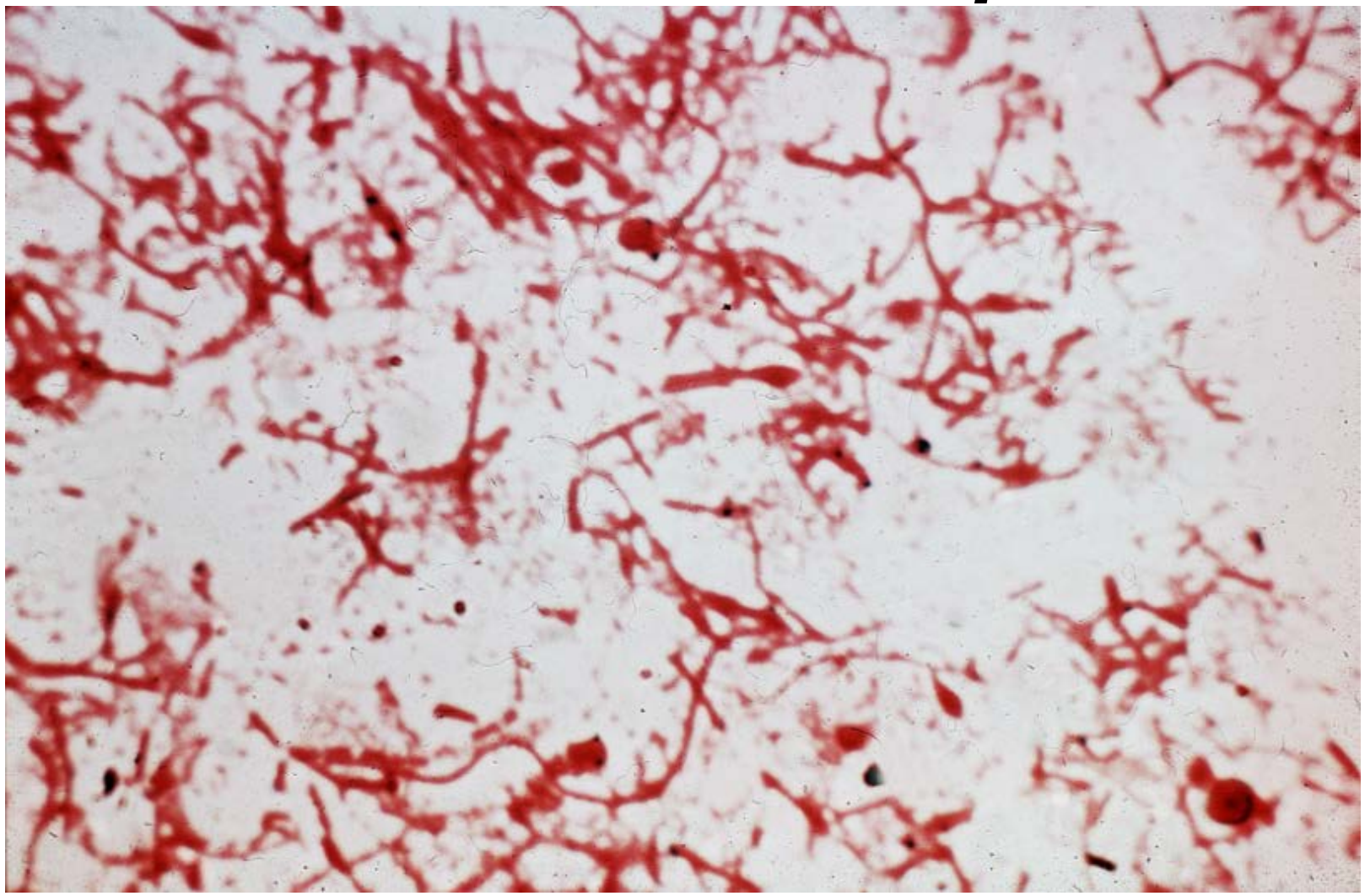
Method: Students with acute sore throat at UAB health clinic

- **Throat swabs for PCR detection of *F. necrophorum, M. pneumoniae* & beta-strep (A & C/G); N=312 and 180 controls**

Results:	***F. necroph***	**Gr A strep**	***M. pneumo***
Symptomatic	**64 (21%)**	**32 (10%)**	**6 (2%)**
Asymptomatic	**17 (9%)**	**2 (1%)**	**0**

Conclusion: *F necrophorum* is more common than Gr A strep in pharyngitis and clinically similar

Fusobacterium necrophorum



Formerly:*Spherophorus necrophorus*

Dr. Centor response to queries

1. **Is PCR test for *F. nucleatum* available to clinicians?**

   Answer: No. "I want a rapid test".

2. **Is penicillin the preferred treatment?**

   Answer: We do not have good treatment studies, but generally use a regimen that is standard for Lemierre disease: metronidazole + penicillin or clindamycin

3. **Do the "Centor criteria" for strep pharyngitis apply to *F. necrophorum* pharyngitis?**

   Answer: Clinical features are similar. We are planning that study

Medical Management of Appendicitis:

? New role for ID physicians

Antibiotic therapy vs Surgery for uncomplicated appendicitis (Salkinen P; JAMA 2015;313:2340)

Background : History & NOTA Trial (DiSaverio S Ann Surg 2014;260:109) questioned uniform need for surgery

Methods: Multicenter trial in Finland of patients age 18-60 yrs with CT-confirmed appendicitis randomized to

1. Early appendectomy vs

2. Antibiotic treatment: ertapenem-3d, then po levoflox/metronidazole-7d

Appendicitis: Medical vs Surgical treatment **(Salminen P JAMA; 2015;313:2340)**

Results	Surgery N=273	Abx N=257
Complications	57 (21%)	8 (3%)
Surgical site infection	24 (9%)	-
Recurrent appendicitis	-	55(21%)
“Sick leave” (median)	19 days	7 days

Varicella-zoster as cause of Giant-cell arteritis (GCA)

Supporting data are robust; treatable with acyclovir-?

Varicella-zoster & Giant Cell Arteritis (Gilden D et al Neurology 2015;84:1948)

<u>Method</u>: GCA-positive temporal artery biopsies (50 sections) examined by immunohistochemistry for VZV.

<u>Results</u>: VZV antigen in 61/82 (74%) cases vs 1/13 (8%) controls.

<u>Issues</u> (Kennedy GE Neurology 2015; 84:1918)

1) **Causal?- Probably; VZV triggers immunopathology**
2) **Practical issue of 50 sections/bx- recommends >10**
3) **Treatment? Acyclovir + steroids VZV vasculopathy**

Successful treatment of GCA & Takayasu arteritis: Case report (Gilden D. Neurology 2015;72:943)

History: 70+ year old women with biopsy-proven GCA complicated by arm pain (pulseless), gangrene left hand; CT angio: extensive large artery disease. Course: She became wasted (30.8 kg), unresponsive to steroids (20 mg/D); arterial biopsies showed VZV in GCA-pos temporal arteries + other large arteries (14/17 sections).

Treatment: IV acyclovir 15 mg/kg tid x 14 days; then po valacyclovir

Response: “dramatic” with energy, appetite, 10 kg weight gain, return of pulses.

Clostridium difficile infection (CDI)

New priority, new treatment, new epidemiology, ? First use of microbiome

Burden of *C. difficile* infection in US

Lessa FC et al, N Engl J Med 2015;372:825

Method: Lab based surveillance in 10 US regions (pop 500,000, 2011)

Results: Total cases: 15,461; projected: 453,000/year

- ***Healthcare-associated: 293,000 (66%)**
- ***Community-onset: 159,000; 82% had contact with Healthcare System**
- ***Relapse rate: 83,000 (18%)**
- ***Mortality: 29,000 (6%)**
- ***Dominant strain: NAP 1- 31% HCA; 19% CA**

Stool transplant for relapsing CDI
(Cammarota G Alim Pharm Ther 2015;41:835)

First Randomized trial!

Method: Recurrent CDI x >1, positive toxin assay, plus >3 watery stools/d randomized to:

- **Colonoscopy insertion of donor stool vs.**
- **Oral vancomycin 125 mg qid x 10 days, then pulse oral vanco x 3 weeks**

Cure rates: Oral vanco 5/19 (26%)

Stool tx 18/20 (90%)

Study stopped prematurely (question answered)

CDI: British Health System

NHS: CDI epidemic throughout the UK

↓

Decrease rate mandate → **Fired Administrators**

↓

Response:

1) Epidemiology: NAP-1
2) "Stopped" FQ (+ cephalosporins)
3) Gene sequencing- Infection control

↓

Result: Rates ↓ 77%!

C. difficile testing -UK

Source: Planche T et al Lancet Infect Dis 2013;13:936

Method: Test 4 univ hospitals, 6,522 diarrheal stools

Tested 3 targets-1) Toxin (sensitive EIA,cytotoxin);2) C dif (GDH EIA, cytotoxin culture) & 3) toxin gene (PCR)

Results correlated w/lab (mortality,WBC,albumin,colitis)

Results: Best test based on clinical correlates- Cytotoxin

Classification: 1) "*C difficile* infection"-cytotoxin pos

2)"*C difficile* excretor": cytotoxin neg & (PCR or cytotoxin culture +)

UK DH: Best practice guidance for diagnosis & reporting of *C difficile*

Diagnosis: Two test combination: Toxin, Toxin gene, microbe

Screening test: PCR (toxin gene)or GDH (*C. difficile*)

Second test: sensitive toxin EIA or cytotoxin (toxin)

Reporting: 1) (GDH or PCR pos) plus (sensitive toxin EIA or cytotoxin): PPV 91%; Mandatory reporting

2) (GDH EIA or PCR pos) plus negative stool toxin: "*C difficile* excretor", Not reported, but transmission potential

3) (GDH & toxin EIA) neg: NPV-99%; Not reported

C. difficile: Miscellaneous issues

1) Zacharioudakis IM. Am J Gastro 215;110:381 : Pooled prevalence of 8,725 hospitalized patients showed 8.1% were colonized with *C. diff* on admission. Relative risk of CDI was 5.9 vs controls

2) Aroniadis OC. Clin Gastro 2015 (in press): Stool transplant in 17 patients with severe and complicated CDI showed 15 achieved cure and 2 relapsed

3) Johnson S CID 2014;59:345: Oral vancomycin was superior to oral metronidazole (and tolevamer); N=563; Cure rate 71% vs 81% (p=0.06)

4. Whitney R Infect Control Hosp Epid 2015; 36:217: Review of 120 requests for *C diff* PCR showed 50% had received laxatives within 48 hrs.

C. difficile produces unique odor of P-cresol; Dog's olfactory sense-300x that of humans

(Bomers MK. BMJ 2012;345:e7396)

Stools	Positive	Negative
Patient stools	30/30 (100%)	270/270 (100%)
Ward	25/30 (83%)	265/270 (98%)

Antibiotic Stewardship

Justified priority

Issues are how to do it and how to measure it

Assessment of empirical antibiotic use (Braylkov N Lancet Infect Dis 2014; 14:1220)

Method: Chart review – inpatients on abx; 6 diverse hospitals; analysis: broadness of spectrum (graded 1-4), lab/culture results, site of infection etc. Candidate cases = 1200; ID-trained physicians did reviews and judgements

Results: Afebrile and normal WBC: 30%

Appropriate cultures : 59%; 58% neg

Broad spectrum agent(s): 50-90%

Antibiotics narrowed (with micro report): 22%

Conclusion: Suggests big challenge for stewardship.

Regulating antibiotics in era of resistance

S Podolsky, J Powers Ann Intern Med 2015;163:386

1950s: Abx approved by in vitro tests & safety (not efficacy)

Concern for a market out of control led by Drs Finland & Dowling

1959:Kefauver hearings: Required well-controlled trials

1969: FDA review- removal of Panalba after approval based on "totality of evidence".New standard was randomized controlled clinical trials.

Modern era: The anguish over resistance has led some to plead for a lesser standard in an effort to get new antibiotics.

Examples of drugs with concerns for FDA-approval based on what some perceive with possible increased mortality or decreased efficacy: Daptomycin, Tigecycline, Doripenem, Telavancin & Ceftazidime/avibactam

Stewardship: Rapidly evolving priority

- CMS considering requiring Stewardship program to be part of the Hospital Safety Network (like infect control)
- If so, need “playbook” of activities to define “compliant” to implement various elements and how to evaluate.
- How measure : example is *C diff* rates (already reported)
- Need antibiotic use measure : Ron Polk’s Antibiotic Administration Ratio: what is expected use vs what is actually used

Short course Antimicrobial Therapy for Intra-abdominal Infection (Sawyer RG et al NEJM 2015;72;1996)

Issue: Duration of antibiotics after surgery for complicated IAS

Method: Complicated IAI with source control randomized to: 1) Abx until 2 days after resolution of: fever, ⬆ WBC, ileus, maximum 10 days Vs 2) fixed 4 day abx course

Outcome: SSI, IAI or death at 30 days

Short course antimicrobial therapy after Surgery for intra-abdominal infection

Results	Controls N=266	4 days N=258
Primary outcome	22%	22%
Days of Antibiotics(mean)	8.0	4.0*
Surgical site infection	15	10*
Intra-abdominal infection	15	11*

*P< 0.01 ; Sawyer RG NEJM 2015;372:1996

Bundled intervention to prevent SSI with cardiac, hip or knee surgery **(Schweizer ML JAMA 2015;313:2162 & editorial 2131)**

Issue: *S. aureus* colonization increases risk of SSI

Plan: Pre-op nasal culture ➡ S. aureus ➡ nasal mupirocin + daily chlorhexidine baths; pre-op abx: Cefazolin/cefuroxime; MRSA-Vanco

Results: Pre-intervention vs post intervention with 42,534 ops in 20 hospitals.

OR for complex *S. aureus* SSI 0.58 (42% reduction)

With full compliance 0.26 (74% reduction)

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