Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

Frequently asked questions in infectious diseases: a case driven interactive discussion

Dirk Vogelaers
Dienst algemene inwendige ziekten, UZ Gent

Jean Cyr Yombi
Service de Maladies Infectieuses, UCL

BVIG/SBMI, 12.12.2014

© 2008 Universitair Ziekenhuis Gent

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

© 2008 Universitair Ziekenhuis Gent

Fig. 1. Schematic representation of biofilm formation. Stage 1: microbial adhesion to the surface. Stage 2: exopolysaccharide production and three-dimensional biofilm development. Stage 3: detachment from biofilm of single and clustered cells.

Francolini I et al, FEMS Immunol Med Microbiol 2010;59:337-38

© 2008 Universitair Ziekenhuis Gent

- **Biofilm => biofilm based device infection.**
  - Higher resistance of bacterial and fungal cells growing as biofilms as compared with planktonic cells.
  - Biofilm is an ideal niche for plasmid (containing genes coding for multidrug resistance) exchange among bacteria (higher conjugation frequency in bacteria growing in a sessile mode than in a planktonic mode).
  - Mechanisms:
    - Slow or incomplete penetration of antimicrobial agents through the biofilm matrix.
    - Physiological response of microorganisms to the heterogeneous chemical environment existing in biofilms.
    - Onset of subpopulations of persister or dormant bacterial cells in a spore-like, non dividing state.
  - Polymicrobial communities (including fungi), altering the sensitivity of each species to antimicrobial agents.

Francolini I et al, FEMS Immunol Med Microbiol 2010;59:337-38

© 2008 Universitair Ziekenhuis Gent

Table 2. Postmarket Surveillance Data: Drug Delivery and Spinal Cord Stimulation Device–related Infections

	Drug Delivery, Postmarket Data, September 1, 2000–March 1, 2002, No./% of 116 Cases with Infection	Spinal Cord Stimulation, Postmarket Data, September 1, 2000–July 1, 2002, No./% of 114 Cases with Infection
Device models	Pumps: 18 ml: 113/97% 10 ml: 3/3%	Power source: IPG: 106/93% RF coupled: 8/7%
Indication		
Noncancer pain	60/52%	114/100%
Cancer pain	1/1%	—
Spasticity	49/42%	—
Not reported	6/5%	—
Perioperative antibiotics		
Antibiotics used	90/78%	99/87%
Antibiotics not used	6/5%	1/1%
Unknown or not reported	20/17%	14/12%
Infected sites or components		
Pocket (IPG or pump)	84/72%	61/54%
Tract (lead or catheter)	10/9%	19/17%
Lumbar site	6/5%	9/8%
Multiple sites	8/7%	16/14%
Other, or site not reported	8/7%	9/8%
Any site plus meningitis	10/9%, in addition to other sites	—
Bacterial cultures		
Cultures performed	94/81%	95/83%
Cultures not performed	3/3%	5/4%
Unknown or not reported	19/16%	14/12%
	No./% of 94 Cultures Performed	No./% of 95 Cultures Performed

Follett KA et al, Anesthesiology 2004;100:1582-94

© 2008 Universitair Ziekenhuis Gent

Table 2. Postmarket Surveillance Data: Drug Delivery and Spinal Cord Stimulation Device–related Infections

	Drug Delivery, Postmarket Data, September 1, 2000–March 1, 2002, No./% of 116 Cases with Infection	Spinal Cord Stimulation, Postmarket Data, September 1, 2000–July 1, 2002, No./% of 114 Cases with Infection
Culture results		
Staphylococcus species	55/59%	46/48%
Pseudomonas species	3/3%	3/3%
Multiple or other species	7/7%	6/6%
No growth	10/9%	17/18%
Unknown or not reported	19/20%	23/24%
Antibiotic treatment		
Intravenous	50/43%	46/40%
Oral	5/4%	18/16%
Intravenous and oral	41/35%	45/39%
Not reported	20/17%	5/4%
Device explantation		
Total	110/95%	94/82%
Partial	3/3%	14/12%
Not explanted	2/2%	4/4%
Not reported	—	2/2%
Interval: implantation to explantation, range, months	1–43	1–104
≤ 1 month	46/40%	43/38%
≤ 2 months	15/13%	21/18%
> 2 months	39/34%	39/34%
Device not explanted	—	1/1%
Interval not reported	10/9%	10/9%
No. of risk factors*		
Zero	35/30%	71/62%
One	55/47%	34/30%
Two	19/16%	7/6%
Three or more	8/7%	2/2%
Outcome		
Resolved, no complications	88/76%	104/91%
Resolved, drug withdrawal	15/13%	—
Event ongoing at time of report	3/3%	3/3%
Death (cause)	1/1% (meningitis and sepsis)	—
Outcome not reported	8/7%	7/6%

* Risk factors for infection or poor wound healing included diabetes, debilitated status, malnutrition, extremely thin body habitus, obesity, autoimmune disorder, corticosteroid use, decubitus ulcers, preexisting infection, poor hygiene, urinary or fecal incontinence, and malabsorption syndrome.

IPG = implantable pulse generator; RF = radiofrequency.

Follett KA et al, Anesthesiology 2004;100:1582-94

© 2008 Universitair Ziekenhuis Gent

Table 1. *Methods to decrease the rate of implantable pain therapy surgical site infections*

Preoperative	Intraoperative	Postoperative
- Identifying patient risk factors - Optimization of immune and nutritional status - Optimizing comorbidities such as diabetes, immunosuppression, and dental disease - Preoperative screening and decolonization for SA carriers - Appropriate selection of intravenous antibiotic prophylaxis based on hospital pathogens - Weight-based dosing antibiotics - Appropriate hair removal - Evaluation for skin lesions or areas of local infection	- Appropriate agent selection for skin antisepsis - Wide prep and drape - Operating rooms with laminar flow and HEPA filters - Limit OR traffic - Adequate hemostasis - Limit tissue trauma and avoid the electrocautery at tissue surface - Vigorous wound irrigation - Careful attention to wound closure and careful tissue approximation - Limit surgical time	- Occlusive dressing for a minimum of 24 to 48 hours - Attention to tape allergies and skin irritants - Continued comorbidity optimization - Education regarding fever and warning signs of early infection - Close postoperative wound surveillance - Consult with an infectious disease specialist if any sign or warning signals of infection are present

SA = Staphylococcus Aureus; HEPA = High-Efficiency Particulate Air; OR = Operating Room

Deer TR et al, Pain Physician 2013;16:E125-8

© 2008 Universitair Ziekenhuis Gent

Table 4. Recommendations for the Prevention and Management of DD and SCS Device Infection

Treatment of established infection

Category II

- Remove infected components or entire system as indicated.
- Taper intrathecal drugs or administer substitute medication systemically or both to prevent or treat intrathecal baclofen or opioid withdrawal when a drug delivery system is removed because of infection.
- Administer antibiotics directed at the responsible organism as determined by wound cultures and stains.

Device reimplantation after treatment of infection

Category II

- Ensure complete and permanent eradication of the infection off antibiotic therapy before device reimplantation.
- Implant the new device in a site that was not involved in the previous infection.

Follett KA et al, Anesthesiology 2004;100:1582-94

© 2008 Universitair Ziekenhuis Gent

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

2. Invasive aspergillosis.

Pinto PS, Radiology 2004;230:109-10

© 2008 Universitair Ziekenhuis Gent

2. Invasive aspergillosis.

Aspergilus		-	++	++	+++	++	++	9
Aspergilus		-	++	++	+++	++	++	9
Aspergilus		-	++	++	+++	++	-	

© 2008 Universitair Ziekenhuis Gent

Sanfordguide to Antimicrobial Therapy, 23rd BeLux Edition, table 9E

2. Invasive aspergillosis.

*:Primary [illegible]

[illegible]

[illegible]ber

*[illegible]

°3Amphotericin [illegible] lipid [illegible]

[illegible]lex

°iAmphotericin [illegible]

°[illegible] [4]: 70 mg iv on day 1, then [illegible] 76 .)

°[illegible]

Use of antifungal agents with patients [illegible] aspergillosis is probable [illegible]

- [illegible] [1] in [illegible] (guideline 7.ref 86) and effective in [illegible] [illegible]noidal [1].
- Invasive aspergillosis due to *Aspergillus* [illegible] [4], should be treated with [illegible] 7.6ref [illegible] formulation Amphotericin [illegible] [illegible]city 7.ref 07 7.ref 17 .)
- [illegible] [4] also proven to be safe and effective (primary or salvage therapy) in patients with chronic invasive [illegible]pergillosis [irrespective of their immunological status 7.ref 27 .])
- **Combination** [illegible] [illegible] results [illegible] 7.ref 37 7.ref 477,7ref 5.)
- **Patients** [illegible] [illegible] (therapy 7.ref 77)] or amphotericin [illegible] (colloidal formulation) or posaconazole) [illegible] 7.ref 87 .])
- **Cerebral** caspofungin: [illegible] posaconazole), [illegible] (only available). [illegible]

with patients failure renal [illegible] for

- [illegible] voriconazole iv [illegible]
- [illegible]
- [illegible]azole
- [illegible] formulation Amphotericin [illegible]].

These alternatives should also be used in case [illegible] (potentially) interactions drug

Patients with hepatic dysfunction [illegible]

Duration

- Until recovery of neutrophil count (> 500/mm3) + disappearance [illegible] always imply progression of disease and should be [illegible]reated 7.80ref .)
- [illegible]side [illegible] to be preferred [illegible] because [illegible] immunosuppression] until

Therapeutic voriconazole Monitoring [4] serum levels highly recommended at least once after the initiation of [illegible]ation: 7.82ref 7.83ref [illegible] ents show subtherapeutic [illegible] 7.84ref .)

[illegible]esting susceptibility Resistance [illegible] *Aspergillus* azoles to [5] is low in Belgium [< 2% (data National Reference [illegible] Center [illegible]

Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America

Thomas J. Walsh,[1,a] Elias J. Anaissie,[2] David W. Denning,[13] Raoul Herbrecht,[14] Dimitrios P. Kontoyiannis,[3] Kieren A. Marr,[5] Vicki A. Morrison,[6,7] Brahm H Segal,[8] William J. Steinbach,[9] David A. Stevens,[10,11] Jo-Anne van Burik,[7] John R. Wingard,[12] and Thomas F. Patterson[4,a]

Table 2. Summary of recommendations for the treatment of aspergillosis.

Condition	Therapy[a]	
	Primary	Alternative[b]
Invasive pulmonary aspergillosis	Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)	L-AMB (3–5 mg/kg/day IV), ABLC (5 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), micafungin (IV 100–150 mg/day; dose not established[c]), posaconazole (200 mg QID initially, then 400 mg BID PO after stabilization of disease[d]), itraconazole (dosage depends upon formulation)[e]

Clin Infect Dis 2008;46:327-60

© 2008 Universitair Ziekenhuis Gent

2. Invasive aspergillosis.

- Voriconazole is antifungal agent of choice as it has been proven more effective than amphotericin B colloidal suspension in one large randomized trial and effective in an open series of patients refractory to or intolerant of amphotericin B colloidal suspension (***Herbrecht et al, N Engl J Med 2002;347:408-15***).
- Invasive aspergillosis due to *Aspergillus terreus* is often resistant to treatment with amphotericin B, should be treated with voriconazole (***Sambatakou H et al, Am J Med 2006;119;527.e17-24***). Administration of higher doses of amphotericin B lipid formulation (10 mg/kg iv q24h) offers no additional benefit, increases nephrotoxicity (***Ainaissie EJ, Clin Infect Dis 2007;44:1298-306; Cornely OA et al, Clin Infect Dis 2007;44:1289-97;***).

© 2008 Universitair Ziekenhuis Gent

2. Invasive aspergillosis.

- Voriconazole also proven to be safe and effective (primary or salvage therapy) in patients with chronic forms of invasive aspergillosis [irrespective of their immunological status (***Steinbach WJ et al, Clin Infect Dis 2004;39:192-8***)].
- Combination therapy: while new drugs may increase clinical response as well as survival rates, invasive pulmonary aspergillosis remains one of the most refractory fungal infections. This has led to the use of combination therapies, but as yet no results of controlled clinical trials have been reported to support this (***Walsh TJ et al, Clin Infect Dis 2007;44:2-12; Miceli MH et al, Cancer 2007;110:112-20; Viscoli C, Clin Infect Dis 2004;39:803-5***).

© 2008 Universitair Ziekenhuis Gent

2. Invasive aspergillosis.

- Patients intolerant of, failing on or refractory to voriconazole (***van der Linden JW et al, Clin Infect Dis 2009;48:1111-3***): caspofungin [good efficacy reported in salvage therapy (***Maertens J et al, Clin Infect Dis 2004;39:1563-71***)] or amphotericin B (colloidal suspension or lipid formulation) or posaconazole[4] [400 mg q12h po (***Singh N et al, Transplantation 2006;81:320-5***)].
- Cerebral aspergillosis: no caspofungin (penetration of CSF is poor and only a few patients with cerebral invasive aspergillosis have been treated with caspofungin), no posaconazole (only po formulation available).

© 2008 Universitair Ziekenhuis Gent

2. Invasive aspergillosis.

- **Patients with renal failure.**
  - Immediate switch from voriconazole iv to voriconazole po.
  - Direct start with voriconazole po.
  - If oral treatment is impossible, voriconazole iv should only be used after a careful risk benefit assessment.
  - Use of alternative agents [caspofungin or amphotericin B (lipid formulation)].
- **Cave:**
  - Potential drug-drug interactions.
  - Dosing in patients with hepatic dysfucntion.
  - Monitoring of voriconazole (at least once highly recommended): target concentration is to 2 to 5 µg/ml (15% of patients have subtherapeutic levels when treated with recommended doses)

© 2008 Universitair Ziekenhuis Gent

What after vorico?

- **Initial combination therapy vorico + caspofungin in rapidly evolving serious or already progressive cases of IA**
  - Awaiting documentation of adequate therapeutic levels (>1.5) in TDM
  - In future also until proven azole-susceptibility (Cyp51 mutations) (which treshold of resistance to be considered?)
- **No difference in endpoints for probable/proven invasive aspergillosis vorico + placebo vs vorico + anidulafungin**

© 2008 Universitair Ziekenhuis Gent

Monitoring plasma voriconazole levels following intravenous administration in critically ill patients: an observational study

Data relating to the pharmacokinetics of voriconazole in critically ill patients are lacking. A prospective observational study was conducted on 18 non-consecutive critically ill patients aged 24–97 years, comprising 12 patients with normal renal function (NRF) [creatinine clearance (CL_{Cr}) ≥60 mL/min] and 6 patients with moderate renal impairment (MRI) (CL_{Cr} 40–55 mL/min), administered voriconazole intravenously (6 mg/kg loading dose and 3–4 mg/kg twice daily thereafter) in order to determine the suitability of these doses in this patient population. Steady-state blood levels were monitored and liver and renal function were recorded throughout treatment. Large variability in patient plasma levels was observed, ranging from 37% at ≤1 mg/L (minimum inhibitory concentration at which, for most fungal pathogens, 90% of isolates are susceptible) to 19% at >5.5 mg/L. Moreover, maintaining trough concentrations above clinical breakpoints was not consistently achieved because 16/30 (53%) were ≤1 mg/L. In a few MRI patients, average concentrations were found to be significantly different compared with those of NRF patients administered the same dose, however this difference was not noted in pharmacokinetic parameters following dose normalisation. None of the patients experienced deterioration in renal or liver function. Recommended voriconazole doses are inadequate to achieve drug concentrations >1 μg/mL over the entire dosing interval in some critically ill patients.

© 2008 Universitair Ziekenhuis Gent

Myrianthefs P, et al. Int J Antimicrob Agents 2010

What after vorico?

- **Obligatory class switch?**
  - Paradigm: no azole on azole?
- **Posaco vs vorico: significantly higher intrinsic affinity for active site C14 demethylase Aspergillus spp.**

© 2008 Universitair Ziekenhuis Gent

Triazole Antifungal Agents in Invasive Fungal Infections

A Comparative Review

Oral posaconazole has been assessed in salvage therapy of various invasive fungal infections, including a cohort of 107 patients with aspergillosis.[98] A total of 86 cases showed a 42% favourable response rate in posaconazole-treated patients and a significant improved survival compared with the external control group.

Lass-Flörl C, Drugs 2011;71:2405

© 2008 Universitair Ziekenhuis Gent

Table 5. Successful responses at end of therapy, by primary underlying condition or risk factor.

Condition or risk factor	Proportion of subjects (%)	
	Posaconazole group (n = 107)	Control group (n = 86)
Transplantation		
Autologous HSCT	6/7 (86)	0/4 (0)
Allogeneic HSCT	15/48 (31)	7/34 (21)
Solid organ transplantation	7/12 (58)	5/7 (71)
Primary underlying conditions		
Hematological malignancy	29/79 (37)	16/70 (23)
Nonhematological malignancy	6/13 (46)	1/5 (20)
Acquired immunodeficiency		
All	13/28 (46)	6/19 (32)
Diabetes mellitus	7/15 (47)	3/14 (21)
HIV infection/AIDS	3/7 (43)	1/3 (33)
Congenital immunodeficiency	1/2 (50)	0/3 (0)
No known risk factor for invasive fungal infection	1/1 (100)	0/0 (0)

NOTE. HSCT, hematopoietic stem cell transplantation.

Walsh TJ et al, Clin Infect Dis 2007;44:2

© 2008 Universitair Ziekenhuis Gent

Table 7. Successful response at end of therapy, by *Aspergillus* species.

Aspergillus species	Proportion of subjects (%)	
	Posaconazole group (n = 107)	Control group (n = 86)
Aspergillus fumigatus	12/29 (41)	12/34 (35)
Aspergillus flavus	10/19 (53)	3/16 (19)
Aspergillus terreus	4/14 (29)	2/13(15)
Aspergillus niger	3/5 (60)	2/7 (29)
Aspergillus ochraceus	1/2 (50)	0/0
Aspergillus ustus	1/1 (100)	0/0
Aspergillus nidulans	2/2 (100)	0/0
Aspergillus versicolor	0/1 (0)	0/0
Aspergillus glaucus	0/0 (0)	0/1 (0)
Unidentified *Aspergillus* species[a]	3/9 (33)	0/4 (0)

[a] Cultured but identified only to the genus level.

Walsh TJ et al, Clin Infect Dis 2007;44:2

© 2008 Universitair Ziekenhuis Gent

New posaconazole f

New solid oral formulation has pH sensitive polymer coating allowing improved intestinal absorption.

New iv. formulation contains cyclodextrin based polymer to allow adequate solubility and intravenous adminstration

Significantly improved plasma levels achieved in both AML and HSCT patients

Novel formulations require once daily dosing of 300mg (following a loading dose of 300mg bid) that is irrespective of indication (prophylaxis or treatment), not required to be taken with food and not influenced by pH modifyers (PPI, H2 antagonists & antiacids) nor by gastric motility enhancers (metaclopramide)

© 2008 Universitair Ziekenhuis Gent

Table I. Echinocandin activity against common *Candida* and *Apergillus* species[23,24,42-45]

Organism	Caspofungin	Micafungin	Anidulafungin
***Candida* species**	**MIC_{50}, MIC_{90}**	**MIC_{50}, MIC_{90}**	**MIC_{50}, MIC_{90} (range)**
C. albicans	0.03, 0.06	0.015, 0.03	0.03, 0.06 (0.03–0.25)
C. glabrata	0.03, 0.06	0.015, 0.015	0.06, 0.12 (0.03–1)
C. tropicalis	0.03, 0.06	0.03, 0.06	0.03, 0.06 (0.06–2)
C. krusei	0.12, 0.25	0.06, 0.12	0.06, 0.06 (0.12–1)
C. parapsilosis	0.25, 1	1, 2	2, 2 (0.12 to >2)
C. guilliermondii	0.5, 1	0.5, 1	1, 2 (1–4)
C. lustitaniae	0.25, 0.5	0.06, 0.12	0.5, 0.5 (0.125–2)
C. dubliniensis	–, 0.5	–, 0.03	–, 0.06
***Aspergillus* species**	**MEC_{90}[a] (range)**	**MEC_{90}[a] (range)**	**MEC_{90}[a] (range)**
A. fumigatus	0.12 (0.007–1)	0.03 (0.007–0.25)	0.03 (0.007–0.12)
A. flavus	0.06 (0.007–1)	0.015 (0007–1)	0.015 (0.007–0.25)
A. terreus	0.03 (0.007–2)	0.015 (0.007–0.25)	0.015 (0.007–0.5)

a MEC_{90} values and MEC_{90} range values were from Pfaller et al.[45] and Antachopoulos et al.[44]

MEC = minimum effective concentration; **MIC_{50}** = minimum inhibitory concentration at which the growth of 50% of the isolates tested were inhibited; **MIC_{90}** = minimum inhibitory concentration at which 90% of isolates tested were inhibited; – indicates not available.

Chen SC et al, Drugs 2011;71:11

© 2008 Universitair Ziekenhuis Gent

Table VII. Key clinical studies of echinocandins in candidaemia and invasive candidiasis

Agent and dosing	Comparator	No. of patients evaluated	Favourable outcome	Reference
Caspofungin 70 mg then 50 mg daily	Amphotericin B deoxycholate 0.6–1 mg/kg daily	224	73.4% vs 61.7%	143
Caspofungin 70 mg then 50 mg daily	Caspofungin 150 mg daily	197	71.6% vs 77.9%	165
Micafungin 100 mg daily	Micafungin 150 mg daily; caspofungin 70 mg then 50 mg daily	595	76.4% vs 71.4% 76.4% vs 72.3%	166
Micafungin 100 mg daily	Liposomal amphotericin B 3 mg/kg daily	392	89.6% vs 89.5%	144
Anidulafungin 200 mg then 100 mg daily	Fluconazole 800 mg then 400 mg daily	245	75.6% vs 60.2%	39

Chen SC et al, Drugs 2011;71:11

© 2008 Universitair Ziekenhuis Gent

Table II. Comparison of major properties and key pharmacokinetic parameters of echinocandins in adults[a][17,20,51]

Variable	Caspofungin	Micafungin	Anidulafungin
C_{max} (mg/L) [50 mg single dose]	7.64	4.95	2.07–3.5
Bioavailability (%)	<10	<10	2–7
$t_{½}$ (h)	9–11	11–17	24–26
Vd (L/kg)	0.14	0.22–0.24	0.5
AUC (mg • h/L)	87.9–114.8	111.3	44.4–53
Protein binding (%)	96–97	99.8	>99
Metabolism	Slow peptide hydrolysis, N-acetylation and spontaneous degradation to inactive product	Catechol-*O*-methyltransferase pathway	Not metabolized Slow chemical degradation to inactive metabolites
Cl_T	0.15	0.185	0.26
Fraction excreted unchanged in urine (%)	1.4	0.7	<1
Elimination	35% faeces, 41% urine, 1.4% as unchanged drug	40% faeces, <15% urine	Primarily faeces (<10% as intact drug), 1% urine
CSF penetration (% plasma)	Low	Low	<0.1%
Dose adjustment in renal insufficiency	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed
Dose adjustment in geriatric patients	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed
Dose adjustment in hepatic insufficiency	Child-Pugh 5–6: none Child-Pugh 7–9: significant increase in AUC; reduce maintenance dose to 35 mg/day Child-Pugh >9: no data	Child-Pugh 7–9: C_{max} not altered, AUC significantly decreased compared with healthy subjects	No dose adjustment needed in patients with mild, moderate or severe hepatic dysfunction

a Data are from multiple sources and are not always comparable.

AUC = area under the plasma concentration-time curve; **Cl_T** = total clearance; **C_{max}** = maximum concentration; **CSF** = cerebrospinal fluid; **$t_{½}$** = elimination half-life; **Vd** = volume of distribution.

© 2008 Universitair Ziekenhuis Gent

Chen SC et al, Drugs 2011;71:11

Table IV. Drug interactions with the echinocandins[11-13,138-142]

Drug	Caspofungin	Micafungin	Anidulafungin
CYP/P-glycoprotein interactions	Poor substrate for CYP Not an inhibitor of CYP Not a substrate/inhibitor of P-glycoprotein	Substrate for CYP3A4 Weak inhibitor CYP3A4 Not a substrate/inhibitor of P-glycoprotein	Not a substrate, inducer or inhibitor of CYP
Tacrolimus	AUC, peak and 12-hour concentrations of tacrolimus are decreased by ~20%	No significant effect on tacrolimus	No significant effect on tacrolimus
Sirolimus	No data	Increases AUC of sirolimus by 12%	No data
Ciclosporin	35% increase in the AUC of caspofungin	Decreases clearance of ciclosporin by 16%	22% increase in AUC of anidulafungin; dose adjustment not required
Rifampicin	Decreases steady-state plasma caspofungin concentrations	No significant effect on micafungin	No significant effect on anidulafungin
Voriconazole	No data	No significant effect on micafungin	No significant effect on anidulafungin
Nefidipine	No data	Increases the AUC and C_{max} of nifedipine by 18% and 43%, respectively	No data

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum concentration; **CYP** = cytochrome P450.

© 2008 Universitair Ziekenhuis Gent

Chen SC et al, Drugs 2011;71:11

ANIDULAFUNGIN

- Faster plasma steady state & higher tissue distribution
- Potent *in vitro* activity against Aspergillus & Candida spp including resistant ones
- Undergoes slow clinical degradation in blood rather than metabolization
- No dose reduction for any degree of hepatic impairment
- No significant drug/drug interaction
- Excellent safety profile
- No cross-resistance to polyenes or azoles
- **Cost-effective as compared to fluconazole (Neoh CF et al. J Antimicrob Chemother 2011)**

CASPOFUNGIN

- Less activity against C parapsilosis
- Dose reduction in liver failure
- Drug interactions !
  - cyclosporin (35% ↑ caspo)
  - rifampicin, carbamazepine, dexamethasone (↓ caspo)
  - tacrolimus
  - antiretroviral therapy
- No superiority trial vs fluconazole

© 2008 Universitair Ziekenhuis Gent

Table V. The more common adverse reactions reported in clinical trials (expressed as a percentage of all adverse reactions)[11-13]

Adverse reaction	Caspofungin (%)	Micafungin (%)	Anidulafungin (%)
Pyrexia	21.2	Not documented	0.7
Diarrhoea	14.9	2.1 [gastrointestinal disorders (57.2)]	3.1 [nausea (1)]
Increased liver enzymes	ALT (14.9); AST (12.5); alkaline phosphatase (12.1)	Rare	ALT (2.3); γ-glutamyl transferase (1.3)
Hypokalaemia	11.8	1.8	3.1
Infusion-related reactions	2	45.6	Not documented
Metabolism and nutrition disorders	Not documented	42.7	Not documented
Headache	Not documented	Not documented	1.3
Neutropenia	Not documented	Not documented	1.0

Chen SC et al, Drugs 2011;71:11

© 2008 Universitair Ziekenhuis Gent

There are differences among the three echinocandins with respect to half-life, metabolism, requirements for a loading dose (not needed with micafungin), time to steady state and drug interaction profile. Anidulafungin is the only agent that does not have known clinically significant drug interactions, including with immunosuppressive agents. This agent may have lower MICs against certain *Candida* strains that are considered non-susceptible to caspofungin or micafungin,[54] and may influence the choice of agent. However, on balance, the echinocandins do not appear to demonstrate any differences in clinical efficacy in the disease entities that have been studied and it is unlikely that any one agent would be found to be clearly superior with regard to clinical outcome.

Chen SC et al, Drugs 2011;71:11

© 2008 Universitair Ziekenhuis Gent

Echinocandins

- **Accepted as start therapy for invasive yeast infections (C albicans and non albicans), independent of sensitivity, with the following arguments:**
  - Faster clearing of blood stream infection
  - Activity in biofilm
- **In ECCMID guidelines for the whole treatment duration**
- **In IDSA guidelines for more serious ill patients without distinction between echinocandins**
- **Some exceptions: endophtalmitis (but majority chorioretinitis), CNS infection**
- **Compromise: start therapy with echinocandine + stepdown to fluconazole after documented clearing of BSI**
- **As strategy not validated in RCT**

© 2008 Universitair Ziekenhuis Gent

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

MAJOR ARTICLE

Excess Deaths Associated With Tigecycline After Approval Based on Noninferiority Trials

Paritosh Prasad, Junfeng Sun, Robert L. Danner, and Charles Natanson

Conclusions. Pooling noninferiority studies to examine survival may help ensure the safety and efficacy of new antibiotics. The association of tigecycline with excess deaths and noncure includes indications for which it is approved and marketed. Tigecycline cannot be relied on in serious infections.

Clin Infect Dis 2012;54:1699-709771-7

© 2008 Universitair Ziekenhuis Gent

Figure 5. Cumulative mortality and cumulative noncure rate analyses for the tigecycline noninferiority trials identified in this meta-analysis from mid-2005 (the date when tigecycline received FDA approval as monotherapy for complicated intra-abdominal and skin infections) through the end of 2009 (the date by which the last study in this meta-analysis was completed).

© 2008 Universitair Ziekenhuis Gent

3. Use of tigecycline after FDA warning.

Tygacil (tigecycline): Label Change - Increased Mortality Risk

[Posted 09/01/2010]

AUDIENCE: Infectious Disease, Critical Care Medicine, Internal Medicine

ISSUE: FDA reminded healthcare professionals of an increased mortality risk associated with the use of the intravenous antibacterial Tygacil (tigecycline) compared to that of other drugs used to treat a variety of serious infections. The increased risk was seen most clearly in patients treated for hospital-acquired pneumonia, especially ventilator-associated pneumonia, but was also seen in patients with complicated skin and skin structure infections, complicated intra-abdominal infections and diabetic foot infections. FDA has updated sections of the Tygacil drug label to include information regarding increased mortality risk of Tygacil.

BACKGROUND: Tygacil is approved by FDA for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community acquired pneumonia. Tygacil is not approved for the treatment of hospital-acquired pneumonia (including ventilator-associated pneumonia) or diabetic foot infection. The increased risk was determined using a pooled analysis of clinical trials. See the Data Summary section of the FDA Drug Safety Communication for additional details.

RECOMMENDATION: Alternatives to Tygacil should be considered in patients with severe infections.

© 2008 Universitair Ziekenhuis Gent

- Empirical antibacterial therapy in patients with IgE mediated allergy to penicillins: [(aztreonam or ciprofloxacin or levofloxacin) + 5-nitro-imidazole] or moxifloxacin or, as an alternative, tigecycline.
  - Community acquired hepatic abscess in patients with no recent exposure to antibacterials.
  - Community acquired intraperitoneal (subphrenic, subhepatic, perihepatic, …) abscess in patients with no recent exposure to antibacterials.
  - Perirectal abscess in immunocompetent patient.
  - Gangrenous appendicitis, appendicitis with perforation (local or diffuse), with or without peritonitis).
  - Community acquired cholangitis in absence of device in patients with no recent exposure to antibacterials.
  - Community acquired cholecystitis.
  - Community acquired diverticulitis with or without perforation in patients with no recent exposure to antibacterials.
  - Community acquired gastroduodenal perforation, in patients with no recent exposure to antibacterials, time to surgical intervention > 24 hours.
  - Acute infection of pancreatic or peripancreatic necrotic tissue, acute infection of pancreatic or peripancreatic fluid collections, walled off necrosis (pancreatic abscess), in patients with no recent exposure to antibacterials, no prolonged hospitalisation.
  - Community acquired secondary peritonitis, in patients with no recent exposure to antibacterials.

© 2008 Universitair Ziekenhuis Gent

Sanfordguide to Antimicrobial Therapy, 23rd BeLux Edition, table 1A.

- Empirical antibacterial therapy in patients with IgE mediated allergy to penicillins: [(aztreonam or ciprofloxacin or levofloxacin) + 5-nitro-imidazole] or moxifloxacin or, as an alternative, tigecycline.
  - Community acquired hepatic abscess in patients with no recent exposure to antibacterials.
  - Community acquired intraperitoneal (subphrenic, subhepatic, perihepatic, …) abscess in patients with no recent exposure to antibacterials.
  - Perirectal abscess in immunocompetent patient.
  - Gangrenous appendicitis, appendicitis with perforation (local or diffuse), with or without peritonitis).
  - Community acquired cholangitis in absence of device in patients with no recent exposure to antibacterials.
  - Community acquired cholecystitis.
  - Community acquired diverticulitis with or without perforation in patients with no recent exposure to antibacterials.
  - Community acquired gastroduodenal perforation, in patients with no recent exposure to antibacterials, time to surgical intervention > 24 hours.
  - Acute infection of pancreatic or peripancreatic necrotic tissue, acute infection of pancreatic or peripancreatic fluid collections, walled off necrosis (pancreatic abscess), in patients with no recent exposure to antibacterials, no prolonged hospitalisation.
  - Community acquired secondary peritonitis, in patients with no recent exposure to antibacterials.

© 2008 Universitair Ziekenhuis Gent

Sanfordguide to Antimicrobial Therapy, 23rd BeLux Edition, table 1A.

- Empirical antibacterial therapy in patients with IgE mediated allergy to penicillins: [(aztreonam or ciprofloxacin or levofloxacin) + 5-nitro-imidazole] or moxifloxacin or, as an alternative, tigecycline.
  - Community acquired hepatic abscess in patients with no recent exposure to antibacterials.
  - Community acquired intraperitoneal (subphrenic, subhepatic, perihepatic, …) abscess in patients with no recent exposure to antibacterials.
  - Perirectal abscess in immunocompetent patient.
  - Gangrenous appendicitis, appendicitis with perforation (local or diffuse), with or without peritonitis).
  - Community acquired cholangitis in absence of device in patients with no recent exposure to antibacterials.
  - Community acquired cholecystitis.
  - Community acquired diverticulitis with or without perforation in patients with no recent exposure to antibacterials.
  - Community acquired gastroduodenal perforation, in patients with no recent exposure to antibacterials, time to surgical intervention > 24 hours.
  - Acute infection of pancreatic or peripancreatic necrotic tissue, acute infection of pancreatic or peripancreatic fluid collections, walled off necrosis (pancreatic abscess), in patients with no recent exposure to antibacterials, no prolonged hospitalisation.
  - Community acquired secondary peritonitis, in patients with no recent exposure to antibacterials.

© 2008 Universitair Ziekenhuis Gent

Sanfordguide to Antimicrobial Therapy, 23rd BeLux Edition, table 1A.

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

4. Vaccination against pertussis in pregnant women.

Figure 2.5.23. Rates of reported confirmed pertussis cases, by age and gender, EU/EEA countries, 2010

Source: Country reports from Austria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom.

ECDC, Annual Report, Epidemiological data 2011

© 2008 Universitair Ziekenhuis Gent

4. Vaccination against pertussis in pregnant women.

© 2008 Universitair Ziekenhuis Gent

Tetanus, Diphtheria, and Pertussis (Tdap); & Tetanus and Diphtheria (Td) :

- Health-care personnel should **administer a dose of Tdap during each pregnancy** irrespective of the patient's prior history of receiving Tdap. To maximize the maternal antibody response and passive antibody transfer to the infant, **optimal timing for Tdap administration is between 27 and 36 weeks of gestation** although Tdap may be given at any time during pregnancy. [12]

- For women not previously vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered immediately postpartum.[12]

- Available data from . . . studies do not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine. [13]

1 dose of Boostrix®

© 2008 Universitair Ziekenhuis Gent

Cocooning

The strategy of protecting infants from pertussis by vaccinating those in close contact with them is known as "cocooning." ACIP has recommended cocooning with Tdap vaccine since 2005 and continues to recommend this strategy **for all those with expected close contact with newborns**. Cocooning enhances maternal vaccination to provide maximum protection to the infant. In addition to vaccinating your patients, you should educate them about encouraging others – **including dads, grandparents and other caregivers** – to get vaccinated with Tdap **at least two weeks before coming into contact with their infants**.

Full implementation of cocooning has proven to be a challenge; vaccinating during pregnancy provides the best opportunity to protect infants from pertussis.

© 2008 Universitair Ziekenhuis Gent

Sources of pertussis infection in young infants: A review of key evidence informing targeting of the cocoon strategy

K.E. Wiley[a,b,*], Y. Zuo[c], K.K. Macartney[a,b,d], P.B. McIntyre[a,b,d]

Conclusions: These data suggest that the greatest potential impact of pertussis vaccination of adults to prevent severe disease in young infants comes from vaccinating mothers, followed by fathers, with grandparents having a minor role. Siblings varied in importance and, given recent data regarding waning immunity in vaccinated children, need further study. Non-household sources are also well documented, highlighting the potential limitations of the cocoon strategy to prevent severe infant disease.

Vaccine 2013;31:618-25

© 2008 Universitair Ziekenhuis Gent

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

Post-splenectomy and hyposplenic states

Antonio Di Sabatino, Rita Carsetti, Gino Roberto Corazza

Current guidelines recommend immunisation against *H influenzae* type b and *N meningitidis*, for adults and children. The *H influenzae* type b conjugate vaccine was immunogenic in splenectomised patients, although the antibody response was lower and faded more rapidly in these patients than in control individuals.[105] There is no agreement on the need for reimmunisation in children, and a single vaccination in adults seems sufficient.

© 2008 Universitair Ziekenhuis Gent

Di Sabatino A et al, Lancet 2011;378:86

Post-splenectomy and hyposplenic states

Antonio Di Sabatino, Rita Carsetti, Gino Roberto Corazza

For meningococcal immunisation, the conventional tetravalent vaccine protects against strains A, C, Y, and W135 capsular polysaccharides. Independent of T cells, this vaccine has little efficacy in infants younger than 2–3 years,[106] whereas a conjugate vaccine against meningococcal serogroup C is highly immunogenic in the first few months of life and in adults. A single dose of this vaccine is thought to be sufficient,[107] but because revaccination increases the effective antibody response from 80 to 93%, revaccination has been proposed if protective titres are not achieved. The availability of a new tetravalent conjugate meningococcal vaccine[108] might be useful, especially for hyposplenic or splenectomised patients who travel to countries in which *N meningitidis* is hyperendemic or epidemic.

© 2008 Universitair Ziekenhuis Gent

Di Sabatino A et al, Lancet 2011;378:86

SFAR
Société Française d'Anesthésie et de Réanimation

Tableau 2
Récapitulatif des vaccinations chez l'enfant splénectomisé.

Âge de la dysfonction splénique (=M0)	Vaccination à débuter 2 semaines avant la splénectomie ou le traitement immunosupresseur ou 2 semaines après une chirurgie urgente			
	M0	M0+1 mois	M0+2 mois	Rappel (mois)
<2 ans	PCV13 Hib MenC[a]	PCV13 Hib[b,c]	PCV13 Hib[c]	PCV13 (M0+12) Hib (M0+18)[c] MenACYW à l'âge de 2 ans
>2 ans et <5 ans Non vacciné ou vaccination incomplète avec PCV7	PCV13 Hib[d] MenACYW[d]		PCV13	Pneumo23® (M0+2)
>2 ans et <5 ans Vaccination complète avec PCV7	PCV13 Hib[d] MenACYW[d]			Pneumo23® (M0+2)
>2 ans et <5 ans Vaccination complète avec PCV13	Pneumo23® Hib[d] MenACYW[d]			
>5 ans Indépendamment des vaccinations préalables	Pneumo23® Hib[d] Men ACYW[d]			Pneumo23® (M0+3 à 5 ans)

PCV7 : vaccin conjugué 7-valent ; PCV13 : vaccin conjugué 13-valent ; MenC : vaccin méningococcique C conjugué ; MenACYW : vaccin méningococcique conjugué tétravalent.

[a] Injection inutile si l'enfant a plus de 12 à 24 mois.
[b] Injection inutile si l'enfant est âgé de six à 12 mois.
[c] Injection inutile si l'enfant a plus d'un an.
[d] Rappel en cas de contact à risque.

Dahyot-Fizelier C et al, Ann Fran Anesth Reanim 2013;32:251

© 2008 Universitair Ziekenhuis Gent

Fig. 1. Splenectomy immunoprophylaxis flowchart.

Harji DP et al, Int J Surg 2009;7:421

© 2008 Universitair Ziekenhuis Gent

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

5. Infection due to multidrug resistant organisms (MDRO)

- Methicillin resistant *Staphylococcus aureus* (MRSA).
- Extended spectrum betalactamase (ESBL) producing Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, ...).
- Carbapenamase producing Enterobacteriaceae (CPE).
- Vancomycin resistant enterococci (VRE).

© 2008 Universitair Ziekenhuis Gent

Sanfordguide to Antimicrobial Therapy, 23rd BeLux Edition, table 31C.

- Methicillin resistant *Staphylococcus aureus* (MRSA).
  - Screening.
    - Patients with history of MRSA colonization.
    - Patients admitted to at risk unit (ICU, burn unit, hematology/oncology ward, hemodialysis unit, organ transplant unit, ...).
    - Patients transferred from a unit or facility with high MRSA endemicity.
    - Patients transferred from a home for the elderly or a long term care facility.
    - Patients who were in contact with a known carrier.
    - Patients who were hospitalised in the course of 6 months preceding current admission.
    - Patients with chronic wounds or skin or soft tissue infections.
    - Patients in contact with livestock (veterinarians, farmers, ...).

© 2008 Universitair Ziekenhuis Gent

- Methicillin resistant *Staphylococcus aureus* (MRSA).
  - Sampling.
    - Nasal, throat and perineal swab.
    - Extra specimens in special circumstances: wound, urine if patients is catheterised.
  - Patient placement if MRSA-positive.
    - Prioritisation for single patient room.
    - If no single room available: assessment with infection control team.

© 2008 Universitair Ziekenhuis Gent

- Methicillin resistant *Staphylococcus aureus* (MRSA).
  - Patient decontamination if MRSA-positive.
    - Strain is mupirocin susceptible: topical mupirocin (q8h in each nare x 5 days) + (bathing + hair wash) with (chlorhexidine or povidone iodone) soap/shampoo on days 1 and 5 + daily laundering of textiles x 5 days.
    - Strain is mupirocin resistant: topical (chorhexidine 0.12% rinse or tea tree oil or fusidic acid cream or ointment or povidone gel or nitrofurazone gel or polyhecxanide gel) (q8h x 5 days in each nare) + as above.
    - Failure of first attempt: second attempt can be proposed.
    - Gastro-intestinal carriage may be a source of endogenous recolonisation, but no recommendations for SDD.
    - No indication for systemic use of antibacterials (few exceptions to be discussed with infectious disease specialist).

© 2008 Universitair Ziekenhuis Gent

- Methicillin resistant *Staphylococcus aureus* (MRSA).
  - Further measures.
    - Hand hygiene before putting on and after removing gloves.
    - Health care provider personal protective equipment (PPE):
      - ✓ Gloves (non sterile gloves for all interactions with the patient), to be removed before leaving the patient's room (it may be necessary to changes gloves during the care for a single patient to prevent cross contamination between body sites.
      - ✓ Gown: for all interactions with the patient and his/her environment, to be removed before leaving the patient's room.
      - ✓ Mask: to be worn during all contacts with the patient and his environment to reduce the risk for the health care worker of becoming a carrier.
    - Soiled patient care equipment: has to be handled in a manner that prevents the transfer of micro-organisms from the patient to the environment, the health care providers or other persons. People handling visibly contaminated equipment must ware gloves.
    - Textiles and laundry: as for patient care equipment.

© 2008 Universitair Ziekenhuis Gent

- Methicillin resistant *Staphylococcus aureus* (MRSA).
  - Criteria for discontinuing contact precautions.
    - Possible once 3 consecutive negative cultures have been obtained (sampling with 48 hour intervals) on condition patient has not received any antibacterial active against MRSA.
    - May also be maintained until the patient leaves the unit.

© 2008 Universitair Ziekenhuis Gent

- Extended spectrum betalactamase (ESBL) producing Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, ...).
  - Screening.
    - Patients with a history of colonisation by ESBL producing Enterobacteriaceae.
    - Patients admitted to at risk unit (ICU, burn unit, hematology/oncology ward, hemodialysis unit, organ transplant unit, ...).
    - Patients transferred from a unit or facility with high endemicity.
    - Patients who were in contact with a known carrier.
  - Sampling.
    - Rectal swab or stool sample.
    - Urine in presence of urinary catheter.

© 2008 Universitair Ziekenhuis Gent

- Extended spectrum betalactamase (ESBL) producing Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, ...).
  - Patient placement.
    - Single patient room for patients with colonisation due to ESBL peoducing Enterobacteriaceae other than Escherichia coli, hospitalised in at risk unit.
  - Decontamination not recommended.
  - Further measures.
    - Hand hygiene (as above).
    - Health care provider PPE.
      - ✓ Gloves and gown as above.
      - ✓ Mask and eye protection: standard application of protective measures.
      - ✓ Solied patient care equipment, textiles an laundry: as above.
  - Criteria for discontinuing contact precautions.
    - Patient hospitalised in at risk unit: until the patient leaves the unit.
    - Patient transferred to non at risk unit: standard precautions and and and monitoring for appearance of new colonisation.

© 2008 Universitair Ziekenhuis Gent

- Carbapenemase producing Enterobacteriaceae (CPE).
  - Screening.
    - Patients with a history of colonisation by CPE.
    - Patients admitted to at risk unit (ICU, burn unit, hematology/oncology ward, hemodialysis unit, organ transplant unit, ...).
    - Patients transferred from a unit or facility with high CPE endemicity.
    - Patients who were in contact with a known carrier.
  - Sampling.
    - Rectal swab or stool sample.

© 2008 Universitair Ziekenhuis Gent

- Carbapenemase producing Enterobacteriaceae (CPE).
  - Patient placement.
    - Single patient room.
    - Moves and transfers must be limited.
    - If possible, no admission of students or interim staff.
  - Decontamination not recommended.
  - Further measures.
    - Hand hygiene (as above).
    - Health care provider PPE.
      - ✓ Gloves and gown as above.
      - ✓ Mask and eye protection: standard application of protective measures.
      - ✓ Solied patient care equipment, textiles an laundry: as above.
  - ✓ Criteria for discontinuing contact precautions.
    - Contact precautions have to be maintained until the patient leaves the unit.

© 2008 Universitair Ziekenhuis Gent

Vancomycin resistant enterococci (VRE)

- Screening.
  - Patients with a history of colonisation by VRE.
  - Patients transferred from a unit or facility with high VRE endemicity.
  - Patients who were in contact with a known carrier.

- Sampling.
  - Rectal swab or stool sample.

© 2008 Universitair Ziekenhuis Gent

- Vancomycin resistant enterococci (VRE)
  - Patient placement: single room.
  - Decontamination not recommended.
  - Further measures: as above.
  - Criteria for discontinuing contact precautions.
    - Possible once 3 consecutive negative cultures have been obtained (sampling with 1-week intervals).

© 2008 Universitair Ziekenhuis Gent

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

6. Low grade prosthetic joint infection (LG-PJI).

- PJI: cardinal symptoms of inflammation with a wide spectrum of severity.
  - Most patients present with a long indolent course characterised by a progressive increase in joint pain and occasionally by the formation of cutaneous draining sinuses, not by fever, soft tissue swelling or systemic toxicity.
  - Others present with an acute fulminant illness with high fever, severe joint pain, local swelling, erythema, ...
  - Pattern of clinical presentation is determined mostly by 3 factors:
    - Virulence of the infecting pathogen.
    - Nature of the host tissue in which the infecting pathogen grows.
    - Route of infection.

© 2008 Universitair Ziekenhuis Gent

Table I. Micro-organisms associated with prosthetic joint infection[4,5]

Causative micro-organism(s)	Approximate percentage of infections
Gram-positive cocci	~65
coagulase-negative staphylococci	30–43
Staphylococcus aureus	12–23
streptococci	9–10
enterococci	3–7
Polymicrobial	10–20
Gram-negative bacilli (Enterobacteriaceae, *Pseudomonas aeruginosa*)	3–6
Anaerobes (*Propionibacterium* sp., *Peptostreptococcus* sp., *Finegoldia magna*)	2–4
Fungi (*Candida* sp., *Aspergillus fumigatus*, *Histoplasma capsulatum*, *Sporothrix schenckii*)	~1
No organisms isolated from culture	7–11
Other: *Actinomyces israelii*, *Mycoplasma hominis*, *Tropheryma whipplei*, mycobacteria (including *Mycobacterium tuberculosis*), *Brucella* sp., *Corynebacterium* sp., *Granulicatella* sp., *Abiotrophia* sp.	<1

© 2008 Universitair Ziekenhuis Gent

Shuman EK et al; Drugs Aging 2011;28:13-26

6. Low grade prosthetic joint infection (LG-PJI).

- Virulence of the pathogen:
  - *Staphylococcus aureus*, β-hemolytic streptococci and aerobic Gram-negative bacilli: mostly fulminant PJI.
  - Coagulase-negative staphylococci: indolent course.
- Tissue type (support of microbial growth).
  - Wound hematomas, fresh operative wounds, ischemic wounds, tissues in diabetic and corticoid treated patients: favour fulminant course.

© 2008 Universitair Ziekenhuis Gent

Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America[a]

Douglas R. Osmon,[1] Elie F. Berbari,[1] Anthony R. Berendt,[2] Daniel Lew,[3] Werner Zimmerli,[4] James M. Steckelberg,[1] Nalini Rao,[5,6] Arlen Hanssen,[7] and Walter R. Wilson[1]

Clin Infect Dis 2013;56:e1-25

© 2008 Universitair Ziekenhuis Gent

Definition.

- Definite.
  - Presence of sinus tract communicating with the prosthesis.
  - Presence of acute inflammation as seen on histolgical examination of prosthetic tissue (at the time of surgical debridement or prosthetic hardware removal).
  - Presence of purulence without another known etiology surrounding the prosthesis.
  - 2 or more intra-operative cultures or a combination of pre-operative aspiration and intra-operative cultures yielding the same organism.
- Presence of PJI is possible even if the above criteria are not met (judgment after reviewing all the available information).

Clin Infect Dis 2013;56:e1-25

© 2008 Universitair Ziekenhuis Gent

- PJI to be suspected:
  - Sinus tract over a painful joint prosthesis.
  - Chronic painful prosthesis at any time after implantation, particularly in the first years following implantation or if there is a history of prior wound healing problems or superficial or deep infection.
- Evaluation:
  - Thorough history and physical examination.
  - Test for sedimentation rate or C-reactive protein (combination seems to provide best combination .of sensitivity and specificity).
  - Plain radiograph: lack of specificity and sensitivity, but can show other reasons for chronic pain and serve as a baseline. Bone scans, leukocy-te scans, MRI, CT, PET scans should not be routinely used for diagno-sis (expense, lack of availability, image distortion.
  - Diagnostic arthrocentesis (not necessary iunless diagnosis is evident or if surgery is planned and result is not expected to alter management). Synovial fluid analysis: total cell count, differential leukocute count, culture.
  - Blood cultures (aerobic and anaerobic organisms) if fever is present.

Clin Infect Dis 2013;56:e1-25

© 2008 Universitair Ziekenhuis Gent

Figure 1. Preoperative and intraoperative diagnosis of prosthetic joint infection. Abbreviation: CRP, C-reactive protein.

© 2008 Universitair Ziekenhuis Gent

Clin Infect Dis 2013;56:e1-25

Three types of implant infection

Time	0–2 months	3–24 months	Any time
Type	Early postoperative	Delayed (low grade)	Late
Route	Perioperative		Haematogenous
Signs	Fever, effusion, warmth, drainage	Persistent pain, device loosening, fistula	Acute or subacute
Cause	*S. aureus* Streptococci Enterococci	Coagulase-negative staphylococci *P. acnes*	*S. aureus* *E. coli*

Zimmerli W NEJM 2004 Trampuz A Injury 2006

© 2008 Universitair Ziekenhuis Gent

Definition of implant infection

Infrequently used

- Sinus tract (fistula)
- Purulence
  - Wound secretion, pus around prosthesis

Acute inflammation in tissue histology
- ≥1 to ≥10 neutrophils/high-power field

Leukocytes in synovial fluid[1]
- Knee: ≥1.7 x 10^9/l leukocytes, ≥65% neutrophils
- Hip: ≥4.2 x 10^9/l leukocytes, ≥80% neutrophils

- Microbial growth
  - Synovial fluid
  - ≥3 periprosthetic tissue (for low-virulent organisms >1 positive)
  - Sonication fluid (>50 CFU/ml)

[1] Early postoperative (3 months) and inflammatory joint diseases excluded

Comment : 1 of 2 or 3 (not 1 + 2 + 3…)

© 2008 Universitair Ziekenhuis Gent

Joint aspiration

Stop antibiotics 2-3 weeks before aspiration

Important:

1. Native (Gram & Bacteriology)
2. Native (Cristals)
3. Add EDTA (heparin) for determination of cell count (perform within 24 h) and differentiation
4. Inoculation in blood culture bottles for aerob and anaerobs

© 2008 Universitair Ziekenhuis Gent

Liquid medium: + or -

Agar medium (classic culture): quantitative: increasing significance with ↗ colonies

© 2008 Universitair Ziekenhuis Gent

Adaptation of culture techniques

- > 5 samples
- Large volumes to be cultured
- Aerobic + anaerobic, long culture times (10-14 days)

With positivity in low number of samples and low colony numbers: not signicant

Possible interference of antibiotic exposure

© 2008 Universitair Ziekenhuis Gent

dag	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
				1**	1*	7**	1**	1**	1**	1*	1*	3	1	1**	1**					1	1**
					50	1**	1*	1**	1	1**	2			1**	1**					1	1**
					50	100	1	15	1	1				2**	1**						1
					1	40	11	25						1**	1						1
					4	1	1							1							1
					1	1	3							4							
						13	2							2							
						1	5														
						3	3														
						1	30														
						14	30														
						30															
						1															
						100															
						100															

* : in one sample, one medium
** : in one sample

Analysis of P.acnes positive cultures in prosthesis samples (18 months, UZGent

Samples with *, are negative according to literature criteria!!!!**

© 2008 Universitair Ziek

Tentative interpretation in 145 sample series (prosthesis associated samples/biopsies).

Probable/possible infect

- P.acnes 19
- P.aeruginosa 1
- P.aeruginosa (?) 1
- E.coli (?) 1
- P.mirabilis (?) 1
- S.epiderm 2
- S.capitis 1
- Listeria monocytogenes 1

Contaminants

- P.acnes 17
- Micrococcus 4
- S.capitis, haemolyticus, Warneri,hominis : 15
- Corynebacteria, bacillus,… :
- P. fluorescens, acinetobacter : 2
- Candida : 1
- Fusarium, pseudallescheria : 2
- Other 3

(?): extremely small number of colonies

© 2008 Universitair Ziekenhuis Gent

Culture often negative or inconclusive, hence extra techniques

Sonication: biofilm + sonication= high numbers (positive if > 50 col.)
One year experience UZG: moderate extra yield (maybe due to case mix, antibiotic exposure)

© 2008 Universitair Ziekenhuis Gent

Antibiotics and diagnostic sampling

- **Without etiological diagnosis the surgical intervention is of most importance :** and should be done without previous antibiotic treatment **(if treatment is already going on the 'holiday' should not be 2 days, but weeks (2 weeks or more) : anyway if (chronic) infection is expected, don't start AB treatment before surgey, you have to explore anyway**

- **Otherwise : each surgical intervention creates a 'porte d'entree' for new bacteria, (interventions should b limited) and prophylaxis should be given 'lege artis' (30 minutes before the intervention):** 2 recent studies demonstrate that one 'shot' of antibiotics does not render diagnostic culture negative

© 2008 Universitair Ziekenhuis Gent

Figure 2. Effect of Preoperative Antimicrobial Therapy on Culture Sensitivity in Patients with Prosthetic-Joint Infection.

Multiplex PCR (SeptiFast) in sonication fluid of PJI

Achermann Y et al. *J Clin Microbiol* 2010

PCR: extra positives
if previous antibiotic exposure

Diagnosis of PJI

- **Acute infection: each pos sample indicates pathogen**
- **Chronic infection by "skin microorganisms": problems with sensitivity and specificity**
  - Joint punction: not only in blood culture medium, but also routine sample to lab
  - Surgical joint exploration :
    - 5-6 samples, < (2?) 3 or more with skin commensal: to be considered negative
    - Sonication of prosthesis : < 50 colonies: negative
  - Interpretation of skin commensals remains problematic: little clinical or biologic base for conclusion
  - Antibiotics interfere with yield (sensit en specif)
  - Team management (infectio+microb+ treating physician)

© 2008 Universitair Ziekenhuis Gent

Treatment concept 2014

Trampuz A, Borens O. RMS 2011

© 2008 Universitair Ziekenhuis Gent

- **Surgical strategies.**
  - Retention.
  - 1-stage (direct exchange) strategy.
  - 2-stage exchange strategy.
  - Permanent resection arthroplasty.
  - Amputation.

- **Medical treatment.**
  - After debridement and retention.
  - Following 1-stage exchange.
  - Following resection, planned staged reimplantation.
  - Following amputation.

© 2008 Universitair Ziekenhuis Gent

Clin Infect Dis 2013;56:e1-25

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

7. Use of macrolides for invasive pneumococcal infections and risk of resistance.

TABLE 3M
BACTERIAL RESISTANCE IN BELGIUM: *STREPTOCOCCUS PNEUMONIAE*
PART 2: INVASIVE STRAINS, DATA FROM 2007 UNTIL 2011
(DATA FROM THE NATIONAL REFERENCE CENTER: JAN VERHAEGEN, UNIVERSITAIRE ZIEKENHUIZEN LEUVEN, LEUVEN)

YEAR	NUMBER OF STRAINS TESTED	PENICILLIN		CEFOTAXIME		OFLOXACIN		ERYTHROMYCIN		TETRACYCLINE	
		% I[1]	% R[1]	1% I[1]	% R[1]	% I[1]	% R[1]	% I[1]	% R[1]	% I[1]	% R[1]
2007	1,726	6.7%	3.4%	0.5%	0.2%	0.2%	0.4%	0.1%	25.2%	0.9%	22.2%
2008	1,870	8.4%	0.8%	0.3%	0.0%	0.1%	0.2%	0.0%	25.4%	0.8%	23.1%
2009	2,043	5.7%	1.6%	0.1%	0.05%	0.05%	0.15%	0.05%	24.1%	0.5%	23.9%
2010	1,993	7.5%	2.2%	0.9%	0.05%	0.%	0.25%	0.1%	25.4%	0.8%	24.9%
2011	1,998	9.8%	1.9%	0.3%	0.1%	0.1%	0.25%	-	26.8%	0.3%	27.3%

1. % I = percentage of intermediately susceptible strains versus total number of strains tested.
   % R = percentage of resistant strains versus total number of strains tested.

Worldwide, macrolide resistance has increased considerably over the last decade. Resistance rates (S. Pneumoniae) as well as resistance mechanisms vary depending on the location [highest in Japan (80 to 100%), lowest in Scandinavia (8 to 9%)].

Altenburg J et al, Respiration 2011;81:75-87

© 2008 Universitair Ziekenhuis Gent

Table III. Pathogen- and host-directed anti-inflammatory activities of macrolides

Target	Mechanism of anti-inflammatory action
Pathogen	Inhibition of the production of bacteria-derived, proinflammatory mediators (toxins, adhesins, biofilm, quorum sensors)
Structural cells of the host (epithelial cells, fibroblasts, airway smooth muscle cells)	Inhibition of cytokine/chemokine production, particularly interleukin-8
Monocytes/macrophages	Inhibition of production of reactive oxidant species and cytokines/chemokines[a]
Neutrophils	Inhibition of the generation of reactive oxidant species and adhesion to vascular endothelium; induction of apoptosis[a]

Feldman C et al, Drugs 2011;71:131-53

© 2008 Universitair Ziekenhuis Gent

Immunomodulatory effects of macrolide antibiotics: mechanisms (are consistent across different disease models and individual macrolides).

Fig. 1. Cellular and noncellular effects of macrolides. 1 = Attenuation of biofilm function; 2 = suppression of bacterial quorum sensing; 3 = decrease in bacterial adherence; 4 = loss of flagellar mobility; 5 = reduced production of bacterial toxins; 6 = consolidation of epithelial tight junctions; 7 = increasing ciliary beat frequency; 8 = reduction of sputum quantity; 9 = diminished sputum viscosity; 10 = inhibition of the synthesis of proinflammatory agents by bacteria, eosinophils, neutrophils, and epithelial cells; 11 = reduction of neutrophil chemotaxis; 12 = stimulation of neutrophil degranulation; 13 = acceleration of neutrophil apoptosis; 14 = downregulation of adhesion molecules; 15 = stimulation of phagocytosis by alveolar macrophages; 16 = reduction of T cell numbers and T cell migration; 17 = modulation of dendritic cell function.

Altenburg J et al, Respiration 2011;81:67-74

© 2008 Universitair Ziekenhuis Gent

- **Development of macrolide resistance during long term macrolide therapy.**
  - No increase in R after 3 months of maintenance therapy for COPD (***Banerjee D et al, Respir Med 2005;99:208-15***) and rhinosinusitis (***Wallwork B et al, Laryngoscope 2006;16:189-93***).
  - Long term use in cystic fibrosis patients.
    - Retrospective study: macrolide resistance in all *Staphylococcus aureus* isolates obtained from 100 patients after azithromycin treatment during mean of 3.5 years (***Tamper-Stranders GA et al, Pediatr Infect Dis J 2007;26:8-12***).
    - 98.2% of *Streptococcus pneumoniae* isolates recovered from 57 patients showed macrolide resistance after 4 years of erythro- or clarithromycin maintenance therapy (***Kasahara K et al, J Infect Chemother 2005;11:112-4***).

© 2008 Universitair Ziekenhuis Gent

- Increase in macrolide resistance in respiratory pathogens (clinical significance is ?).
- Parallel increase in oropharyngeal carriage of macrolide-resistant commensals:
  - usually do not cause infection in healthy persons.
  - could cause infection in immunocompromised patients.
  - might transfer resistance to pathogenic bacteria.
- Scientific evidence to justify long term use of macrolides is quite good in the case of COPD, cystic fibrosis and diffuse panbronchiolitis but lacking in non cystic fibrosis bronchiectasis, sinusitis and asthma.
- The combination of excellent cell and tissue penetration, antimicrobial and anti-inflammatory activities appear to account for the apparent efficacy of macrolides as adjuncts to β-lactams in the treatment of severe pneumococcal pneumonia.
- Study results show a beneficial effect on exacerbation frequency, sputum volume, inflammatory markers (COPD). Low dose macrolides should be applied for at least 3 months to establish and maintain these advantageous effects.
- Cave toxicity of long term use.
- Currently: search for new macrolides with potent immunomodulatory effects and without antimicrobial activity.
- Need for prospective clinical trials.

Cameron EJ et al, Clin Experiment Allergy 2012;42:1302-12

Feldman C et al, Drugs 2011;71:131-53

Altenburg J et al, Respiration 2011;81:67-87

© 2008 Universitair Ziekenhuis Gent

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

8. Protective role of asymptomatic bacteriuria.

The Role of Asymptomatic Bacteriuria in Young Women With Recurrent Urinary Tract Infections: To Treat or Not to Treat?

Tommaso Cai,[1] Sandra Mazzoli,[2] Nicola Mondaini,[3] Francesca Meacci,[2] Gabriella Nesi,[4] Carolina D'Elia,[1] Gianni Malossini,[1] Vieri Boddi,[5] and Riccardo Bartoletti[3]

Clin Infect Dis 2012;55:771-7

© 2008 Universitair Ziekenhuis Gent

Figure 1. Study schedule according to the Consolidated Standards of Reporting Trials (CONSORT) group recommendations.

Clin Infect Dis 2012;55:771-7

© 2008 Universitair Ziekenhuis Gent

Inclusion criteria:

- Female gender.
- Aged 18 to 40 years.
- Sexually active, regular intercourse, single partner for ≥ 12 months.
- At least 1 episode of symptomatic UTI treated within 12 months of current episode of asymptomatic bacteriuria (AB) and last symptomatic UTI at least & month prior to enrollment.
- Asymptomatic at enrollment.
- Urine culture with at least 10^5 CFUs/ml of uropathogens (enteric Gram-negative rods, enterococci, *Staphylococcus saprophyticus*, group B streptococci).

Exclusion criteria:

- Pregnancy, lactation.
- Menopause.
- Concomitant presence of major diseases (diabetes, liver failure, renal failure, known anatomical anomalies of the urinary tract, beutropenia, symptoms of acute UTI, ...).
- Recent (< 4 weeks) administration of any kind of antibiotic.
- Vaginitis, cervicitis.
- Positive test for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, HSV 1 and 2, HPV.
- Positive culture for multiple pathogens.

Clin Infect Dis 2012;55:771-7

© 2008 Universitair Ziekenhuis Gent

Materials, methods, considerations.

- AB at enrollment = at least 10^5 CFUs/ml of the same uropathogen in 2 clean-catch midstream urine samples collected over 2 consecutive days from an asymptomatic woman.
- 2 groups with (1:1) simple randomisation.
  - Group A: no treatment (no placebo, non blinded trial).
  - Group B: treatment with antibiotic selected in accordance with the results of the antibiogram.

    Duration of therapy in accordance with antibiotic used.
- Follow-up visits at 3, 6 and 12 months after enrollment (regardless of reported symptoms). Extra visits in case of symptomatic recurrence.
- Principal outcome measure: recurrence free rate at the end of the study period.

- 2

Clin Infect Dis 2012;55:771-7

© 2008 Universitair Ziekenhuis Gent

Table 2. Clinical and Microbiological Data at Each Follow-up Visit

	Follow-up Visit			
	Baseline (Enrollment)	First (3 months)	Second (6 months)	Third (12 months)
Group A				
Symptomatic	0	11	23	41
Asymptomatic	312	301	278	237
QoL score (±SD)	0.82 ± 0.03	0.79 ± 0.07	0.81 ± 0.06	0.82 ± 0.03
No bacterial growth	0	15 (4.9)	27 (9.7)	31 (13.1)
Escherichia coli	120 (38.4)	107 (35.7)	68 (24.4)	26 (11.0)
Enterococcus faecalis	102 (32.7)	101 (33.7)	149 (53.5)	177 (74.7)
Enteroccocus faecium	38 (12.2)	30 (10.0)	10 (3.5)	1 (0.4)
Klebsiella spp	19 (6.1)	18 (6.0)	9 (3.4)	...
Streptococcus agalactiae	17 (5.5)	15 (4.9)	7 (2.6)	...
Serratia spp	16 (5.1)	12 (3.9)	5 (1.7)	1 (0.4)
Proteus mirabilis	...	3 (0.9)	2 (0.8)	1 (0.4)
Pseudomonas spp	...	...	...	...
Citrobacter spp			1 (0.4)	
Group B				
Symptomatic	0	32	98	169
Asymptomatic	361	329	231	62
QoL score	0.81 ± 0.06	0.50 ± 0.01	0.52 ± 0.01	0.51 ± 0.02
No bacterial growth	0	27 (8.2)	21 (9.0)	19 (30.7)
E. coli	142 (39.3)	131 (39.8)	142 (61.5)	17 (27.5)
E. faecalis	120 (33.2)	92 (27.9)	36 (15.6)	11 (17.8)
E. faecium	47 (13.1)	45 (13.6)	10 (4.3)	3 (4.8)
Klebsiella spp	22 (6.1)	19 (5.8)	6 (2.7)	...
Streptococcus agalactiae	16 (4.5)	8 (2.4)	5 (2.2)	...
Serratia spp	14 (3.8)	7 (2.3)	6 (2.7)	...
Proteus mirabilis	...	...	2 (0.8)	4 (6.4)
Pseudomonas spp	...	...	...	3 (4.8)
Citrobacter spp	...	...	3 (1.2)	5 (8.0)

Data are No. (%) unless otherwise specified.

Abbreviations: QoL, quality of life; SD, standard deviation.

Clin Infect Dis 2012;55:771-7

© 2008 Universitair Ziekenhuis Gent

Figure 3. Kaplan-Meier curve analysis performed to calculate the probability of being recurrence-free between the 2 groups. Abbreviations: RR, relative risk; SE, standard error.

Clin Infect Dis 2012;55:771-7

© 2008 Universitair Ziekenhuis Gent

- **Findings.**
  - Treatment of AB in patients affected by recurrent UTI is associated withwith a higher rate of symptomatic UTI over 1 year.
  - Modification of isolated bacteria after an antibiotic treatment (e.g. In cases of AB due to Enterococcus faecalis, growth of MDR Escherichia coli could be found, independent from yhe antibiotic chosen.

- **Conclusion.**
  - AB should not be treated when found in young women affected with recurrent UTI.

Clin Infect Dis 2012;55:771-7

© 2008 Universitair Ziekenhuis Gent

Asymptomatic Bacteriuria—Shift of Paradigm

Florian M. E. Wagenlehner[1] and Kurt G. Naber[2]

In conclusion, well-performed clinical and basic molecular studies have changed our understanding of ABU completely during the last 50 years. ABU is now considered a generally benign and sometimes even protective condition. Not to treat ABU in general (except during pregnancy and before invasive intervention of the urinary tract), and especially not in young women with recurrent UTI as shown by Cai et al (this issue), is highly recommended and should become the standard of care.

Clin Infect Dis 2012;55:778-80

© 2008 Universitair Ziekenhuis Gent

BACTERIURIA (ASYMPTOMATIC)

See also ref 1L.6, ref 1L.7, ref 1L.8.

- Screening for asymptomatic bacteriuria.
  - Recommended:
    - for pregnant women.
    - before an invasive genito-urinary procedure with risk of mucosal bleeding.
    - in kidney transplant recipients during first 6 months after transplantation (screening beyond first 6 months is not recommended).
  - Not recommended for premenopausal non pregnant women, postmenopausal women, women with diabetes, healthy men, older people living in the community, residents of long term care facilities, patients with an indwelling urinary (urethral or suprapubic) catheter or undergoing intermittent catheterization (has to be distinguished from catheter associated urinary tract infection), patients with nephrostomy tubes or ureteral stents, patients with spinal cord injury, patients with candiduria.
  - No recommendation can be made for screening or treatment of asymptomatic bacteriuria in patients with neutropenia.

Bacteriuria (asymptomatic): patients undergoing invasive genito-urinary tract procedures with risk of mucosal bleeding.
See also page 195 (urologic surgery).

° Gram-negative bacilli ° group B[15] streptococci		No empirical therapy, choice of antibacterial agent has to be based on results of culture and susceptibility testing. **Duration of (documented) antibacterial therapy[12]:** 3 days.

Bacteriuria (asymptomatic): pregnant woman.
See also ref 1L.9.

° Gram-negative bacilli ° group B[15] streptococci		If screening result is positive, pregnant women must be treated (ref 1L.10). No empirical treatment, choice of antibacterial agent must be based on results of culture and susceptibility testing (see also table 35). **Screening.** →
		- All pregnant woman must be screened for asymptomatic bacteriuria (ref 1L.11) at 12 to 16 weeks of gestation or at the first prenatal consultation (if later) and during third trimester of pregnancy [the optimal frequency of urine testing during pregnancy is uncertain (ref 1L.12)]. - Pregnant women must be rescreened monthly after first episode of asymptomatic bacteriuria (or have to be treated continuously until delivery). **Duration of (documented) antibacterial therapy[12].** - Fosfomycin: single dose. - Nitrofurantoin and nifurtoinol: 3 to 5 days (not to be used in patients with G6PD deficiency). - TMP-SMX[8]: 3 to 5 days (should not be used during first trimester of pregnancy and administration should be stopped 14 days before expected date of delivery). - Betalactams: 3 to 5 days.

Bacteriuria (asymptomatic): other patients than those mentioned page 75 (pregnant woman and patients undergoing invasive genito-urinary tract procedures with risk of mucosal bleeding) **such as preschool children, patients with neurogenic bladder** [for treatment of symptomatic bacteriuria in these patients, see page 78 (urinary tract infection in adult: acute, complicated, afebrile cystitis in patients with underlying disease)], **patients with indwelling urinary tract catheter** (has to be distinguished from catheter associated urinary tract infection), ...
No symptoms, no culture, no treatment.

No symptoms, no culture, no treatment.

Sanfordguide to Antimicrobial Therapy, 23rd BeLux Edition, pages 75-76

© 2008 Universitair Ziekenhuis Gent

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

Epidemiology of positive serologic tests in "peillaboratoria" in Belgium between 1993 and 2014

WIV-ISP (validated by BVIKM)

© 2008 Universitair Ziekenhuis Gent

Geografic spread of positive serological tests (per 100 000 inhabitants) in surveillance laboratories between 1993 and 2013 per administrative zone in Belgium

WIV-ISP (validated by BVIKM)

© 2008 Universitair Ziekenhuis Gent

Positive serological tests in surveillance laboratories between 1993 and 2013 per age group and gender in Belgium

WIV-ISP (validated by BVIKM)

© 2008 Universitair Ziekenhuis Gent

Hospitalisations for Lyme disease (ICD9) between1999 and 2010, Minimale Klinische Gegevens, Belgium

WIV-ISP (validated by BVIKM)

© 2008 Universitair Ziekenhuis Gent

Clinical stages of Lyme disease

1. Early localised infection (stage 1 or primary Lyme borreliosis): erythema migrans with locoregional lymphadenopathy, rarely Borrelia lymhocytoma

2. Early disseminated infection (stage 2 or secondary Lyme borreliosis): multiple erythema migrans, early neuroborreliosis, carditis, arthritis, ocular manifestations, facial nerve palsy, ...

3. Late disseminated infection (stage 3 or tertiary Lyme): acrodermatitis atrophicans (Pick Herxheimer), arthritis, late neuroborreliosis, ...

4. “Chronic” Lyme disease, “post Lyme syndrome”

© 2008 Universitair Ziekenhuis Gent

Definition of “chronic Lyme disease”

- Not clearly defined, controversial entity or concept
- Terminology to be avoided?
- “Post Lyme syndrome”
  - Aspecific symtoms, occurring after adequate antimicrobial treatment of a patient with correct initial diagnosis: fatigue, musculoskeletal pain, concentration and memory problems, headache, …
  - Terminology proposed for patients, in whom symptoms persist/ are present for at least 6 months

© 2008 Universitair Ziekenhuis Gent

Box 1. Proposed definition of post-Lyme disease syndrome

Inclusion criteria

An adult or child who has a documented episode of early or late Lyme disease fulfilling the case definition of the Centers for Disease Control and Prevention; if based on erythema migrans, the diagnosis must be made and documented by an experienced health care practitioner.

After treatment of the episode of Lyme disease with a generally accepted treatment regimen, there is resolution or stabilization of the objective manifestation(s) of Lyme disease.

Onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a 6-month period after completion of antibiotic therapy:

- Fatigue
- Widespread musculoskeletal pain
- Complaints of cognitive difficulties

Subjective symptoms are of such severity that, when present, they result in substantial reduction in previous levels of occupational, educational, social, or personal activities.

Marques A, Infect Dis Clin North Am 2008;22:341.

© 2008 Universitair Ziekenhuis Gent

Exclusion criteria

An active, untreated, well-documented coinfection, such as babesiosis

The presence of objective abnormalities on physical examination or on neuropsychological testing that may explain the patient's complaints

A diagnosis of fibromyalgia or chronic fatigue syndrome before the onset of Lyme disease

A prolonged history of undiagnosed or unexplained somatic complaints, such as musculoskeletal pains or fatigue, before the onset of Lyme disease.

A diagnosis of an underlying disease or condition that might explain the patient's symptoms

Laboratory or imaging abnormalities that might suggest an undiagnosed process distinct from post–Lyme disease syndrome

Although testing by either culture or polymerase chain reaction for evidence of *Borrelia burgdorferi* infection is not required, should such testing be done by reliable methods, a positive result would be an exclusion.

Marques A, Infect Dis Clin North Am 2008;22:341.

© 2008 Universitair Ziekenhuis Gent

Table 3. Evidence against Active Infection in Patients with Subjective Symptoms Persisting for More Than 6 Months after Antibiotic Treatment for Lyme Disease.

Signs and symptoms

Absence of concomitant objective clinical signs of either disease or inflammation and no progression to objective signs or development of inflammation[29,32]

Similar symptoms common in persons who have never had Lyme disease[24,25,30,31,48]

Laboratory tests

Persistence of symptoms independently of persistent seropositivity[20,29,32,47]

Absence of either positive cultures or positive polymerase-chain-reaction results from clinical specimens[32,40]

Treatment

No substantive response to antibiotic therapy in controlled treatment trials[32-34]

No documented resistance of *Borrelia burgdorferi* to recommended antibiotics[2]

Absence of recognized risks for failure of antibiotic therapy; these include host immunodeficiency or an infection in which there is local ischemia, a foreign body (biofilm), a sequestrum, or an abscess[2]

Other evidence

Certain studies in animals[2]

Lack of precedent for the use of long-term antibiotic treatment in other spirochetal infections[23,49]

Feder HM et al,
N Engl J Med 2007;357:1422.

No proof that vague/aspecific symptoms occur more frequently in this patient group as compared with the general population.

No known physiopathological mechanism that may explain this entity. Different possibilities have been dismissed (auto-immunity, disturbed cytokine production, impaired host defense, …) hitherto without clear conclusions.

Benefit of longstanding or repeated antibiotic therapy not proven. Unnecessary exposure of the patient to possible toxicity, side effects and development of resistant bacteria.

© 2008 Universitair Ziekenhuis Gent

Category 1	Category 2	Category 3	Category 4
Symptoms of unknown cause, with no evidence of *Borrelia burgdorferi* infection	A well-defined illness unrelated to *B. burgdorferi* infection	Symptoms of unknown cause, with antibodies against *B. burgdorferi* but no history of objective clinical findings that are consistent with Lyme disease	Post–Lyme disease syndrome

Figure 1. The Four Predominant Categories of Disease Associated with Chronic Lyme Disease.
Only patients with category 4 disease have post–Lyme disease symptoms.

Feder HM et al, N Engl J Med 2007;357:1422.

© 2008 Universitair Ziekenhuis Gent

Diagnostic tests

- **Clinical and epidemiological context dominant**
- **Serology important in later stages of illness**
- **IgM interpretable within 6-8 weeks after exposure**
- **Enzyme-immunoassay (EIA) and immunoblot standard in which 3 generations**
  - 1st generation sonicate of B burgdorferi sensu lato and intact bacteria: false positive reactions
  - 2nd generation: less aspecific reactions
  - 3rd generation: specific recombinant antigens of B b s.l or synthetic peptide C6
  - Specificity IgG 80-95 %; sensitivity in Europe lower
  - Higher specificity immunoblot
- **LTT: not standardized and validated for B burgdorferi and consequently not recommended**
- **PCR: tool in diagnosis of cutaneous and articular manifestations**
- **PCR: low value in neurologic disease (sensitivity 10-50 %); no clear value for blood, serum or plasma**

© 2008 Universitair Ziekenhuis Gent

Interpretation of serology

- Seroprevalence of Borrrelia may increase up to 50% in certain regions or groups (job or leisure in nature)
- To avoid serology in absence of specific clinical signs (e.g. persistent fatigue, aspecific diffuse longstanding pain,…)
- Prolonged positive serology, even after antibiotherapy, without indication for control (no parameter of illness activity); cave overinterpretation of serology in general)
- Reinfection possible: IgG↗ in association with manifestations of Lyme borreliosis

© 2008 Universitair Ziekenhuis Gent

Interpretation of serology

- Erythema migrans: clinical diagnosis; no indication of serological confirmation (sensitivity IgG and IgM ± 50%; 70% of followup after 4 weeks); abortive response after antibiotherapy)
- When in doubt: skin biopsy with suggestive APD
- Borrelia lymfocytoma: serology often positive; sensitivity 70% and with negative initial result seroconversion in the short term; skin biopsy only in case of uncertain diagnosis; PCR sensitivity 67%
- Early neuroborreliosis: IgM/IgG generally positive; within 3 weeks 21%, after 6 weeks 90%; until 98% at control at least 4 weeks after 1st serology

© 2008 Universitair Ziekenhuis Gent

Interpretation Borrelia serology

- CSF: pleiocytosis (lymphocytosis) + moderate ↗ lymphocytosis + CSF index + limited sensitivity of PCR on CSF (10-50 %)
- Carditis: generally pos serology (> 80 %) with high IgG titers
- Lyme arthritis: always pos serology with high IgG; PCR on joint fluid
- Late neuroborreliosis: always pos serology on blood; CSF + medical imaging always abnormal
- ACA: always pos serology with high IgG + specific APD

© 2008 Universitair Ziekenhuis Gent

- Consider classical syndromes as key for a diagnosis of Lyme
- However, take atypical presentations into account and a (restrictive interpretation of) a grey zone, certainly in combination with a positive serology
- Emphasize the reliability of conventional serology and avoid the trap of sophistic reasoning/thought, typical for the chronic Lyme hype
- Consider in the grey zone a single classic treatment schedule/regimen for Lyme with maximum 1 month of doxycycline or ceftriaxone
- Avoid non-contributory/unhelpful discussions on the interpretation of negative vs positive serology/PCR/LTT
- Avoid the trap of following patient expectations in the sympathic mode; stay empathic but true to evidence based medicine

© 2008 Universitair Ziekenhuis Gent

- Affirmatory reassurance on the basis of a solid general internal medicine assessment
- Offering of an alternative explanatory model, with the advice to abandon the unhelpful search and fixation of/on a pure and simple biologic explanation
- Try to facilitate a bridge towards a biopsychosocial model of care

© 2008 Universitair Ziekenhuis Gent

ADVICE TO CLINICIANS

How should clinicians handle the referral of symptomatic patients who are purported to have chronic Lyme disease? The scientific evidence against the concept of chronic Lyme disease should be discussed and the patient should be advised about the risks of unnecessary antibiotic therapy. The patient should be thoroughly evaluated for medical conditions that could explain the symptoms. If a diagnosis for which there is a specific treatment cannot be made, the goal should be to provide emotional support and management of pain, fatigue, or other symptoms as required.[54-56] Explaining that there is no medication, such as an antibiotic, to cure the condition is one of the most difficult aspects of caring for such patients. Nevertheless, failure to do so in clear and empathetic language leaves the patient susceptible to those who would offer unproven and potentially dangerous therapies.

Feder HM et al,
N Engl J Med 2007;357:1422.

© 2008 Universitair Ziekenhuis Gent

1. Infection in patient with pain pump.
2. Antimycotics in patient with invasive aspergillosis.
3. Use of tigecycline after FDA warning.
4. Vaccination against pertussis in pregnant women.
5. Vaccination after splenectomy
6. Prevention of infection due to MDRO.
7. Low grade infections.
8. Use of macrolides for invasive pneumococcal infections and risk of resistance.
9. Protective role of asymptomatic bacteriuria.
10. Chronic Lyme: how to deal adequately with the hype
11. Bundle approach of S aureus bacteremia

© 2008 Universitair Ziekenhuis Gent

Epidemiology SAB

Top 3 pathogens bacteremia

1. *E. coli*
2. *S. aureus*
3. *S. pneumoniae*

Laupland, CMI 2013

© 2008 Universitair Ziekenhuis Gent

- **Complications of SAB**
  - Risk of metastatic infection
  - Endocarditis (up to 25% of patients with catheter)
  - Osteomyelitis/spondylodiscitis
  - Renal abscess
  - Splenic abscess
  - Splinter hemorraghe

© 2008 Universitair Ziekenhuis Gent

Kathib & Sharma, Medicine 2013
Naber, CID 2009

Antibiotherapy in SAB

- Uncomplicated vs complicated?
- MSSA or MRSA?

1. MSSA uncomplicated: Flucloxacillin 6x2g IV, at least 14d
2. MRSA uncomplicated (or IgE-mediated allergy Beta-lactams): Vancomycin or Linezolid

3. Complicated infection

    - MSSA-endocarditis: **aortic/mitral**: 4-6w Flucloxacillin, 3-5d Gentamicin
    - MSSA-endocarditis: **tricuspid**: 2w Flucloxacillin if +3-5d Gentamicin or 4w Flucloxacillin
    - **MRSA**-endocarditis: 4-6w Vancomycin+ 3-5d Gentamycin
    - **Osteomyelitis**: 6-8w therapy

© 2008 Universitair Ziekenhuis Gent

The Sanford Guide to antimicrobial therapy 2012-2013
Chong et al, Antimicrob Agents Chemother 2013

A) Sepsis met vermoeden van een Gram-positieve infectie

1. Hemoculturen afnemen
2. Empirische antibioticatherapie opstarten
   - beta-lactam
   - beta-lactam in combinatie met vancomycine i.g.v.
     - kritisch zieke patiënten
     - patiënten met een verhoogd risico voor MRSA-infecties

B) Positieve hemoculturen voor *Staphylococcus aureus*

Antibioticabeleid	Katheterbeleid	Echocardiografie
1. Keuze antibioticum ***MSSA:*** Flucloxacilline (FLOXAPEN®): • Posologie volwassene: 6 x 2 g IV • Posologie kinderen: 200mg/kg/d IV in 6x (max. dagdosis: 8g) <u>Opm:</u> IgE gemedieerde allergie: Vancomycine (VANCOCIN ®) of linezolid (ZYVOXID®) ***MRSA:*** Vancomycine (VANCOCIN®): • Posologie volwassenen:15 mg/kg oplaaddosis, vervolgens 30 mg/kg/24u in continu infuus (cfr schema intranet) • Posologie kinderen: 20mg/kg oplaaddosis, vervolgens 40mg/kg over 24u Linezolid (ZYVOXID®) • Posologie volwassenen: 2 x 600 mg IV of PO • Posologie kinderen: raadpleeg kinderinfectioloog • Enkel terugbetaling na voorafgaandelijke behandeling met vancomycine **2. Duur therapie** Twee weken of langer te behandelen afhankelijk van katheterbeleid en echocardiografie.	**Perifeer of centraal veneuze katheter:** ***Ongecompliceerd verloop:*** Verwijder katheter en behandel ≥ 14 dagen met systemisch antibioticum ***Gecompliceerd verloop:*** Verwijder katheter en behandel 4 à 6 weken met systemisch antibioticum (6 à 8 weken i.g.v. osteomyelitis) **Permanente katheter of intravasculair device:** ***Ongecompliceerd verloop:*** Verwijder katheter/device (tenzij sterk contra-indicatie) en behandel ≥ 14 dagen met systemisch antibioticum Bij behoud van de katheter/device, behandel 4 weken met systemisch en AB-lock therapie (vancomycine AB-lock (3 ml) met vancomycine 0,5 mg/ml + heparine 100 UI/ml) ***Gecompliceerd verloop:*** Verwijder katheter/device en behandel 4 à 6 weken met systemisch antibioticum (6 à 8 weken i.g.v. osteomyelitis)	Echocardiografie minstens één keer binnen de 2 weken uitvoeren. • Snel bij het klinisch vermoeden van endocarditis • Vóór het stoppen van de antibiotica-therapie (dag 10 tot 14) voor het uitsluiten van latente endocarditis Sneller bij volgende risicofactoren: • Persisterende koorts/bacteriëmie • Community-acquisition • Klepprothesen en abnormaliteiten, onderliggende hartziekte, voorgeschiedenis van endocarditis • Ongekende bron/onverwijderde bron • IV druggebruik <u>Opm:</u> 1. TEE (transoesofagale echocardiografie) krijgt steeds de voorkeur op TTE (transthoracale echocardiografie) (tenzij contra-indicatie). 2. Positieve TEE duidt op endocarditis ->therapie 4 à 6 weken aanhouden 3. Bij blijvende koorts -> hemoculturen herhalen

© 2008 Universitair Ziekenhuis Gent

Glims 8.10.9

Start Record Bewerken Weergave Venster Context Help

http://vuziis5/labview/scripts/lab/labviewcwsctx.asp?...

Afnamedatum en uur	Stopgezet			
Staal Specificatie	Stopgezet			
Staal Specificatie	Hemokultuur aeroob			
Kweek (isolaten, ABgram...)	Stopgezet			
Haemokultuur resultaat	Negatief			Val

140130-2913 30/01/2014 21:20 INT04 1002109589

Staal Specificatie	Anaer.Portacath- Set1			
Staal Specificatie	Hemokultuur anaeroob			
Kweek (isolaten, ABgram...)	Stopgezet			
Haemokultuur resultaat	Negatief			Val

140130-2912 30/01/2014 21:19 INT04 1002109589

Staal Specificatie	Aer.Portacath - Set 1			
Staal Specificatie	Hemokultuur aeroob			
	UZG-MFC-J-010 Richtlijn behandeling			
Kweek (isolaten, ABgram...)	1: : Staphylococcus aureus.			Val
Antibiogram		1		Val
	Methicilline/oxacilline	S		
	Penicilline	R		
	Cotrimoxazol	S		
	Erythromycine	S		
	Rifampicine	S		
	Clindamycine	S		
	Nitrofurantoine	S		
	Gentamycine	S		

140129-1913 29/01/2014 11:00 INT04 1002109589

Staal Specificatie	insteekplaats PEG sonde, etter				
Staal Specificatie	Uitstrijkje				
Gramkleuring	WBC ++ gram+ coccen +++ difteroide staafjes +-				Val
Kweek (isolaten, ABgram...)	1: : Staphylococcus aureus ++ 2: : Klebsiella pneumoniae + 3: : Streptococcus anginosus groep (syn S. milleri) ++				Val
Antibiogram		1	2	3	Val
	Methicilline/oxacilline	S			
	Penicilline	R			
	Ampicilline		R	S	
	Cotrimoxazol	S	S		
	Erythromycine	S			
	Vancomycine			S	
	Rifampicine	S			
	Clindamycine	S		S	

Catheter management

- Catheter to be removed asap
- If not possible
  - In case of permanent/difficult to remove catheter (difficult access)
  - Consider **antibiotic lock**
  - Principle of high antibiotic concentrations (for SAB: Vancomycin 5 mg/mL) in catheter lumen when not in use
  - In combination with systemic therapy
- Fernandez-Hidalgo et al: 45% failure in SAB (9/20)

The Sanford Guide to antimicrobial therapy 2012-2013
Fernandez-Hidalgo et al, JAC 2006

© 2008 Universitair Ziekenhuis Gent

ABS kwaliteitsindicatoren

- **EU project "ABS International - Implementing antibiotic strategies for appropriate use of antibiotics in hospitals in member states of the European Union"**
  - 2006-2008
  - Co-financiering door de EU, DG Health and Consumer Protection
- **Doel: ontwikkeling en validatie van kwaliteitsindicatoren m.b.t. AB**
  - www.abs-international.eu
- **Wetenschappelijke coördinator: Marc Struelens**

© 2008 Universitair Ziekenhuis Gent

SAB: 3 procesindicatoren

- **Percentage patiënten die een TTE of TEE ondergingen binnen de 10 dagen na aanvang van de SAB (community-acquired)**
- **Percentage patiënten bij wie de katheter (PK of CVC of PAC) verwijderd werd binnen de 10 dagen na aanvang van de SAB (indien katheter aanwezig bij aanvang)**
- Percentage met een methicilline-gevoelige SA (MSSA) die minstens 10 dagen IV Beta-latam AB toegediend kregen

© 2008 Universitair Ziekenhuis Gent

Resultaten UZG

Universitair Ziekenhuis Gent

© 2008 Universitair Ziekenhuis Gent

Resultaten 2013

- 10 maand (1/1/2013-1/11/2013)
- 64 episodes
- Exclusie van 6 episodes (< 18j, palliatieve setting, overleden binnen de 5d)
- 58 episodes: 9 MRSA (15%) - 49 MSSA
- Actievere rol MIT

- Resultaten AB en katheterverwijdering goed
- “Pijnpunt”: echo cor

© 2008 Universitair Ziekenhuis Gent

Resultaten 2013: echo cor

- 49/58 echo cor
- 23/58 na 10-14 dagen
- 17/58 < 10 dagen, bij 3 o.w.v. kliniek,
- 9/48 > 14 dagen

- Moeten alle patiënten met SAB wel een echo cor krijgen??

© 2008 Universitair Ziekenhuis Gent

Echo cor bij SAB

Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

Cost-Effectiveness of Transesophageal Echocardiography To Determine the Duration of Therapy for Intravascular Catheter–Associated *Staphylococcus aureus* Bacteremia

Allison B. Rosen, MPH; Vance G. Fowler Jr., MD; G. Ralph Corey, MD; Stephen M. Downs, MD, MS; Andrea K. Biddle, PhD; Jennifer Li, MD; and James G. Jollis, MD

- Bij ongecompliceerde kathetergerelateerde SAB
- Geen info over eventuele andere metastatische infecties
- Wellicht niet bruikbaar bij IV-druggebruik, permanente intravasculaire devices, immuungecompromitteerde patiënten
- Wellicht enkel bruikbaar bij gunstige klinische evolutie

© 2008 Universitair Ziekenhuis Gent

Rosen et al, Ann Int med 1999

Echo cor bij SAB

Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

Management of *Staphylococcus aureus* bacteremia and endocarditis: progresses and challenges

Winfried V. Kern

- Bij **community-onset SAB**, IV druggebruik, persisterende bacteriëmie, permanente IV devices, hemodialyse

IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children: Executive Summary

- Bij alle volwassenen met SAB

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

Kern, Curr Opin Infect Dis 2010
Mortara & Bayer, Infect Dis Clin North Am 1993
Liu et al, Clin Infect Dis 2011

© 2008 Universitair Ziekenhuis Gent

Echo cor bij SAB

Use of a Simple Criteria Set for Guiding Echocardiography in Nosocomial *Staphylococcus aureus* Bacteremia

Achim J. Kaasch,[1] Vance G. Fowler Jr.,[5] Siegbert Rieg,[4] Gabriele Peyerl-Hoffmann,[4] Hanna Birkholz,[2] Martin Hellmich,[3] Winfried V. Kern,[4] and Harald Seifert[1]

- Retrospectieve analyse van 2 prospectieve SAB-cohortes
  - INSTINCT (n=304)
  - SABG (n=432)
- Criteria
  - Langdurige bacteriëmie (> 4d)
  - Permanent intracardiaal device
  - Hemodialyse
  - Spinale infectie
  - Non-vertebrale osteomyelitis

Kaasch et al, CID 2011
Seifert et al, Dtsch Med Wochenschr 2008
Fowler et al, Arch Intern Med 2003

© 2008 Universitair Ziekenhuis Gent

Figure 1. Flow diagram of patients recruited in the Invasive *S. aureus* Infection Cohort (INSTINCT) cohort.

© 2008 Universitair Ziekenhuis Gent

Kaasch et al, CID 2011

Figure 2. Flow diagram of patients recruited in the *S. aureus* Bacteremia Group (SABG) cohort.

Kaasch et al, CID 2011

Universitair Ziekenhuis Gent

Table 3. Sensitivity, Specificity, and Positive and Negative Predictive Values of the Clinical Prediction Criteria Set

Variable	Percentage (95% CI)	
	INSTINCT	SABG
Sensitivity	100 (77.2–100)	97.5 (87.1–99.9)
Specificity	28.5 (23.6–34)	31.6 (27.2–36.4)
Positive predictive value	5.9 (3.5–9.8)	12.7 (9.4–16.9)
Negative predictive value	100 (95.6–100)	99.2 (95.6–100)

NOTE. Ninety-five percent confidence intervals (CIs) were determined on the basis of the Wilson method. INSTINCT, Invasive *Staphylococcus aureus* Infection Cohort; SABG, *S. aureus* Bacteremia Group

Figure 3. Relative frequency of infective endocarditis by number of positive criteria (error bars denote exact 95% confidence intervals) in the Invasive *S. aureus* Infection Cohort (INSTINCT; $n = 304$) and *S. aureus* Bacteremia Group (SABG; $n = 432$) cohorts. *P* values refer to intragroup (INSTINCT and SABG) comparisons of the relative frequency of infective endocarditis by the number of positive criteria (determined by the Fisher exact test).

Kaasch et al, CID 2011

Echo cor bij SAB: MIT

- Criteria
  - Langdurige bacteriëmie (> 4d)
  - Permanent intracardiaal device
  - Hemodialyse
  - Spinale infectie
  - Non-vertebrale osteomyelitis
  - Kleplijden/endocarditis in de VG

- Geen onderscheid tussen CA, HCA of NOSO
- Belang van de correcte timing
- TEE > TTE
- Ongevraagd consult
- Systematische follow-up

© 2008 Universitair Ziekenhuis Gent

A) Sepsis met vermoeden van een Gram-positieve infectie

1. Hemoculturen afnemen
2. Empirische antibioticatherapie opstarten
   - beta-lactam
   - beta-lactam in combinatie met vancomycine i.g.v.
     - kritisch zieke patiënten
     - patiënten met een verhoogd risico voor MRSA-infecties

B) Positieve hemoculturen voor *Staphylococcus aureus*

Antibioticabeleid	Katheterbeleid	Echocardiografie
1. Keuze antibioticum ***MSSA:*** Flucloxacilline (FLOXAPEN®): • Posologie volwassene: 6 x 2 g IV • Posologie kinderen: 200mg/kg/d IV in 6x (max. dagdosis: 8g) Opm: IgE gemedieerde allergie: Vancomycine (VANCOCIN ®) of linezolid (ZYVOXID®) ***MRSA:*** Vancomycine (VANCOCIN®): • Posologie volwassenen:15 mg/kg oplaaddosis, vervolgens 30 mg/kg/24u in continu infuus (cfr schema intranet) • Posologie kinderen: 20mg/kg oplaaddosis, vervolgens 40mg/kg over 24u Linezolid (ZYVOXID®) • Posologie volwassenen: 2 x 600 mg IV of PO • Posologie kinderen: raadpleeg kinderinfectioloog • Enkel terugbetaling na voorafgaandelijke behandeling met vancomycine **2. Duur therapie** Twee weken of langer te behandelen afhankelijk van katheterbeleid en echocardiografie.	**Perifeer of centraal veneuze katheter:** ***Ongecompliceerd verloop:*** Verwijder katheter en behandel ≥ 14 dagen met systemisch antibioticum ***Gecompliceerd verloop:*** Verwijder katheter en behandel 4 à 6 weken met systemisch antibioticum (6 à 8 weken i.g.v. osteomyelitis) **Permanente katheter of intravasculair device:** ***Ongecompliceerd verloop:*** Verwijder katheter/device (tenzij sterk contra-indicatie) en behandel ≥ 14 dagen met systemisch antibioticum Bij behoud van de katheter/device, behandel 4 weken met systemisch en AB-lock therapie (vancomycine AB-lock (3 ml) met vancomycine 0,5 mg/ml + heparine 100 UI/ml) ***Gecompliceerd verloop:*** Verwijder katheter/device en behandel 4 à 6 weken met systemisch antibioticum (6 à 8 weken i.g.v. osteomyelitis)	Echocardiografie minstens één keer binnen de 2 weken uitvoeren. • Snel bij het klinisch vermoeden van endocarditis • Vóór het stoppen van de antibiotica-therapie (dag 10 tot 14) voor het uitsluiten van latente endocarditis Sneller bij volgende risicofactoren: • Persisterende koorts/bacteriëmie • Community-acquisition • Klepprothesen en abnormaliteiten, onderliggende hartziekte, voorgeschiedenis van endocarditis • Ongekende bron/onverwijderde bron • IV druggebruik Opm: 1. TEE (transoesofagale echocardiografie) krijgt steeds de voorkeur op TTE (transthoracale echocardiografie) (tenzij contra-indicatie). 2. Positieve TEE duidt op endocarditis ->therapie 4 à 6 weken aanhouden 3. Bij blijvende koorts -> hemoculturen herhalen

© 2008 Universitair Ziekenhuis Gent