24th ECCMID Barcelona, Spain 10 – 13 May 2014

Educational Workshop

EW12: Bloodstream infections: opportunities for outcome improvement

Arranged with the ESCMID Study Group for Bloodstream Infections and Sepsis (ESGBIS)

Convenors: **Esther Calbo (Barcelona, ES)**

Winfried V. Kern (Freiburg, DE)

Faculty: **Martin Sundqvist (Orebro, Sweden)**

Pilar Retamar Gentil (Seville, Spain) - no handout available

Sibel Ascioglu (Ankara, Turkey)

Winfried V. Kern (Freiburg, Germany) - no handout available

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Rapid Diagnostic Tests and Early Reporting

Martin Sundqvist
MD, PhD

Clinical Microbiology,
Dept of Laboratory Medicine, University Hospital
Örebro, Sweden

Educational workshop. ECCMID 2014.
Bloodstream infections: opportunities for outcome improvement

Disclosures

- Lectures for
  - Abbott Diagnostics (Sweden)
- Research projects in collaboration with
  - BD/Kiestra
  - Q-linea
  - Luminex

The patient with sepsis

- Comes to the ER 24/7/365
- Is severely ill!
- Will benefit from rapid institution of antibiotics

But!

- The patient does not always arrive at the ”correct” hospital
- The personnel do not always have the right incentives to handle the samples correctly
- Increasing antibiotic resistance puts emphasis on tailored therapy
- The laboratory is not always open 24/7/365

WHAT MAKES A RAPID TEST RAPID?

Pre analysis

- Transports
- Knowledge
- Opening hours
- External Blood-culture cabinets
- Decentralized ER laboratories
- Electronic referrals

In the lab

- Opening hours
- Dedicated staff
- Knowledge
- Prioritize the diagnosis of sepsis
- Reports
  - Electronic
  - Transparent
  - Preliminary
  - Telephone

In the ward

- Electronic chart systems
- Knowledge
- Consultants available for instant discussion regarding antibiotic therapy

What you can do on monday

- Make your automated blood culture system available for the introduction of vials 24/7/365
  (van der Welden 2010, Schneiderhan 2013)
- ”Active culturing”

WHAT IS AVAILABLE IN SEPSIS DIAGNOSTICS?

Tests in the ER

- History of the patient!
- Clinical Investigation

- CRP
- PCT
- WBC, neutrophils
- Lactate
- Etc…

Dynamic tests – To be followed over time!

BLOOD CULTURE

Automated Blood-culture systems

- Aerobic and anaerobic culture
  - Pediatric, Mycosis?
- Several systems
  - BacTAlert (Biomerieux)
  - BacTec (BD)
  - VersaTrek (ThermoFischer)

Rapid ID from positive BC vials (1)

- PCR for a range of pathogens
  - The most common pathogens
  - Some resistance genes
  - 2-6h to ID
- Broad range PCR
  - At least 2-6 hours to ID
  - Needs sequencing
- Quick-FISH (PNA-FISH)
  - Gram stain 10 min
  - Quick-FISH 20 min
  - The most common pathogens in smaller panels (Calderaro CMI 2013)

Rapid ID from BC vials (2)

- MALDI-TOF (direct method)
  - 10-30 min
- ”Active culturing” and MALDI-TOF
  - Rapid incubation on nutritious agar in different environments
  - 3 hours at its best to species ID

MALDI-TOF and Sepsis

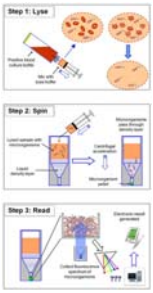
- Positive Blood culture
- Centrifugation and extraction steps (10-30 min)
- Lower limit for genus/species ID has been suggested.

- ID obtained in 66 - 99% (Martiny CMI 2012, Lagacé-Wiens 2012, Klein 2012, Machen PLoS One 2014, Schieffer JAM 2014)

- Impact of Rapid ID
  - Time to species ID 84→56h
    - time to effective tx 30→20h
    - time to optimal tx 90 → 47h (Huang CID 2013)
  - Change of treatment in 13% of adults.
    - 37% helpful in peadiatrics as the result showed contamination. (Martiny CMI 2013)
  - 58h earlier report if 24/7 introduction of BC vials and MALDI 24/7. (Schneiderhan Clin Chem 2013)

In pipeline

- Intrinsic fluorescens



Walsh mBio 2013

But don´t forget!

- Gram stain
- Agglutination tests
- Rapid coagulase test
- Other culture results!

- And microbiologistics!!

SPECIES ID DIRECTLY FROM BLOOD

ID before enrichment

Antigentests

- Pneumococci (urine, CSF)
- Legionella (urine)
- Meningococci (CSF)

- Limited sensitivity
- Acceptable specificity
- Predicitive value?

Nucleic acid detection

- SeptiFast, Roche
- SepsiTest, Molzym
- Magicplex, Seegene
- Vyoo, Bionity
- Inhouse methods

- Limited sensitivity
- Acceptable specificity
- Predicitive value?

NAT directly from blood

Benefit

- Could decrease time to Species ID
- Less problem with insignificant pathogens
- Limited Species-panels
- Can detect bacteria after ab-tx is initiated
- Could be of value for ”Rule-In” diagnostics

Draw back

- Low Sensitivity!
  - 1 – 1.5 mL whole blood
- Will be batched → reduce the speed.
- Needs trained personell.
- Sometimes a second sequencing step is needed.

In pipeline

PlexID (Abbott)

- Lysis and Extraction 2h
- PCR 2h
- ESI-MS and interpretation 70 min
- 6-8h

SUSCEPTIBILITY TESTING IN SEPSIS

General aspects of AST

- Resistance detection ≠ Susceptibility testing
- So far no techniques with high sensitivity for detection of resistance mechanisms directly from blood sample
- All commercial and/or molecular systems are less dynamic to local epidemiology

Molecular techniques

- Detects well known resistance mechanisms
- Well validated for MRSA
- Some panels for Carbapenemases and ESBLs
- Some specific assays for VRE

Phenotypic AST

- Susceptibility testing
- DD or Gradient strip
  - 6-8h
    (Jonasson et al Poster ECCMID 2014, Sundqvist et al, manuscript, Eurostar project)
- Automated
  - 16h (5-16h)
    (Wimmer JCM 2012, Machen PLoS One 2014)

Disk Diffusion

- Directly from BC-vials
  - Non-standardised inocloum
  - Over night incubation or short as below
- Eurostar Rapid Disk
  - EUCAST methodology (www.eucast.org)
  - BUT! Short incubation time.
    - Enterobacteriaceae (6h)
    - Pseudomonas, Enterococci, *S.aureus* (8h)
    - *Haemophilus influenzae* and *Pneumococci* (8h)

Sundqvist et al Posters at ECCMID 2012, 2013, 2014
Manuscripts in progress

In pipeline

- MALDI-TOF (Jung et al EJCMID 2013)
- Microcalorimetry (Braissant et al JCM 2014)
- Combined Broth Dilution and PCR → AST

Future perspectives

- Molecular based detection from whole blood
  - Black box
  - Random access
  - Affordable
  - If accomplished: preliminary report in 6-8h?
- Culture (usually positive within 20h)
  - MALDI-TOF + rapid DD → definitive report in <30h?

Future perspectives

- Microbiology lab
  - Open 24/7/365
  - Skilled staff 24/7/365
  - Don´t forget other samples from the critically ill patient
  - Take control of the transport organization and the referrals!

Questions?

OPTIMIZING THE TREATMENT OF BLOOD STREAM INFECTIONS

Sibel Ascioglu, MD, ScD

Plan

1. Host factors
2. Source
3. Empirical treatment
4. Directed treatment-role of MIC
5. Escalation vs. de-escalation
6. Duration
7. Special cases

Any modifiable host factor?

- TPN - consider stopping, changing to enteral
- Neutropenia - consider growth factors
- Chemotherapy/immunosuppressive trt- stop?
- CVC-Is it still necessary?

Source of BSI

- ★Vascular access
- Lung
- Abdomen
- Genitourinary tract
- Any local infection……

Source control – ASAP

- Identification if unknown
- Implementation of source control measures
  - Drain the abscess
  - Tissue debridment
  - Remove intravascular device
    - Exchange vs complete removal

Empirical treatment

- Local epidemiology is the most important guide

Important considerations

- Bactericidal vs. bacteriostatic
- Covering MDR or not?
- Combination vs. monotherapy

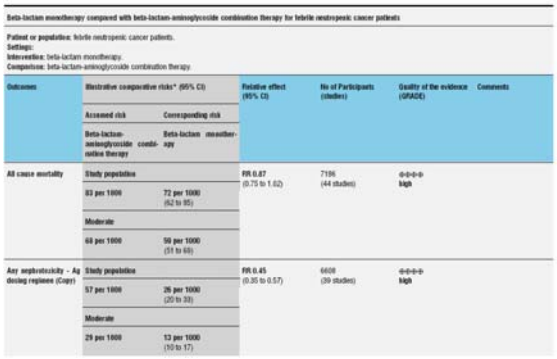
Kumar A et al. Crit Care Med 2010;38:1651

Covering MDR empirically

- Depends on local epidemiology
- Recommended in
  - Severly ill
  - Septic shock
  - Neutropenic
  - History of colonization
  - End-stage liver disease

Mermel et al. CID 2009;49:1-45

Combination vs. monotherapy?

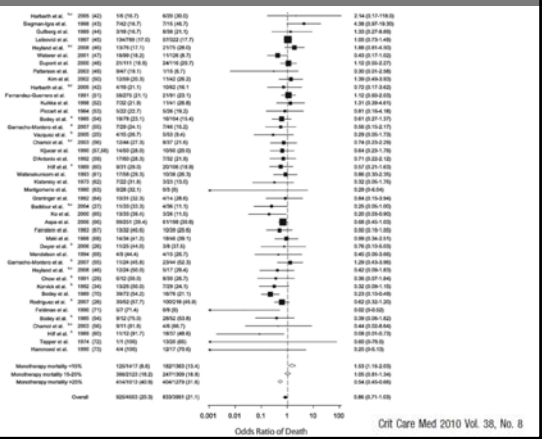


Beta-lactam monotherapy compared with beta-lactam-aminoglycoside combination therapy for febrile neutropenic cancer patients

Patient or population: febrile neutropenic cancer patients.
Settings:
Intervention: beta-lactam monotherapy
Comparison: beta-lactam-aminoglycoside combination therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Beta-lactam-aminoglycoside combination therapy	Beta-lactam monotherapy				
All cause mortality	Study population		RR 0.87 (0.75 to 1.02)	7186 (44 studies)	⊕⊕⊕⊕ high	
	83 per 1000	72 per 1000 (62 to 85)				
	Moderate					
	68 per 1000	59 per 1000 (51 to 69)				
Any nephrotoxicity - Aminoglycoside containing regimens (Copy)	Study population		RR 0.45 (0.35 to 0.57)	6608 (39 studies)	⊕⊕⊕⊕ high	
	57 per 1000	26 per 1000 (20 to 33)				
	Moderate					
	29 per 1000	13 per 1000 (10 to 17)				

Paul et al. Beta-lactam vs. beta-lactam AG combination The Cochrane Coll. 2014, issue 2



Crit Care Med 2010 Vol. 38, No. 8

Directed therapy

- Adjustment after culture results become available
- Narrow the spectrum
- Choose bactericidal if possible
  - Change vancomycin with a β-lactam if MSSA
- Consider PK/PD

Taccone et al. Critical Care 2010, 14:R126
http://ccforum.com/content/14/4/R126

CRITICAL CARE

RESEARCH Open Access

Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock

- Recommended doses of piperacillin-tazobactam, cefepime and ceftazidime provided serum drug concentrations during the first 24 hours of treatment that were insufficient to cover *P. aeruginosa* and other less susceptible bacteria
- Recommended doses of meropenem resulted in adequate concentrations in 75% of patients
- In patients treated with piperacillin-tazobactam, renal dysfunction is associated with a better adequacy of drug concentrations compared with normal renal function.
- Therapeutic drug monitoring is necessary to optimize β-lactam concentrations as no clinical or biological variable can predict β-lactam concentrations in this population.

Pharmacokinetics of β-lactams

- Activity of β-lactams predominantly time-dependent
- Requires serum and tissue antibiotic concentrations above MIC of the pathogen to achieve adequate killing
- This effect is independent of peak levels
- Maximum killing occurs when serum concentrations are maintained above the MIC for extended periods

Pharmacokinetics in sepsis

- During severe sepsis and septic shock, increased volume of distribution and cardiac output can reduce serum drug concentrations, whereas decreased protein binding and end-organ dysfunction induce higher antibiotic levels
- Optimizing antibiotic dosage strategy should involve PK parameters, but therapeutic drug monitoring is necessary in septic patients because large inter-individual PK variations make it difficult to predict antibiotic levels

Taccone et al. Critical Care 2010, 14:R126
http://ccforum.com/content/14/4/R126

Table 4: Probability of target T >4 × MIC attainment for various MICs

MIC (μg/mL)	Target concentration (μg/mL)	Adequate PK N (%)			
		meropenem (n = 16)	ceftazidime (n = 18)	cefepime (n = 19)	piperacillin-tazobactam (n = 27)
32	128	0	0	0	1 (4)
16	64	0	0	1 (5)	**12 (44)**
8	32	0	**5 (28)**	**3 (16)**	15 (56)
4	16	3 (18)	14 (78)	7 (36)	21 (78)
2	8	**12 (75)**	18 (100)	15 (79)	25 (93)
1	4	15 (94)	18 (100)	17 (90)	27 (100)
0.5	2	16 (100)	18 (100)	19 (100)	27 (100)

Data are expressed as counts (percentage). In bold: MIC corresponding to European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for *Pseudomonas aeruginosa*.
MIC, minimal inhibitory concentration; PK, pharmacokinetics.

Therapeutic Drug Monitoring (TDM)

- β-lactams are the most commonly prescribed antibacterials in the critically ill
- Primarily hydrophilic, with a low volume of distribution, and predominantly renally excreted.
- Bacterial killing is considered time dependent,
- Duration the free drug concentration remains above MIC
- Ideally this should be 90% to 100% of the dosing interval, with maximal bacterial killing achieved at concentrations 4-5 times the MIC

TDM or Not?

- A number of studies have concluded that many tests for therapeutic drug monitoring may be inappropriate owing to lack of indication, redundancy, improper collection, and improper interpretation!

What Proportion of Vancomycin Trough Levels Are Drawn Too Early?

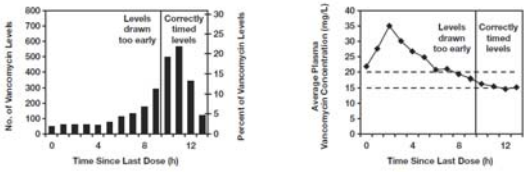
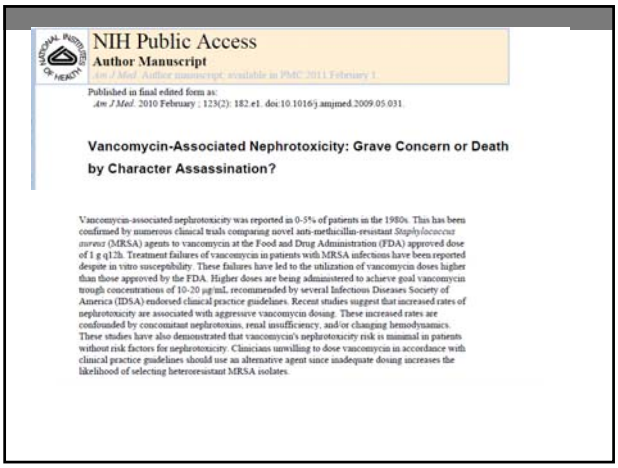


Table 2B
Effect of Sample Timing on Plasma Vancomycin Concentration and Clinical Actions*

Characteristic	Early Levels (n = 1,875)	Correctly Timed Levels (n = 1,522)	P
Plasma vancomycin concentration (mg/L)†	22.1 ± 11.7	15.5 ± 8.6	< .001
Vancomycin levels (mg/L)			
>20	578 (53.8)	395 (26.0)	< .001
15-20	214 (19.9)	334 (21.9)	NS
<15	283 (26.3)	793 (52.1)	< .001
Clinical action taken in response			
Held, decreased, or discontinued dose	275 (25.6)	326 (21.4)	< .02
Dose increase	76 (7.1)	206 (13.5)	< .001
Repeat vancomycin level only; no dosing adjustment	312 (29.0)	304 (20.0)	< .001

NS, not significant.
* Values are given as mean ± SD or number (percentage).

Ascioglu - Optimising therapy



NIH Public Access
Author Manuscript
Am J Med. Author manuscript; available in PMC 2011 February 1.

Published in final edited form as:
Am J Med. 2010 February ; 123(2): 182.e1. doi:10.1016/j.amjmed.2009.05.031.

Vancomycin-Associated Nephrotoxicity: Grave Concern or Death by Character Assassination?

Vancomycin-associated nephrotoxicity was reported in 0-5% of patients in the 1980s. This has been confirmed by numerous clinical trials comparing novel anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents to vancomycin at the Food and Drug Administration (FDA) approved dose of 1 g q12h. Treatment failures of vancomycin in patients with MRSA infections have been reported despite in vitro susceptibility. These failures have led to the utilization of vancomycin doses higher than those approved by the FDA. Higher doses are being administered to achieve goal vancomycin trough concentrations of 10-20 μg/mL recommended by several Infectious Diseases Society of America (IDSA) endorsed clinical practice guidelines. Recent studies suggest that increased rates of nephrotoxicity are associated with aggressive vancomycin dosing. These increased rates are confounded by concomitant nephrotoxins, renal insufficiency, and/or changing hemodynamics. These studies have also demonstrated that vancomycin's nephrotoxicity risk is minimal in patients without risk factors for nephrotoxicity. Clinicians unwilling to dose vancomycin in accordance with clinical practice guidelines should use an alternative agent since inadequate dosing increases the likelihood of selecting heteroresistant MRSA isolates.

De-escalation of treatment

- There is no adequate direct evidence as to whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis, severe sepsis or septic shock.
- This uncertainty warrants further research via RCTs and the authors are awaiting the results of an ongoing
- RCT testing the de-escalation of empirical antimicrobial therapy for severe sepsis.