EARLY LABORATORY BIOMARKERS FOR SEPSIS PREDICTION: ROLE OF BD GLUCAN IN NEONATOLOGY
RANI LABORATORIJSKI BIOMARKERI ZA PREDIKCIJU SEPSE: PRIMENA BD GLUKANA U NEONATOLOGIJI

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QUOTES FROM SEPSIS.ORG

- In the United States, more than 75,000 children develop severe sepsis each year.
- This works out to about 200 per day and the number is increasing by 8% every year.
- Almost 7,000 of these children die – this is more than those who die of pediatric cancers. Sepsis in the developing world is even more serious, causing many more deaths.
- Many children who survive sepsis are left with long-term problems. More than 1 in 3 children (34%) who survive are left with a change in cognitive skills still at 28 days following their discharge from the hospital.
- Nearly half (47%) need to be readmitted to the hospital at least once after surviving sepsis.

WHICH CHILD HAS SEPSIS?

- Child is not the same as it used to be, say parents.
- Child does not want to eat or drink, he/she is irresponsive, say parents.
- Might have fever.

ADVICE TO PARENTS

- If in doubt, bring a child to a paediatrician.

SIGNS AND SYMPTOMS OF NEONATAL SEPSIS

- Body temperature changes, Breathing problems
- Diarrhea, Low blood sugar
- Reduced movements, Reduced sucking
- Seizures
- Slow heart rate
- Swollen belly, Vomiting
- Yellow skin and whites of the eyes (jaundice)

SIGNS OF SEPSIS IN CHILDREN INCLUDE

- High fever
- General illness or a previous injury, such as a scrape or cut
- Shortness of breath
- Very rapid heart beat
- Drop in or no urine output

STEPS IN HOSPITAL

- Time is ticking
- You have less than 1 hour to give antibiotic.
- Take all necessary samples for microbiology before antibiotic.
- Do not wait with antibiotic till you get all the results from the lab or from radiology department.
- You can still discontinue antibiotic when you get the results.
- Biomarkers?

NEONATUS THAT WILL BE ADMITTED TO ICU – DIAGNOSTIC PROCEDURES

- To be more certain that child has sepsis, we can use biomarkers.
- WBC or CRP lack specificity, CRP is good for follow up.
- PCT good for follow up but has specificity problems because it is raised when visceral organs are damaged.
- nCD64 is currently the best biomarker for severe bacterial infection but doing it 24/7 is expensive, need flow cytometer
- Affordable option is sCD14-ST

LATE-ONSET SEPSIS OCCURS AT 4-90 DAYS OF LIFE AND IS ACQUIRED FROM THE CAREGIVING ENVIRONMENT.

CONS, Staphylococcus aureus, Enterobacteriacea like E coli

Pseudomonas

Candida

GBS

Acinetobacter

Anaerobes

INVASIVE FUNGAL INFECTION IS RARE EVENT IN CHILDREN UP TO ONE YEAR OLD

- We rarely see it.
- It is always a surprise
- Symptom and signs are unspecific.
- Neonatal sepsis is hard to recognize
- Differentiation between bacterial or fungal infection is even harder.
- IFI has the same signs as severe bacterial infection. Children with impaired immune system and hospitalized with risk factors might get IFI.
- Pneumocystis pneumonia (PCP) can also be a colonization of upper respiratory tract.

5 YEARS DETECTION OF CANDIDA SPP. FROM BLOOD CULTURES

BC taken	BC positive	Age (days)	Isolate	Ag in serum
27.01.2012	04.02.2012	222	Candida utilis	BG< 8o
23.04.2012	28.04.2012	10	Candida albicans	
22.09.2012	27.09.2012	268	Candida parapsilosis	BG >500
10.07.2013	15.07.2013	108	Candida albicans	
08.10.2013	14.10.2013	13	Candida albicans	
05.07.2015	07.07.2015	9	Candida albicans	
12.10.2015	16.10.2015	18	Candida albicans	
30.12.2015	02.01.2016	491	Candida albicans	
27.04.2016	02.05.2016	22	Candida albicans	BG>500, galaktomanan >9
21.05.2016	25.05.2016	38	Candida albicans	
14.08.2017	19.08.2017	1	Candida albicans	

ROLE OF 1,3 – B – D-GLUCAN (BG) IN INVASIVE FUNGAL INFECTION (IFI) AND PCP IN ADULTS

- PCP sen 96%, spec 84% and AOC 0.96
- IFI sen 80%, spec 82% and AOC 0.88.
- Conclusion

The diagnostic accuracy of the BG assay is high for PJP and moderate for IFI. Because the sensitivity for PJP is particularly high, the BG assay can be used as a screening tool for PJP.

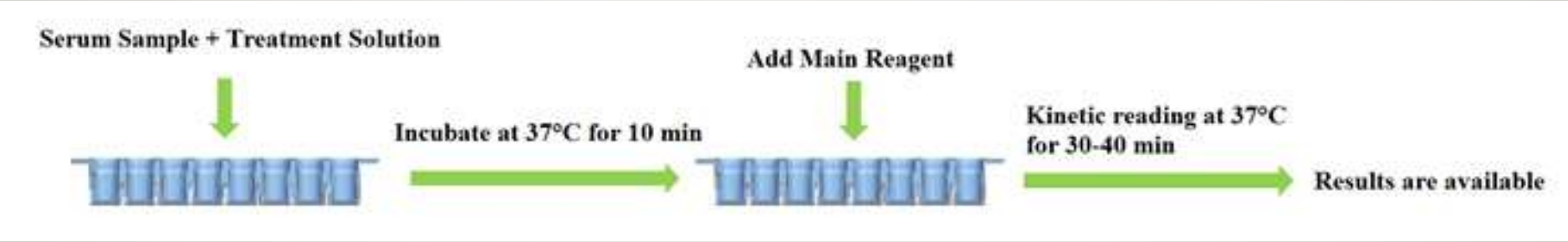
Onishi A, JCM 2012

BG IN NEONATES OR CHILDREN

- Not enough studies!
- Current recommendations do not include BG as a useful marker for diagnostic or follow up.
- But on the other hand the same situation 10 years ago in adults.

ASSAYS FOR BG

- Commercially available kits for the detection of BG from clinical specimens:
- Fungitell assay (Associates of Cape Cod, Inc., Falmouth, MA), Fungitec G-test (Seikagaku Corporation, Tokyo, Japan) and Fungus (1-3)-β-D-Glucan Assay (DNK, China).



ASSAYS FOR RESEARCH USE ONLY

- Endosafe PTS glucan assay (Charles River, USA).

PNEUMOCYSTIS JIROVECII PNEUMONIA IN CHILDREN

- First cases published in 70s - children with ALL.
- Children are almost all colonized with the fungi in the upper respiratory tract.
- If we find Pneumocystis DNA in lower tract, concentrations of amplified DNA are low and we must always rule out colonization or contamination of the sample while taking it.

PCP IN CHILDREN - CASE FROM OUR LAB

- 4 years old child with ALL on chemotherapy.
- Presented in acute respiratory distress that needed intubation and ICU treatment.
- Sample from upper respiratory tract positive for P. jirovecii DNA (Ct 31 – intermediate concentrations of DNA), BG > 523 pg/ml.
- Does this child have PCP?

PCP IN CHILDREN - CASE FROM OUR LAB

- Lower respiratory tract sample negative for P. jirovecii DNA.
- Child has severely damaged intestinal mucosa because of the chemotherapy.
- Blood cultures all negative for Candida spp., Candida found in faeces.
- Trimetoprim/sulfametoksazol therapy for PCP was introduced, but child‘s condition did not improve.
- Question of resistance to trimetoprim/sulfametoksazol was raised.

PROPHYLAXIS OR BETTER DIAGNOSTICS IN NEONATES

- Prophylaxis prevents some invasive fungal infections (C. albicans) but resistance to azoles and shift to non - C. albicans yeast is always near.
- Diagnostics takes time, you get results after several days.
- Blood cultures are not sensitive enough, BG assays are expensive.
- Prophylaxis also influences PCR, antimicotic therapy even more.

AS A CONCLUSION

Septic child – take blood cultures – give ATB - try to rule out bacterial infection – wait for 2 to 3 days before you swich antibiotic – on day 5 start thinking about antimicotic – take blood cultures, urine, take whole blood for PCR, take serum for BG – give antimicotic – when you get back the results from the lab and BG is negative – **patient in front of you most probably does not have invasive candida infection** – if patient is still septic, do pan Candida PCR from whole blood - search for others reason for deteriorating health - de-escalate or stop antimicotics especially if PCR is negative.

Antimicotic might help if BG concentrations in serum are high.