

## Rapid detection of *S. pneumoniae*

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## Rapid & point-of-care tests for *S. pneumoniae*

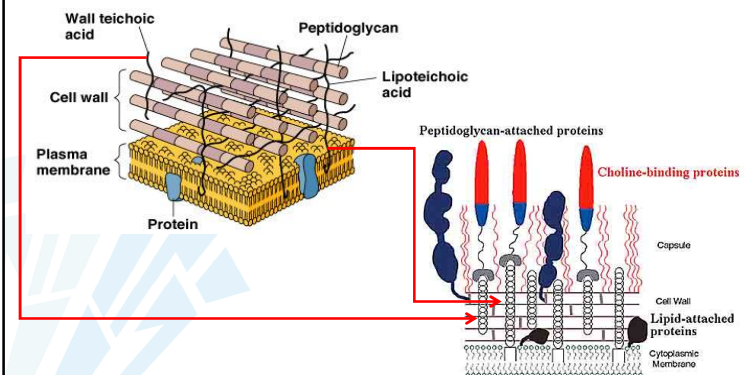
- Aim :
  - prevent misuse of antibiotics & rapid institution of antibiotic therapy
  - reduce costs, length of stay, improve outcome
  - Specific settings : after hours, emergency departments
- Which tests ?
  - Sputum Gram-stain : 57% sens, 97% spec if high quality sample before start Tx
  - PCR : varying sens depending on sample, high specificity but not yet rapid format
  - Latex : low sensitivity, high rate false-positives

## Binax *S. pneumoniae* antigen tests

- Detection of pneumococcal C-polysaccharide antigen
  - Immunochromatographic method (ICT)
  - Very simple in use
  - 15 min TAT
  - Designed for non-concentrated urine
  - Can also be used with other samples

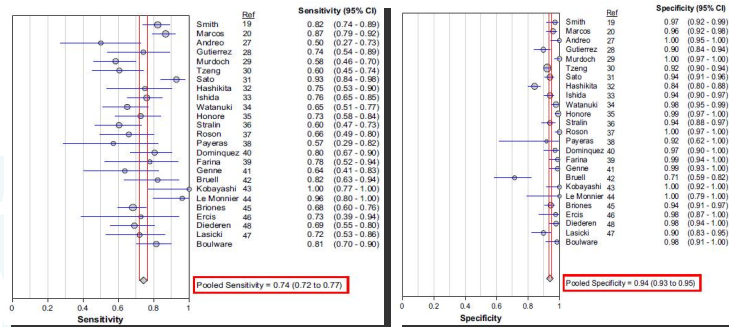


## pneumococcal C-polysaccharide = (lipo)teichoic acid





## Binax S. pneumoniae antigen tests general performance



Community-acquired pneumonia

Boulware 07

## Binax S. pneumoniae antigen tests : general performance

- Community acquired pneumonia:
  - Binax on non-concentrated urine vs pooled blood culture or sputum culture or Gram-stain :
    - Sens = 74 % (range : 75-85 %); spec = 94% (> 90%)
    - PPV = 79 % (60- 95%); NPV = 92 % (85-95%)
    - Additional yield = 23% 15-30% )
      - » Boulware 07
  - Concentration of urine increases sensitivity, lowers specificity

## Binax S. pneumoniae antigen tests : general performance

- Community acquired pneumonia:
  - Binax on non-concentrated urine (adults):
    - Better results in more severe illness
    - Not affected by HIV status, ICU admittance
      - » Smith 03, Roson 04, Marcos 03, Gutierrez 03, Ishida 04, Briones 06, Genne 06, Boulware 07, Lasocki 06
    - Not affected prior use AB
    - Tests can remain positive several weeks (up to 6 months in unconcentrated urine)
      - 1 month in 40-70% patients after pneumococcal pneumonia
      - cave recurrent infections eg false positives due to previous episode in AE COPD
        - » Marcos 03, Boulware 07, Andreo 09, Andreo 09
  - Binax on pleural fluid (adults, children):
    - Sens = 70-79 % but lower than urine, spec = 90%
    - Can give additional true positives in neg urine results
      - » Ploton 06, Andreo 06, Porcel 07, Porcel 09
  - Binax on BAL (adults):
    - Sens = 95.0% ; spec = 86.8%
      - » Jacobs 05

## Binax S. pneumoniae antigen tests : general performance

- Pneumococcal meningitis :
  - CSF (vs culture): sens = 95-100%; spec = 95-100%
  - Can detect 30% additional cases compared to culture
  - Can be positive up to 20 days after start Tx
    - » Marcos 01, Samra 03, Saha 05
- Pneumococcal empyema :
  - Pleural fluid : 97% sens , > 95 spec
  - Sens culture : 57% - PCR : 100% - Latex : 90%
    - » Le Monnier 05

## Binax *S. pneumoniae* antigen tests : general performance

- Pneumococcal AOM

TABLE 1. Summary of Binax NOW results in relation to findings of *S. pneumoniae* in the middle ear

Middle ear finding	No. of episodes	No. of patients with antibiotic treatment/total no. of patients	No. of positive Binax NOW tests/total no. of tests (% positive)		
			Middle ear	Nasopharynx	Urine
<i>S. pneumoniae</i> alone (culture positive)	19	4/19	16/18 (89)	14/17 (82)	8/15 (53)
<i>S. pneumoniae</i> plus other pathogen (culture positive)	3	0/3	3/3 (100)	2/2 (100)	0/1 (0)
<i>S. pneumoniae</i> (PCR positive, culture negative)	8	7/8	5/8 (62)	3/6 (50)	1/4 (25)
No <i>S. pneumoniae</i> (culture and/or PCR negative)	44	20/44	4/43 (9 <sup>a</sup> )	18/40 (45)	7/29 (24)

<sup>a</sup> In three of the four cases, *S. pneumoniae* was detected either in bone tissues (culture,  $n = 1$ ; PCR,  $n = 1$ ) or in secretions from the nasopharynx (culture,  $n = 1$ ). In the final case, the specimens from the mastoid bone, the middle ear, and the nasopharynx were all Binax NOW positive.

Gisselsson-Solén 07

## Binax *S. pneumoniae* antigen tests : false negatives

- Low level antigenuria
  - Early infection, low levels pathogens
    - No differences in test sensitivity relative to duration of symptoms or time to positive blood cultures
      - » Boulware 07
  - Antigen sequestration in blood by antibodies
    - Concentration urine increases sensitivity 15-20%
      - » Murdoch 01, Marcos 03, Gutierrez 03
- Urinary antigen sequestration by antibodies
  - NH<sub>4</sub>Cl dissociation of antigen-antibody complexes ?
    - » Amdahl 95

## Binax *S. pneumoniae* antigen tests : false positives

- Children : % false positives depending mainly on % carriage
  - Colonisation with *S. pneumoniae* (up to 50% of healthy child-carriers)
    - » Dowell 01, Adegbola 01, Esposito 04, Saha 05, Charkaluk 06
  - Pneumococcal vaccination
    - » Kelly 97, Navarro
  - Carriage *S. mitis* & *S. oralis* : contain same C-polysaccharide
    - » Navarro 04
  - Mixed viral-pneumococcal infection in 30% children
    - » Madhi 04
- Adults : ≤ 5%
  - Carriage *S. mitis* & *S. oralis*
    - » Gillespie 93
  - Persistent antigen shedding after prior pneumococcal infection
    - 40-70% still positive after 1 month
      - » Dominguez 01, Marcos 03, Strain 04, Boulware 07
  - Co-infection with unconfirmed pneumococcal presence
    - » Ishida 04, Briones 06

## Binax *S. pneumoniae* antigen tests : clinical utility

- 219 pts mild pneumonia
  - Prospective targeted Tx according to ICT
    - Pos result : amox - Neg result : clarithro
  - 90% success rate with amox – 94% in clarithro (NS)
    - » Guchev 05
- 152 older hospitalised pts
  - All empirical β-lactam monotherapy
  - 92% success in ICT pos pts vs 76% in ICT neg
    - ICT can safely target β-lactam monotherapy
      - » Strain 05

### **Binax *S. pneumoniae* antigen tests : clinical utility**

- **RCT comparing empirical vs targeted Tx based on urine antigen in hospitalized adults with CAP .**
- Falguera et al, Thorax, 09
- 89 pts empirical Tx vs 88 targeted Tx
- Targeted Tx
  - Higher overall cost (1657 vs 1617.20 € , p= 0.28)
  - Reduction adverse events (9 versus 18%, p= 0.12)
  - Lower exposure to broad-spectrum antimicrobials (154.4 versus 183.3 DDD/100PD)
  - No significant differences in other outcome parameters
  - In 25 pts on targeted Tx, oral antibiotic treatment started according to results of antigen tests
    - significant higher risk of clinical relapse (12 versus 3%, p= 0.04)

### **Binax *S. pneumoniae* antigen tests : clinical utility**

- **Can urine antigen testing be reliably performed & interpreted by adult emergency department staff ?**
- Weatherall et al, Emerg med J, 08
- 95 pts of whom 9 pos ICT
  - 98% concordance with lab
  - TAT 2h 39min vs 19h 40min
  - Antibiotic prescribing not affected

### **Binax *S. pneumoniae* antigen tests : clinical utility**

- **Urine antigen test in severe pneumonia in children**
- Cheong et al, J Microbiol Immunol Infect, 08
- 245 children severe pneumonia (Rx thorax)
  - Group 1: ICT & penicillin if pos, amp-sulbactam/cefur if neg
  - Group 2: ICT & empirical Tx irrespective result (ceftriax, oxa, cefa, piper, genta, cefe, ampi, vanco, ampi-sulb, clinda, mero)
  - Group 3: no ICT & empirical Tx following IDST
  - Group 4: no ICT & empirical Tx
- Clinical outcome (fever resolution) 1>2>3>4

### **Binax *S. pneumoniae* antigen tests : conclusions**

- **Advantages :**
    - AB do not reduce sensitivity ; no effect prior Tx
    - C-polysaccharide cold stable
    - C-polysaccharide conserved in all capsular serotypes
  - **Disadvantages :**
    - False negatives in 20% adult pneumonia → cannot be used to rule out *S. pneumoniae*
    - False positives (7-15 % in children)
    - No real clinical benefit demonstrated yet
- adjunct to currently used diagnostics

## Other antigens – future tests

- Pneumolysin antigen detection
  - Urine and CSF : inferior results to C-polysaccharide
  - Combined assays for increased specificity ?
    - » Ciam-Cabal 03, Garcia-Suarez 07, Rajalakshmi 02, Kanungo 04
- New assay for C-polysaccharide detection: ODK0501
  - ODK0501 on sputum samples vs Binax on paired urine samples & culture + PCR as gold standard
    - ODK0501 : 90% sens, less false positives
    - Binax : 62% sens
      - » Izumikawa 09