Société belge d'infectiologie et de microbiologie clinique
Belgische vereniging voor infectiologie en klinische microbiologie

30th Symposium : What will change in your daily practice with the new
Elewijt, 26-05-2008 EUCAST breakpoints for antibiotic susceptibility testing

Consequences for the clinicians

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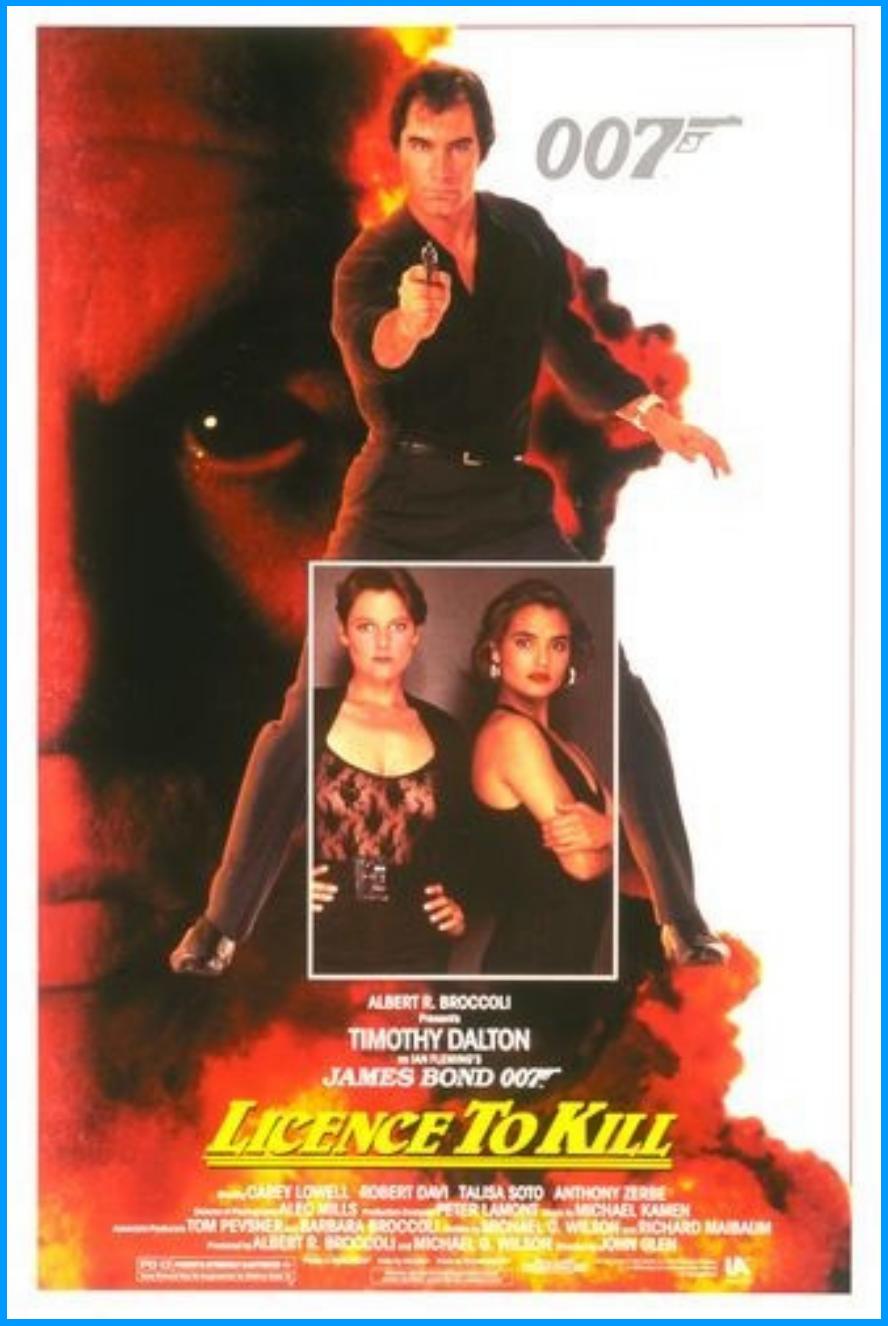
Shall you loose your….


007
ALBERT R. BROCCOLI
Presents
TIMOTHY DALTON
IN IAN FLEMING'S
JAMES BOND 007
LICENCE TO KILL
CAREY LOWELL ROBERT DAVI TALISA SOTO ANTHONY ZERBE
ALEC MILLS PETER LAMONT MICHAEL KAMEN
TOM PEVSNER BARBARA BROCCOLI MICHAEL G. WILSON RICHARD MAIBAUM
ALBERT R. BROCCOLI AND MICHAEL G. WILSON JOHN GLEN
UA

No, everything shall not change….

- Some patients shall still die,
  despite adequate therapy….
- Others shall survive,
  despite you (and me…)….

Because patients are NOT statistical models

…….

Other factors

- Host immunity may lead to:
  -cure in 70% of S.pneumoniae septicemia
  -death in some TSS, due to abnormal super Ag induced TNF α answer
- Specificity of the pathogen:
  -PVL (+) cMRSA CAP, leading to extensive necrosis

However,…

- New » frontiers » could :
  - allow to treat some patients more adequately in the future
  - help to understand discrepancies in results of studies on the impact of appropriate initial AB therapy on outcome

In Vitro Veritas ?

Recent data on major antibiotics

- Empirical therapy of nosocomial infections:
  -often include coverage for
  multi R Gram (+) patogens (MRSA,…)
  typically *vancomycin*
  -more often betalactams with
  potential activity against GNB ,
  including P.aeruginosa
  as *cefepime or pip/tazo*

All brand new studies,

less than 1 year old …

As this nice new car!

Accused Cefepime: what do you have to say?

- Efficacy and safety of cefepime: a systematic review and meta-analysis Yahav at al

  Lancet Infect Diseases May 2007

  Systematic review of randomised trials:

  cefepime/another βlactam AB
  (+/- another non β lactam AB)

  →57 trials included:

  Mortality (all cause) at D 30:
  higher for cefepime RR 1.26 (1.08-1.49)

Accused Cefepime: what do you have to say?

- Mortality criteria is relatively « rough »,

  ..but one of the most objective !

- No specific cause for the increased mortality, nor a specific patient population at risk (except neutropenic pat.)

- Explanation?

Accused Cefepime: what do you have to say?

- Undiagnosed toxicity ??
- Inadequate AB efficacy in vivo?

Authors didn't report :

the daily dose

BID or TID administration rate

but most studies performed in the US/Asia…

with ≤ 4 g / day

Cefepime again…

- Failure of current cefepime breakpoints to predict clinical outcomes of bacteremia caused by GN organisms
  Bhat et al AAC December 2007
- Discrepancies between CLSI and EUCAST breakpoints:
  - CLSI: S ≤ 8 I : 16 R ≥ 32 for all GNB
  - EUCAST: -for Enterobacteriaceae :
    S ≤ 1 I : 2-8 R > 8
    -for P.aeruginosa:
    S ≤ 8 R > 8

Cefepime again…

- *Retrospective* study on mortality at D 28

  (3 hosp. in the US, 1 in Australia)

  → 204 episodes ,treated with 1-2 g BID

  † episodes with MIC≥ 8 : 55%

  with MIC< 8 : 24% (p= 0.001)

  Same results with P.aeruginosa bacteremia

  → Multivariate analysis: MIC ≥ 8

  ≡independent predictor of mortality

  (p ≤0.001; OR 8.2)

Cefepime again…

- Explanation?

  Two models show:

  1. with 1g BID: 40% probability of T> MIC
     higher than 50% if MIC is 8
  2. with 1 g BID : 2%…..
     2 g BID : 21%…
     2g TID : 88% !!

  So, a MIC of 8 shouldn't mean « sensitive »
  if less than 2g TID is used empirically!!

And now pip/tazo..!!!???

And now pip/tazo ??

- Pip/tazo for P.aeruginosa infection: clinical implications of an extended infusion dosing strategy

  Lodise et al CID February 2007

- Cohort (*retrospective*) study:

  -1/2000 to 1/2001: intermittent (30') infusion

  3.375 g IV 4-6 x/day: 92 pat.

  -2/2002 to 6/2004: extended infusion(4 h)

  3.375 g IV 3x/day : 102 pat.

And now pip/tazo ??

- No differences in baseline clinical characteristics
- Among patients with a APACHE II ≥17:
  - lower † at day 14: 12,2% >< 31,6% (p=0.04)
  - shorter length of stay: 21 >< 38 days (p=0.02)

But what is the link?

- Monte Carlo simulation at their hospital:

  Probability of achieving a near bactericidal effect (T > MIC of 50%)

  - 100% with 4 h infusion if MIC < 16

    >< 20% with intermit. infusion !

  - 100% with interm. infusion if MIC 2/4

  .....

Are you sure..?? YES !

- Outcome of bacteremia due to P.aeruginosa with reduced susceptibility to Pip/Tazo: implications on the appropriateness of the R breakpoint
  Tam et al CID
  March 2008
- *Retrospective* study of 34 cases (2002-2006)
  with MIC 32-64, treated within 24 h of results
  7 with pip/tazo
  7 with a carbapenem
  11 with a cephalosporin
  4 with a FQ and 5 with an aminoglycoside

Are you sure..?? YES !

- All patients had conventional infusion rates
- Baseline demographic data similar

Clinical outcome:

† Day 30: 86% if pip/tazo (6/7)

22% in the controls (6/27)

(p=0.004)

Are you sure..?? YES !

- Multivariate analysis,after adjust. for age:
  - -APACHE II >15
  - -length of stay before (+) BC
  - -pip/tazo therapy

  were independent risk factors for 30 day †

  (p=0.009 ; OR : 220)

NB: 2ary analysis of bacteremia with strains

with MIC≤ 16 : † 30% >< 20%,ND)

Rods, ok…but cocci??

- Influence of vancomycin MIC on the treatment of MRSA bacteremia

  Soriano et al CID January 2008

  414 episodes of MRSA bacteremia in 1 spanish hospital between 1991 and 2005,with appropriate empirical vancomycin therapy (trough concentration >10)
  - MIC 1: 38 episodes
  - MIC 1,5: 90 episodes
  - MIC 2 : 40 episodes

And now Vancomycin…

- In the multivariate analysis :
  empirical vancomycin and a MIC =2 had the higher OR(6.39 ;1.68-24.3)
  as predictor of mortality

Suggesting that vanco is not an optimal option for strains with MIC> 1 if trough levels of 10 are the target OR that the breakpoint should be changed…

Is it the only publication…?

NO

- Several papers from Sakoulas, Moise, Hidayat,…

  show the same relation

  since 2004….

  -Sakoulas(JCM 2004): 10% success rate if MIC 1-2

  -Moise (AAC 2007) : 21% success rate if MIC=2

- And those strains are more frequent in patients treated with vanco within 30 days prior to their MRSA bacteremia (Moise, JAC 2008)

Conclusions

- Few things shall change for infection that are
  either not severe, …..
  either not linked to real bacterial
  invasive disease….
  either in the UTI….
- However, for the most severe /nosocomial
  infections linked to less sensitive pathogens,
  new EUCAST breakpoints should lead to…

The lost of your ……