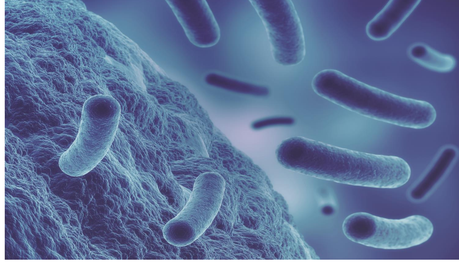
Poster # 1602

Benefit:Risk Evaluation in Diagnostics: An Example Comparing Two Rapid Molecular Diagnostics Testing Imipenem Susceptibility in *Acinetobacter* spp.

Scott Evans[1], Hongyu Jiang[2], Andrea M. Hujer[3], Kristine M. Hujer[3], Claudia Manca[4], Carol Hill[5], Barry N. Kreiswirth[4], Michael R. Jacobs[3], Liang Chen[4], Rangarajan Sampath[6], Thomas Hall[6], Christine Marzan[6], Robert A. Bonomo[3] and The Antibiotic Resistance Leadership Group (ARLG)

[1]Harvard University, Boston, MA, [2]Center for Biostatistics in AIDS Research- Harvard T.H. Chan School of Public Health, Boston, MA, [3]Louis Stokes Cleveland VAMC- CWRU School of Medicine, Cleveland, OH, [4]Public Health Research Institute Center, Newark, NJ, [5]Duke Clinical Research Institute- Duke University, Durham, NC, [6]IBIS Biosciences Inc.- An Abbott Company, Carlsbad, CA

ARLG
Antibacterial Resistance Leadership Group



Abstract

Background

Methods to assess benefit:risk of diagnostic methods to help clinicians treat multidrug-resistant *Acinetobacter* spp. are needed. Important considerations include effects on diagnostic yield [(i.e., the distribution of true resistance (TR), false resistance (FR), true susceptibility (TS), and false susceptibility (FS)], which is affected by the susceptibility rate.

Methods

We developed a slide-rule profile plot of the expected diagnostic yield as a function of the susceptibility rate. The number-needed-to-test (NNT) for susceptibility (NNT-S) [i.e., the expected number of susceptible patients that must be tested with one test (vs. another test) to result in one additional TS] was defined, as was the NNT for resistance (NNT-R). We apply this method to the evaluation of two rapid molecular diagnostic platforms [PCR/ESI-MS and Molecular Beacons™ (MB)] utilized for imipenem susceptibility testing based on the presence/absence of bla_{MBLs} and bla_{OXA} genes vs. MIC determination in *Acinetobacter* spp. (*Ab*) infection. Expected diagnostic yield was evaluated based on a population of 12,000 *Ab* cases.

Results

When the imipenem susceptibility rate is 40%, the expected yield for MB is (TR=6408; FR=384; TS=4416; FS=792) and for PCR/ESI-MS is (TR=6912; FR=816; TS=3984; FS=288). Thus the between-platform difference in expected yield is 504 more TR for PCR/ESI-MS and 432 more TS for MB. When the susceptibility rate is 60%, the difference in expected yield is 336 more TR for PCR/ESI-MS and 648 more TS for MB (Figure 2). Tradeoffs for any susceptibility rate can be obtained (Figure 3). The NNT-S is 11.1 (MB vs. PCR/ESI-MS), and the NNT-R is 14.3 (PCR/ESI-MS vs. MB).

Conclusion

Here we develop profile plots to illustrate how diagnostic yield varies by susceptibility rate. Between-platform differences in TR and TS plotted as a function of the susceptibility rates and NNTs provide a relative comparison of two AST methodologies. Applying these approaches helps us understand the benefits and risks of each new diagnostic platform when applied to treatment decisions.

Background

Acinetobacter

- A gram-negative pathogen that can cause pneumonia, skin and soft tissue and blood stream infections among critically ill patients.
- In the US, ~12,000 cases of multidrug-resistant *Acinetobacter* spp. infections occur, associated with ~500 deaths per year.
- ~63% are multi-drug resistant (CDC, 2013).
- Treatment options include carbapenems, beta-lactam/beta-lactamase inhibitor combinations, tigecycline and colistin (used as a "last resort"). Resistance to these agents limits choices.
- Presently rapid molecular diagnostics (RMDs) that detect resistant phenotypes do not exist.

Challenge

- Standard evaluation of diagnostics consists of estimating sensitivity, specificity, positive / negative predictive values and likelihood ratios, and accuracy.
- Although useful, these statistics do not comprehensively describe the clinical impact of diagnostic application.
- The clinical impact consists of potential benefits and harms resulting from correct / incorrect diagnoses within the context of a specific prevalence.

Benefit:Risk Goal

- The medical community is calling for more systematic benefit:risk evaluation and more pragmatic evaluations with increased value for medical decision-making
  - Progress has been made in the intervention setting
  - Less progress has been made for diagnostics
- Our goal is to develop an analytical approach that helps the clinician evaluate the benefits and shortcomings of an RMD platform. We employed a collection of MDR *Acinetobacter* spp. to illustrate this application.

PRIMERS III

- Blinded evaluation of two RMD platforms (PCR/ESI-MS and Molecular Beacons™ [MB]) for discriminating resistance/susceptibility to carbapenems in *Acinetobacter* spp.
- 200 strains
  - Results based on the absence / presence of 7 genes: bla_{OXA-23}, $_{-40}$, $_{-58}$, bla_{NDM}, $_{-KPC}$, $_{-VIM}$, and $_{-IMP}$
  - Reference standard: MIC
- 48.5% (n=97/200) of isolates were imipenem-resistant
- Resistance Sensitivity: probability that the result is resistant when the MIC result is resistant (N=97)
  - PCR/ESI-MS: 96%, 95% CI = (91%, 99%)
  - MB: 89%, 95% CI = (81%, 94%)
- Susceptibility Sensitivity: probability that the result is susceptible when the MIC result is susceptible (N=103)
  - PCR/ESI-MS: 83%, 95% CI = (74%, 89%)
  - MB: 92% 95% CI = (85%, 97%)
- For details see: Poster Board 1604: Abstract 52116: Session 227: Informing Antibiotic Treatment Decisions: Evaluating Rapid Molecular Diagnostics (RMDs) to Identify Susceptibility and Resistance to Carbapenems against *Acinetobacter* spp. PRIMERS –III

Methods

- We develop/apply the Benefit:risk Evaluation of Diagnostics FRAMEwork (BED-FRAME) to PRIMERS III

Diagnostic Yield

- Refers to the distribution of true positives, true negatives, false positives, and false negatives when a diagnostic is utilized in practice
- In the case of susceptibility testing, this refers to the distribution of true susceptibilities (TSs), true resistances (TRs), false susceptibilities (FSs), and false resistances (FRs)
- Conveys the broad clinical impact of diagnostic application lacking with use of traditional diagnostic evaluation measures

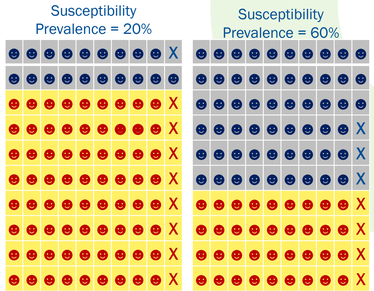
BED-FRAME

- A strategy for pragmatic benefit:risk evaluation of diagnostics
- Evaluates *diagnostic yield*
- Addresses two key issues
  - Diagnostic yield depends on prevalence
  - Different errors carry different consequences

Diagnostic Yield Depends on Prevalence

- Suppose the susceptibility/resistance sensitivities of a diagnostic are 95% and 90% respectively.
- If the diagnostic was applied to a population where the susceptibility prevalence is 20%, then the expected diagnostic yield for every 100 people tested is (Figure 1A): TS=19, TR=72, FS=8, FR=1.
- If applied to a population where the susceptibility prevalence is 60%, then the expected diagnostic yield for every 100 people tested is (Figure 1B): TS=57, TR=36, FS=4, FR=3.

Figure 1: Expected Diagnostic Yield Plots

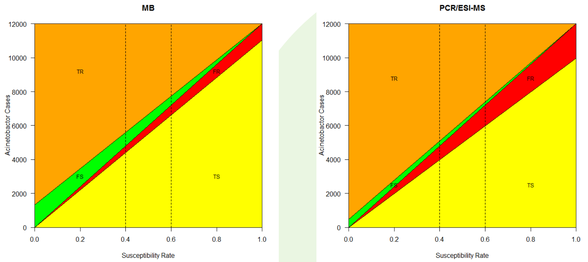


Susceptibility Sensitivity = 95%; Resistance Sensitivity = 90%

Results

We recognize that the prevalence of susceptibility / resistance to antibiotics of *Acinetobacter* can vary over time and can depend upon location. As a result we displayed the diagnostic yield as the prevalence varies. The Expected Diagnostic Yield Profile Plot with Slide Rule illustrates how the diagnostic yield varies as the susceptibility rate varies.

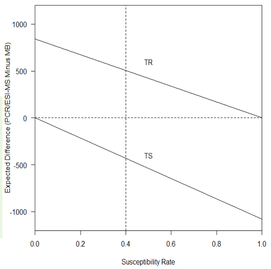
Figure 2: Slide-Rule Profile Plots of Diagnostic Yield for Imipenem Susceptibility Testing in *Ab*



When the imipenem susceptibility rate is 40%, the expected yield for MB is (TR=6408; FR=384; TS=4416; FS=792) and for PCR/ESI-MS is (TR=6912; FR=816; TS=3984; FS=288). Thus the between-platform difference in expected yield is 504 more TR for PCR/ESI-MS and 432 more TS for MB. When the susceptibility rate is 60%, the difference in expected yield is 336 more TR for PCR/ESI-MS and 648 more TS for MB.

Expected between-diagnostic differences in the numbers of: (1) TS diagnoses and (2) TR diagnoses can be plotted as a function of the susceptibility rate to illustrate trade-offs.

Figure 3: Between-Platform Difference in TR and TS as a Function of the Susceptibility Rate



- PCR/ESI-MS has a higher resistance sensitivity and thus will have more TR.
- MB has a higher susceptibility sensitivity and thus always has more TS.

Number-Needed-to-Test (NNT)

- It is important to appreciate the number of patients needed to be diagnosed to see a between-diagnostic difference.
- The number-needed-to-test (NNT) for susceptibility (NNT-S) is the expected number of susceptible patients that must be tested with one test (vs. another test) to result in one additional TS. The NNT for resistance (NNT-R) was similarly defined
- The NNT-S is 11.1 (MB vs. PCR/ESI-MS), implying that if 11 TS patients were tested, we expect that MB would correctly classify one more than PCR/ESI-MS.
- the NNT-R is 14.3 (PCR/ESI-MS vs. MB) implying that if 14 TR patients were tested, we expect that PCR/ESI-MS would correctly classify one more than MB.

Accuracy

- Accuracy (i.e., overall percent correctly classified) is often reported
- Let p= prevalence of susceptibility
- Accuracy = (p)(susceptibility sensitivity) + (1-p)(resistance sensitivity)
- Ranges from 0-100%; higher levels better
- Two issues with the accuracy statistic
  - Accuracy treats all errors as if they are equivalently important
  - Since it depends on prevalence, it is not generally comparable from study to study and should therefore be reported as a function of prevalence

Differential Error Consequences

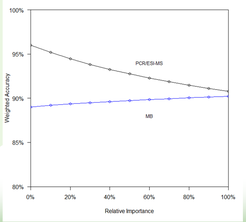
Failing to identify resistance is a more important error than failing to identify susceptibility

- Failing to identify susceptibility implies failure to treat with effective imipenem thus exposing the patient to colistin
- Failing to identify resistance implies treating with ineffective antibiotic (e.g., imipenem)

Weighted Accuracy

- Interpreted as the adjusted accuracy (adjusted for differential error costs)
- Ranges from 0-100%: higher is better
- Define the *relative importance* (r) of false resistance relative to false susceptibility (false susceptibility is worse): $0 \le r \le 1$.
- Weighted accuracy = [r(p)(susceptibility sensitivity) + (1-p)(resistance sensitivity)] (1/(1-p+pr))
- Allows for a comparison of diagnostics under varied p and r.

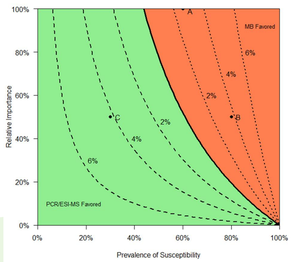
Figure 4: Weighted Accuracy vs. Relative Importance by Platform when the Susceptibility Rate = 40%



Comprehensive Comparison

- A comparison PCR/ESI-MS and MB depends on p and r. Surveillance can inform regarding p. Surveys could be conducted to inform r.
- Figure 5 displays a comparison (PCR/ESI-MS vs. MB) of weighted accuracy as a function of r and p.

Figure 5: Comparison of Weighted Accuracy as a Function of the Relative Importance and Prevalence of Susceptibility: PCR/ESI-MS vs. MB



- The green area indicates combinations of r and p where PCR/ESI-MS is favorable while the red area indicates combinations where MB is favorable.
- The solid black line indicates where PCR/ESI-MS and MB are equivalent.
- Contours indicate the magnitude of weighted accuracy differences. Consider the 3 points labeled A, B, and C:
  - A (r = 100% (errors are equivalent); p = 60%): ~3% higher weighted accuracy for MB.
  - B (r = 50% (false resistance half as important as false susceptibility); p = 80%): ~4% higher weighted accuracy for MB.
  - C (r = 50%; p = 30% (resistance outbreak)): ~4% higher weighted accuracy for PCR/ESI-MS.

Conclusions

We developed an approach to help clinicians evaluate the results of diagnostic tests when applied to MDR pathogens.

Analyses and comparison of diagnostics depend on prevalence and the relative importance of potential errors. BED-FRAME was designed to evaluate diagnostics as these factors vary.

BED-FRAME

- A strategy for pragmatic evaluation of diagnostics, illuminating benefits and risks when applied in practice
- Evaluates *diagnostic yield, weighted accuracy, and* novel plots as tools for communicating the clinical impact of application
- Incorporates prevalence and differential error consequences into evaluation
- Proposed as a fundamental component to the analysis of diagnostic studies.

Acknowledgments

Research reported in this publication was supported by the National Institute Of Allergy And Infectious Diseases of the National Institutes of Health under Award Number UM1AI104681. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Contact

Scott Evans
Harvard School of Public Health
FXB Building, Room 513
Boston, MA 02115
Phone: 617-432-2998
Fax: 617-432-3163
evans@sdac.harvard.edu