USE OR PRESERVE? HOW PRACTICE PATTERNS IMPACT UPON MARKETS FOR NEW AND IMPROVED ANTIBIOTICS

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BACKGROUND

- Despite a major public health need, industry has been slow to develop new agents against resistant pathogens (RP).
- We sought to investigate to what extent extending antibiotic activity-spectrum would inhibit agent use, making development of extended-spectrum antibiotics less economically attractive.

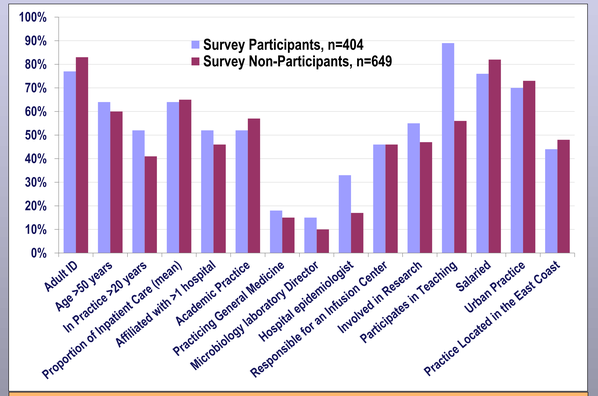
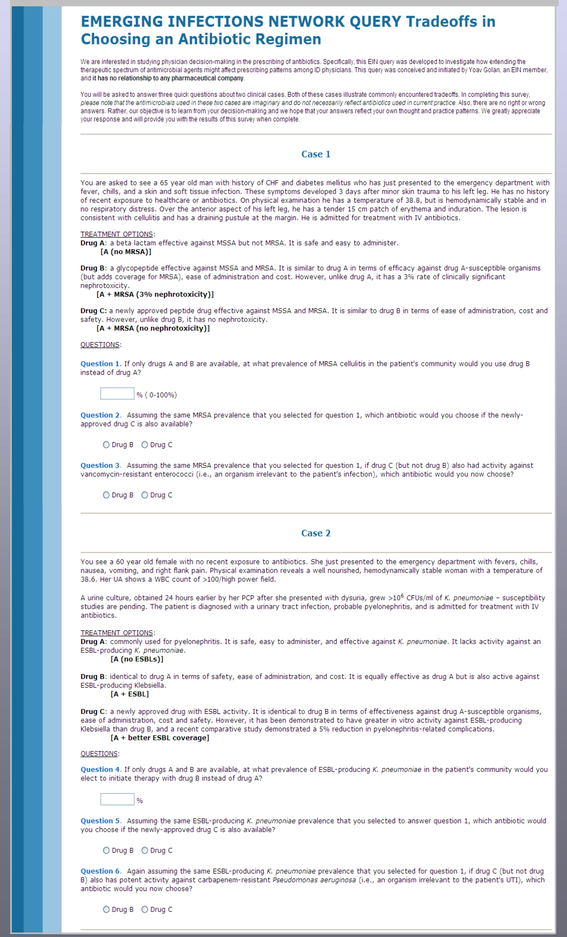


Figure 1. Characteristics of Survey Participants and Non-Participants

METHODS

- Using 2 case vignettes (Figure 1), we examined how often infectious disease specialists (ID) would avoid using a new antibiotic against antibiotic-resistant pathogens despite its potential value for their prospective patient.
- Participants were asked: how high the odds of an abx-RP should be for them to cover it empirically; when covering abx-RP, would they use an older or a new and improved abx (similar costs); if favoring the new abx, would they still use it if it's active against RP irrelevant to their prospective patient.
- After accepting an approval by the EIN board of directors, the survey was sent to members of the IDSA/CDC Emerging Infections Network in October 2006 and resent to non responders in Nov.
- EIN is a provider-based emerging infections sentinel networks. It was established in In September of 1995 when the CDC granted a Cooperative Agreement Program award to the Infectious Diseases Society of America (IDSA). Among the purposes of EIN are: detection of new or unusual clinical events, case definition, acquisition of knowledge, research collaboration, communication and education. EIN has approximately 1050 members, of whom approximately 80% practice adult ID and 20% pediatric ID.

CLINICAL VIGNETTES



EMERGING INFECTIONS NETWORK QUERY Tradeoffs in Choosing an Antibiotic Regimen

We are interested in studying physician decision-making in the prescribing of antibiotics. Specifically, this EIN query was developed to investigate how extending the therapeutic spectrum of antimicrobial agents might affect prescribing patterns among ID physicians. This query was conceived and initiated by Yoav Golan, an EIN member, and it has no relationship to any pharmaceutical company.

You will be asked to answer three quick questions about two clinical cases. Both of these cases illustrate commonly encountered tradeoffs. In completing this survey, *please note that the antimicrobials used in these two cases are imaginary and do not necessarily reflect antibiotics used in current practice.* Also, there are no right or wrong answers. Rather, our objective is to learn from your decision-making and we hope that your answers reflect your own thought and practice patterns. We greatly appreciate your response and will provide you with the results of this survey when complete.

Case 1

You are asked to see a 65 year old man with history of CHF and diabetes mellitus who has just presented to the emergency department with fever, chills, and a skin and soft tissue infection. These symptoms developed 3 days after minor skin trauma to his left leg. He has no history of recent exposure to healthcare or antibiotics. On physical examination he has a temperature of 38.8, but is hemodynamically stable and in no respiratory distress. Over the anterior aspect of his left leg, he has a tender 15 cm patch of erythema and induration. The lesion is consistent with cellulitis and has a draining pustule at the margin. He is admitted for treatment with IV antibiotics.

TREATMENT OPTIONS:
Drug A: a beta lactam effective against MSSA but not MRSA. It is safe and easy to administer.
[A (no MRSA)]

Drug B: a glycopeptide effective against MSSA and MRSA. It is similar to drug A in terms of efficacy against drug A-susceptible organisms (but adds coverage for MRSA), ease of administration and cost. However, unlike drug A, it has a 3% rate of clinically significant nephrotoxicity.
[A + MRSA (3% nephrotoxicity)]

Drug C: a newly approved peptide drug effective against MSSA and MRSA. It is similar to drug B in terms of ease of administration, cost and safety. However, unlike drug B, it has no nephrotoxicity.
[A + MRSA (no nephrotoxicity)]

QUESTIONS:

Question 1. If only drugs A and B are available, at what prevalence of MRSA cellulitis in the patient's community would you use drug B instead of drug A?

[ ] % (0-100%)

Question 2. Assuming the same MRSA prevalence that you selected for question 1, which antibiotic would you choose if the newly-approved drug C is also available?

○ Drug B ○ Drug C

Question 3. Assuming the same MRSA prevalence that you selected for question 1, if drug C (but not drug B) also had activity against vancomycin-resistant enterococci (i.e., an organism irrelevant to the patient's infection), which antibiotic would you now choose?

○ Drug B ○ Drug C

Case 2

You see a 60 year old female with no recent exposure to antibiotics. She just presented to the emergency department with fevers, chills, nausea, vomiting, and right flank pain. Physical examination reveals a well nourished, hemodynamically stable woman with a temperature of 38.6. Her UA shows a WBC count of >100/high power field.

A urine culture, obtained 24 hours earlier by her PCP after she presented with dysuria, grew $>10^6$ CFUs/ml of *K. pneumoniae* - susceptibility studies are pending. The patient is diagnosed with a urinary tract infection, probable pyelonephritis, and is admitted for treatment with IV antibiotics.

TREATMENT OPTIONS:
Drug A: commonly used for pyelonephritis. It is safe, easy to administer, and effective against *K. pneumoniae*. It lacks activity against an ESBL-producing *K. pneumoniae*.
[A (no ESBLs)]

Drug B: identical to drug A in terms of safety, ease of administration, and cost. It is equally effective as drug A but is also active against ESBL-producing Klebsiella.
[A + ESBL]

Drug C: a newly approved drug with ESBL activity. It is identical to drug B in terms of effectiveness against drug A-susceptible organisms, ease of administration, cost and safety. However, it has been demonstrated to have greater in vitro activity against ESBL-producing Klebsiella than drug B, and a recent comparative study demonstrated a 5% reduction in pyelonephritis-related complications.
[A + better ESBL coverage]

QUESTIONS:

Question 4. If only drugs A and B are available, at what prevalence of ESBL-producing *K. pneumoniae* in the patient's community would you elect to initiate therapy with drug B instead of drug A?

[ ] %

Question 5. Assuming the same ESBL-producing *K. pneumoniae* prevalence that you selected to answer question 1, which antibiotic would you choose if the newly-approved drug C is also available?

○ Drug B ○ Drug C

Question 6. Again assuming the same ESBL-producing *K. pneumoniae* prevalence that you selected for question 1, if drug C (but not drug B) also has potent activity against carbapenem-resistant *Pseudomonas aeruginosa* (i.e., an organism irrelevant to the patient's UTI), which antibiotic would you now choose?

○ Drug B ○ Drug C

RESULTS

- Of 1053 EIN members, 404 participated (38%).
- For most variables, characteristics of participants and non-participants were similar. Participants were more likely to participate in teaching activities and serve as hospital epidemiologists (Figure 1).
- Despite its potential value, participants avoided use of a new and improved antibiotic against RP in 58% and 70% of cases, when treating Gram-positive (GP) and Gram-negative (GN) pathogens, respectively.
- Reasons for avoiding use were: acceptance of possible failure against abx-RP (25% for GP, 20% for GN); preferring an older agent over a newer abx (32% for GP 41% for GN); avoiding an antibiotic with activity against very RP (12% for GP, 21% for GN).
- Of those who initially favored a new antibiotic, 18%-36% (GP-GN) switched to a 2nd best when informed that the new antibiotic is active against VRE (in a case of Staphylococcal cellulitis) or MDR Pseudomonas (case of Klebsiella pyelonephritis).
- Trends in antibiotic use were similar between adult and pediatric ID as well as participants with different demographics, practice type or geography.

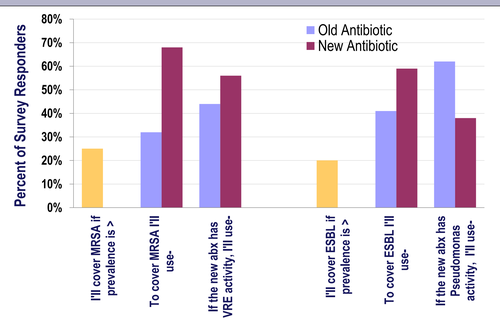


Figure 2. Clinical Vignettes: Results

CONCLUSIONS

- The use of a new and improved antibiotic by ID specialists is substantially reduced when spectrums are extended to cover RP and especially very RP, such as VRE or MDR Pseudomonas.
- The motivator for such a practice pattern is the prevention of antibiotic-resistance that would diminish future treatment options. But limited use of new and improved antibiotics would decrease the market for such antibiotics, making their development less economically attractive, thus resulting in diminished future treatment options.
- Given this, innovative incentive structures may be needed to encourage development of such agents.

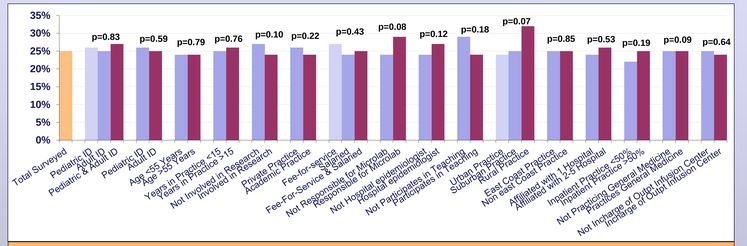


Figure 3. MRSA Prevalence Required for Coverage Stratified by Participants' Characteristics

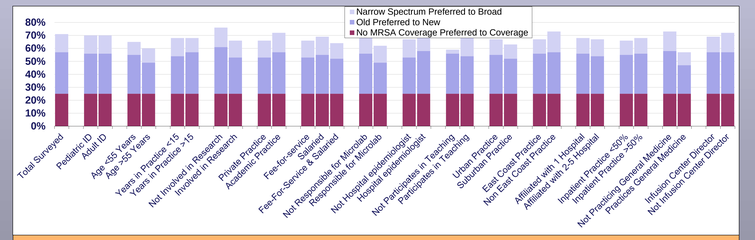


Figure 4. Percent of Responders Who Would Avoid Using a Newer Antibiotic and the Reasons for Such a Choice

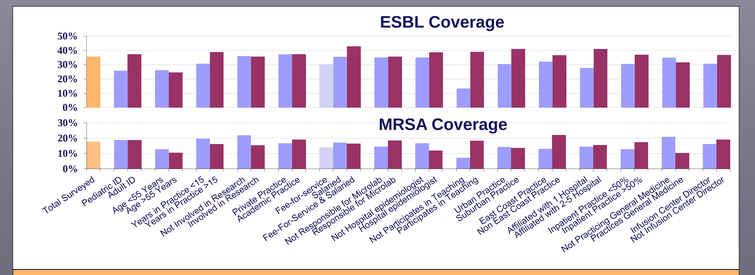


Figure 5. The Relative Reduction in Use of a New and Improved Antibiotic That is Attributable to a Too-Broad Spectrum of Activity