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Managing Antibiotic Resistance—An Imperative for Future Medical Care

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Antibiotics are the most commonly used pharmacologic treatment in every hospital. Without effective antibiotics, failure rates for prophylaxis of surgical infections and medical treatment for all infectious syndromes increase dramatically, resulting in increased patient deaths, length of hospital stay, and readmissions. However, overuse of broad-spectrum antibiotics in hospitals is causing an accelerating prevalence of resistant organisms because of the collateral killing of normal bacterial populations. Without changes to our antibiotic use process, we are setting ourselves up for catastrophic consequences.

Antimicrobial Resistance in the News: "We Are Nearing Antimicrobial Armageddon!"

In March of this year, the Centers for Disease Control and Prevention (CDC) issued a major report on antimicrobial resistance.[1] It stated that "The increase in the number of rare, but potentially deadly superbugs resistant to nearly all last-resort antibiotics has prompted health officials to renew warnings for US hospitals, nursing homes, and other healthcare settings." A rare but potentially deadly superbug has now been identified as carbapenem-resistant enterobacteriaceae (CRE). These organisms elude carbapenem antibiotics and other antibiotic classes, and typically strike people already vulnerable to infectious agents because of their use of devices such as ventilators or catheters. The report goes on to discuss how to limit these organisms, and recommends that health providers act "aggressively to prevent the emergence and spread of these unusual CRE organisms."

Almost immediately the CDC report was followed by a paper from the United Kingdom's chief medical director declaring antibiotic resistance a "nightmare."[2] Following up on this release, Reuters News Service related that CRE is only a small part of the superbug story.[3] The truth is many other superbugs, such as MRSA (killing around 19,000 every year in the United States), are emerging and becoming increasingly resistant to current antibiotics. The other side of the story is that the pipeline for new antibiotics to address these resistant organisms is not forthcoming. The Figure[4] shows the decline of new antibiotics under development in recent years.

This situation has been on the radar for the World Bank, which has included antimicrobial resistance as one of the top 10 threats to global economic progress for the past several years.[5] These conclusions are supported by overwhelming evidence gathered by the CDC, the World Health Organization, and the Cochrane Collaboration.

The continuing threat of antimicrobial resistance is not just hype—it is real. In fact, it is late in the game and the superbugs are winning!

How Antimicrobial Resistance Happens

As noted above, resistance is promoted by use of broad-spectrum antibiotics which kill off all but the most resistant bacteria. When patients are initially admitted in critical condition, broad-spectrum antibiotics are needed to cover all potential bacterial species. As patients improve and more data become available, physicians are often reluctant to narrow the spectrum of antibiotics to targeted treatment of the organism identified. Physicians often hesitate to "de-escalate," even when culture reports indicate it is safe to do so. Most of this reluctance is related to fear of therapeutic failure, potential liability, and detailed education about antimicrobial resistance and precise selection of alternative agents. Close teamwork with pharmacists to select the best narrower-spectrum agents, as well as providing dosing based on weight, optimized infusion timing, and duration are becoming more and more important for success given the prevalence of

PRACTICAL IMPLICATIONS

When one considers that resistance will continue to grow without a change in antibiotic use process, and there will be few new agents available, the need for effective use of antibiotics is clear:

- Optimal selection, dose, and administration of empiric treatment for all admitting diagnoses—regardless of prescriber
- Rapid de-escalation to narrower-spectrum agents when diagnosis clearer and patient more stable
- Change to oral/OPAT agents as soon as possible, and discharge to minimize acquisition of hospital bacteria

obesity, and the high blood levels required for successful treatment of relatively resistant bacteria.

Another common contribution to antimicrobial resistance is the use of an antibiotic when the infection is most likely viral. In Sweden, where there are stricter guidelines for casual antibiotic use, and less pressure for their use by patients, resistance is less common.

Resistance Is Not the Same Everywhere

Antimicrobial resistance patterns in hospitals vary and are susceptible to various local conditions, including the:

- population of patients treated
- prescriber expertise for antibiotic selection
- use of locally derived guidelines regarding antibiotic use by infection type
- involvement of clinical pharmacists to optimize dosing, recommend alternatives, and support de-escalation when patients are more stable, and culture data are available

The only way for a hospital to know how its antimicrobial program compares with similar facilities (for use, cost, and resistance) is by assessing its current use process, then benchmarking its data and practices to discover the extent of antimicrobial resistance and the reasons driving it.

Scenarios for Responding to Increased Antimicrobial Resistance

Hospitals have 2 basic choices when dealing with antimicrobial resistance. The first is to carry on business "as usual." The second is to be proactive, seeking better ways to handle these problem bugs. The problem of carrying on as usual, hoping it will go away, is it provides no solution at all. Without a fundamental change in antibiotic use, resistance always increases, and becomes exponentially more difficult to control with advanced resistance. The following features have been noted with more advanced resistance:

- a dwindling arsenal of effective antibiotics
- an increase in therapeutic failures
- an increase in length of hospital stay of 6.4 to 12.7 days
- increased medical costs ranging from $18,588 to $29,069 per infected case
- increases in readmission due to infections, which under current reimbursement schemes is financially penalized
- an increase of resistance-attributable mortality of 6.5%
- an increase in medical liability cases
- missing quality and accreditation standards for infection

The second option, of being proactive, begins by performing a baseline assessment of the hospital's antimicrobial program. With this information, a medical-staff-approved antimicrobial stewardship program (AMSP) can be developed and implemented. These programs have been shown to reverse the trend toward antimicrobial Armageddon.

The Clinical and Business Cases for Antimicrobial Assessment and Stewardship

The following case study illustrates the assessment data useful for driving change. Since physicians, pharmacists, nurses, and other personnel often have difficulty sharing their frank insights with internal personnel, it has been found that it is most effective to have this

Figure. Decline of New Antibiotics Under Development in Recent Years[4]

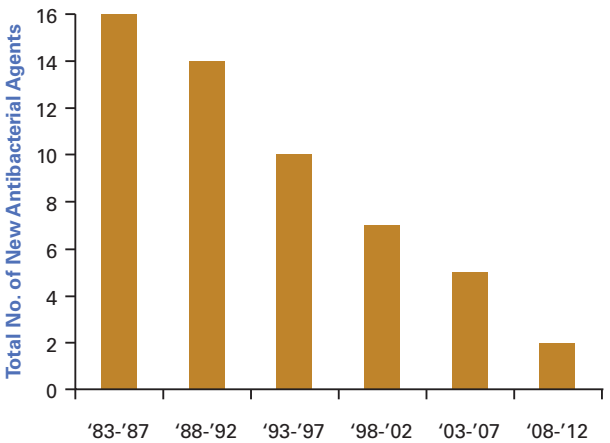

Table 1. Areas Where the Case Study Hospital Performed Well

Benchmark	Versus the Benchmark for Similar Hospitals
Total drug cost ($)/patient day	78%
Total drug cost ($)/admission	65%
C difficile infections/patient day × 1000	22%
Days of antibiotic therapy/1000 patient days	
cefazolin	51%
clindamycin	39%
Daily defined doses/1000 patient days	
cefazolin	49%
clindamycin	27%

assessment performed by a knowledgeable independent consultant.

Case Study—Information generated by a programmatic antimicrobial assessment:

Hospital—This is a community hospital that averages 250 beds

- Annual admissions = 17,500
- Annual patient days = 65,000
- Intensive care units = 5 (8-12 beds)
- Average patient stay = 3.72 days
- Medicare acuity index during the assessment = 1.45

Antimicrobial Assessment Findings—An independent consultant performed an assessment of this hospital's antimicrobial program and provided it with an analysis of its status. During this process, any issues noted by the assessment team were reported to the hospital group to work in concert to develop a sequential approach to ongoing AMSP improvements (Tables 1-2).

When compared with similar institutions, this hospital's antimicrobial resistance was much higher. There was an overuse of antibiotics, especially of broad spectrum and expensive antibiotics. Also, there was a tendency not to use narrower-spectrum, less costly antibiotics when culture reports and clinical pharmacists indicated effective alternatives were available. The consultant's finding was that this hospital had the potential for significant clinical improvement as well as antimicrobial cost savings in the range of $250 to $400 K per year with implementation of an effective AMSP. This is currently being considered by the hospital's medical staff executive committee.

Recommendations for this hospital included:

- Development of a set of performance standards for improving antibiotic use that are routinely measured, and an ongoing process to review results and take actions to improve them where appropriate
- Creation and implementation of guidelines for treatment of common infections such as urinary tract infections and pneumonia to improve antibiotic use and optimize duration of therapy within the hospital and, if needed, at discharge
- Flow charting the antibiotic ordering and dispensing process from the time an antibiotic order is written until the first dose is administered
  - Then identify where bottlenecks occur and take action to reduce them, with the goal of decreasing your average overall time of 3 hours and 20 minutes to the recommended 1 hour
- Increase the clinical involvement and supervision of its microbiology program
- Add 1 full-time equivalent infectious disease pharmacy specialist or provide funds and training for a pharmacist to gain additional knowledge of antimicrobial therapy
  - Savings from the improved AMSP will more than pay for additional staff and/or training
- Routinely review written pharmacist chart notes to the medical staff as part of the pharmacy department's quality improvement program
- Develop standard protocols for chart notes or other preferred ways to contact physicians
  - Track feedback to ensure that communication methods are timely
- Reactivate the institution's antimicrobial stewardship committee with new and committed physician leadership
  - Committee to also include microbiology, pharmacy, and infection prevention/control membership. This committee should meet regularly to be effective

Table 2. Areas Where the Case Study Hospital Can Improve

Benchmark	Versus Other Similar Hospitals
Antimicrobial resistance (current)	High for [a]: MRSA VRE ESBLs *P aeruginosa* ▪ Cipro: 91% effective in 1998—now 62% ▪ Zosyn: 100% effective in 2004—now 78% ▪ Imipenem: 95% effective in 1998—now 76% ▪ Aminoglycosides: 100% effective in 2004—now 76%
Proportion of patients on specific antibiotics relative to benchmark hospitals	109%
Days of antibiotic therapy/1000 patient days	
levofloxacin	138%
vancomycin	273%
ciprofloxacin	950%
azithromycin	389%
ceftriaxone	127%
Zosyn (Pip-Tazo)	190%
daptomycin	200%
linezolid	233%
Proportion of IV antibiotics	112%
Daily defined doses/1000 patient days	121%
levofloxacin	253%
azithromycin	595%
ciprofloxacin	672%
vancomycin	239%
ceftriaxone	191%
Zosyn (Pip-Tazo)	220%
linezolid	450%
imipenem	317%
daptomycin	183%
Proportion of total drug cost for antibiotics	173%
Antibiotic cost/patient day[b]	105%
Antibiotic cost/occupied bed (at any time)	142%
Time to first antibiotic dose	3 hours, 20 minutes

IV indicates intravenous.
[a]Caveat: older population with high proportion of long-term care patients.
[b]Unadjusted for patient mix

- Provide routine training on the use of Theradoc
- Consider greater controls of pharmaceutical industry representatives throughout the hospital

Achieving Improved Antimicrobial Use and Less Antimicrobial Resistance

The strongest evidence for improving antimicrobial use and reducing antimicrobial resistance is in implementing a hospitalwide, medical staff–approved antimicrobial stewardship program (AMSP).[6-10] A well-implemented AMSP can produce the following beneficial results in clinical quality and financial performance:

- reduced antimicrobial use of 11 to 38%[6-10]
- increase in the appropriate antibiotic use by 20 to 24%
- reduced duration of antibiotic therapy by 18%
- more cures and less therapeutic failures
- reduced stay by 0.5 to 1 day for patients with infection
- reduced 30-day readmissions for infection by 0.5 to 0.8%
- reduced antimicrobial resistance
- reduced cost—comprehensive AMSPs have routinely demonstrated annual savings of $200,000 to $900,000 in both larger academic hospitals and smaller community hospitals

SUMMARY

The evidence is robust that antimicrobial resistance has become an increasingly critical issue in healthcare institutions everywhere. For hospitals, solutions cannot be found by traditional management of hospital departments. Instead, a hospitalwide program that coordinates physicians and their ordering profiles, pharmacists, infection control practitioners, discharge planners, and others is needed for success.

The most effective place for most facilities to begin is to have an assessment carried out by an independent team that is uninvolved with the issues and departmental biases. From this review, a new process can be formulated, negotiated, and implemented. Most clinicians are unaware of their specific hospital issues and comparisons, and have not thought of acting outside of traditional approaches of treating patients 1 at a time without a strategic vision of how their current prescribing habits impact future effectiveness of antibiotics for all patients in their hospital and community.

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