Empiric Antibiotic Use and Resistant Microbes

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attacks. Unfortunately, quite a few referrals are asthmatic outliers with perennial asthma who do not respond well to any of the current approaches to therapy, alone or in combination.

It has been known for years that patients, patients’ families, and patients’ physicians frequently underestimate the severity of asthma.1–3 Despite the widespread use of peak flowmeters in the home, I think the tendency is still to underestimate the severity of the disease in adults. Perhaps my view is skewed. Quite often, my first encounter with an individual asthmatic patient is in the medical ICU, and most of these patients require intubation and mechanical ventilatory support. Each patient seems to have a similar story: a failure to recognize the severity of the disease in adults. Perhaps my view is skewed.

Quite often, my first encounter with an individual asthmatic patient is in the medical ICU, and most of these patients require intubation and mechanical ventilatory support. Each patient seems to have a similar story: a failure to recognize the severity of the disease, leading to undertreatment.

Years ago, our therapeutic armamentarium was limited. Now long-acting β2-agonists, supplemented with effective shorter-acting β2-agonists as well as improved inhaled corticosteroids, are available. Newer drugs for preventing acute exacerbations include antagonists of metabolites of both lipooxygenase and cyclooxygenase arms of the arachidonic acid pathway. Leukotriene inhibitors have proven quite effective in some patients. In this issue of CHEST (see page 73), Tamaoki et al present data on the efficacy of a thromboxane α2-receptor antagonist in reducing the quantity and viscosity of sputum in stable asthmatics. Theophylline, long out of favor as a therapy for adults, has an immunomodulatory effect at low doses and should be readdressed.4 Manipulation of the variety of therapeutic modalities now available, in order to provide the most effective program for the individual patient with asthma, will undoubtedly be helpful in preventing acute exacerbations. However, our ongoing assessment of the severity and “brittleness” of a patient’s disease must improve if we are to reduce morbidity and mortality.

As an intensivist who sees the morbidity and mortality of asthma almost daily, I remain convinced that regularly scheduled inhaled bronchodilators are the mainstay of maintenance therapy in all but the very mildest of asthmatic patients (“the open airway approach”). Both β2-agonists and anticholinergic bronchodilators, alone or preferably in combination, are effective in patients with asthma (the dichotomy, β2-agonists for asthma, anticholinergics for COPD, does not hold).

My major concern is that patients with the disease called asthma be treated individually and vigorously, that tapering doses of systemic corticosteroids be used early and liberally with exacerbations, and that the severity of the patient’s disease not be underestimated. I would be happy never to admit another patient with status asthmaticus to my unit.

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A “Catch-22” for the 21st Century

Over the past decade, clinicians have witnessed an unprecedented increase in the emergence and spread of antibiotic-resistant bacteria.1–3 These include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococcus (VRE), multiple drug-resistant Gram-negative rods, and resistant Streptococcus pneumoniae. ICUs are the leading incubators of many of these resistant organisms.1–6

In this issue of CHEST (see page 146), Kollef and colleagues demonstrate that ineffective therapy of resistant microorganisms is associated with increased mortality in critically ill patients. Clinicians at Barnes-Jewish Hospital used effective antibiotics empirically for the vast majority of patients with Gram-negative rod bacteremias. However, for patients with certain pathogens (MRSA, VRE, and Candida), the initial antibiotics used were not effective. Delays in instituting effective agents resulted in a higher mortality rate among these patients. Independent risk factors for development of resistant infections included previous treatment with antibiotics, presence of a central venous catheter (for longer duration), and low serum albumin levels.

References
These factors are likely to help identify “at-risk” patients at most institutions. Should we assume infections with antibiotic-resistant pathogens in every patient with one of these risk factors? If not, at what prevalence of antibiotic resistance should we include coverage of resistant organisms in empiric treatments? If we liberalize our use of the ever-decreasing list of effective antibiotics, aren’t we promoting emergence of more multiresistant organisms, including the dreaded vancomycin-resistant staphylococci? The emergence of antibiotic-resistant organisms is not new. Microorganisms have always been endowed with genetic mechanisms for attaining resistance. Clearly, our overuse of broad-spectrum antibiotics has accelerated the process of microbial resistance. Resistance rates are highest in the ICUs of most institutions due largely to overuse of antibiotics and cross-transmission. We can no longer assume that this is arcane “test-tube science” that can be ignored, counting on the pharmaceutical industry to stay one step ahead of resistant microbes through development of new antibiotics. We must lead in scrutinizing our (personal and aggregate) antibiotic prescribing patterns and in developing comprehensive institutional programs to minimize the emergence and further spread of these microbes. To the extent that patients move in and out of the ICU to various units of the hospital, our efforts will fail if control measures are limited only to the ICU. Solutions will necessarily require collaboration with other hospital personnel and integration of efforts, a consistent, systematic, unified front.

What should be our “first-line agents” in this era of resistant pathogens? Since the prevalence of resistant bacteria varies between and within institutions, the appropriate antibiotic choices for empiric therapy will necessarily vary between hospitals and will change with time. Interestingly, the problem of resistance had already impacted clinicians at Barnes-Jewish Hospital insofar as vancomycin was used “commonly” in their empiric cocktails of antibiotics. At many centers, where MRSA is not so prevalent, vancomycin is not used routinely. A prevalence of 15 to 20% resistance is, perhaps, a reasonable threshold to begin routine empiric coverage for resistant organisms in critically ill patients. The following general concepts are relevant to the discussion:

1. Initial Approach to Individual Patients: Clinicians should consider the balance between host (immunocompetence) and microbe (virulence) in determining the risks and benefits of immediate vs deferred and broad- vs narrow-spectrum treatment. The available clinical data (ie, the likely site of infection and organisms to which the host is susceptible) and the microbial resistance patterns at the institution should be considered in selecting antibiotics of adequate, but not unnecessarily broad, spectrum to cover the probable causes of infection.

2. Use Microbiology Antibiotic Susceptibility Results To Narrow the Attack: We must obtain culture/sensitivity results promptly, and modify the antibiotic(s) with the narrowest spectrum and/or lowest resistance potential to which the isolated organism is sensitive.

3. Use Optimum Doses for a Full Course of Treatment: The optimum doses of antibiotics should be continued for the full course to reduce the likelihood of selecting a resistant pathogen that will cause recurrent clinical disease. Unfortunately, for some sites of infection insufficient data exist to inform the optimal duration of therapy. Moreover, optimal duration could vary depending on the causative microbe, the severity of infection, and the immunocompetence of the host.

4. Avoid Antibiotic “Surfing”: Clinicians should allow a reasonable time (which may vary for differing hosts/infections) for clinical improvement before declaring an antibiotic failure. In some severe infections, fevers may persist for up to a week. If the microbe is sensitive (in the laboratory) and the patient is otherwise improving, persistent fever should not, in itself, be considered treatment failure.

5. Hospital Infection Control: Resistant microbes will continue to emerge, but we can attenuate the rate of spread by implementing effective control measures. We must continually remind all staff who care for, or come in direct contact with, patients to adhere to standard precautions because we (healthcare workers) are vectors for nosocomial infections. The available data suggest that we are abysmal in both the frequency and quality with which we wash our hands between patient contacts. Multiple drug-resistant nosocomial infections are unlikely to be reigned in unless this simple, yet difficult, step is taken. Physician-leaders should lead by example.

The risk of transmission is greatest while awaiting culture results. Extra precautions should be initiated when the admission data suggest the possibility of resistant, highly transmissible pathogens like VRE or MRSA. Waiting until cultures return unnecessarily increases risk of transmission to other patients. One approach is to place all patients with risk factors (history of MRSA or VRE infection, transfer from nursing homes, Gram’s stain data indicating Gram-positive cocci in clusters, and/or long-term IV catheters) in contact isolation until infection/colonization has been ruled out. For example, in our critical care unit, patients are placed in precautionary contact
isolation if any Gram’s stain of a body fluid reveals Gram-positive cocci in clusters, or cultures reveal staphylococcal infection and we are awaiting antibiotic sensitivities. But, this common-sense, preventative measure has not been proven to reduce the frequency of such infections and may not be cost-effective.

6. Institutional Restrictions on Antibiotic Use:
Selective restriction, removal, or control of antimicrobial agents, particularly those with high resistance potential, may be important means of reducing the emergence of multiple drug resistance. Implementation of such measures in some institutions has resulted in reductions in the prevalence of resistant organisms.\textsuperscript{15,16} Arbitrary rotation of classes or agents used in empiric cocktails may inadvertently increase the prevalence of multiple drug resistance. Such strategies are only likely to be helpful if they utilize microbial surveillance data to switch classes/agents when resistance emerges. Moreover, the use of centralized formulary restrictions and rotating crops of agents can only be successful if all stakeholders—intensivists, infectious disease specialists, hospital epidemiologists, pharmacists, and policy makers—coordinate their efforts (and staff physicians are convinced of the importance of such initiatives).

The emergence of multiple drug-resistant pathogens poses a new challenge to all. As intensivists, our critically ill patients will pay the heaviest price. Thus, we must lead the way in modifying clinicians’ behaviors (ie, appropriate antibiotic selection and dosing, and hand washing) and formulate comprehensive strategies to contain resistant infections, thus reducing the risk to present and future patients. Increasing scientific attention to this problem will yield proven solutions that can be instituted in the future. In the meantime, let’s make hand washing between patient contacts, one proven method of infection control, the 11th commandment in the ICU (and throughout the hospital).

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