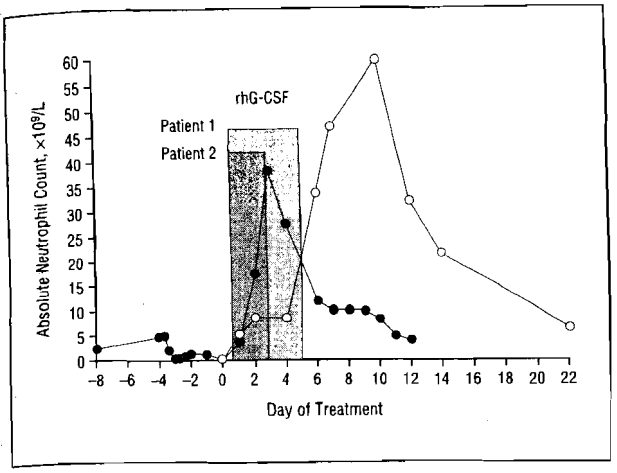

Absolute neutrophil count in response to the administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) for the previous patient (open circles) and the current patient (shaded circles). The time curves for absolute neutrophil count are superimposed so that the initiation of treatment with rhG-CSF coincides on day 0.

Comment. As in the previous report,[1] we saw no evidence of systemic drug toxicity following treatment with rhG-CSF, but differences in the time course and magnitude of the cellular response were seen. Time courses for both patients are shown in the **Figure**. In both patients, the absolute neutrophil count rose rapidly following the first dose of rhG-CSF. The absolute neutrophil count peaked in our patient several hours after his third and final dose, then rapidly declined to a normal range. The absolute neutrophil count of the patient of Murray et al peaked 6 days following the fifth and final subcutaneous dose, with a more gradual decline. There were several differences between the two patients that might explain their responses to rhG-CSF. The patient of Murray et al was neutropenic at birth and hypotensive shortly thereafter. Our patient acquired *Klebsiella* sepsis associated with necrotizing enterocolitis but without hypotension at 8 days of age. Both patients received standard doses of intravenous immunoglobulin; however, our patient did not receive granulocytes. Our patient received three daily intravenous doses of rhG-CSF and the patient of Murray et al received five subcutaneous doses. Our patient is perhaps more representative of the neutropenic and septic premature infant's response to rhG-CSF, without the complicating issue of granulocyte transfusion. As reported in a recent abstract,[2] rhG-CSF use in 12 preterm infants indicates a wide range of cellular response. We concur that continued investigation into this area is indicated to determine if rhG-CSF should be added to the armamentarium of treatment of sepsis-associated neutropenia in the neonate.

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In reply

We appreciate Nankervis and Seguin's patient report of another neonate who apparently benefited from rhG-CSF administration during bacterial sepsis. They aptly note the main differences in the two cases, namely route and duration of cytokine administration and neutrophil count response. Each patient had a very rapid rise in the neutrophil count, likely due to the release of mature neutrophils from the bone marrow neutrophil storage pool.[1] The differences in the duration of neutrophilia in the two cases may have reflected the subcutaneous vs intravenous routes of administration (prolonged systemic uptake from a subcutaneous drug depot in our case), the total number of doses given, or both. We disagree, however, that the single granulocyte transfusion that our patient received altered the degree of neutrophilia or natural outcome of his rhG-CSF response, since transfused granulocytes have such a short life span.[2,3]

While both patients received aggressive supportive care that included intravenous immunoglobulin therapy, it seems that their overall clinical course was affected more favorably by the rhG-CSF. The method and duration of rhG-CSF administration in this setting is certainly unclear and may be different from that involved with postchemotherapy cytokine support. Despite the apparent absence of side effects in these two patients and the general optimism we have for cytokine use, we emphasize that data must be analyzed from ongoing prospective clinical trials before the routine use of rhG-CSF during neonatal sepsis can be advocated.

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Antichlamydial Antimicrobial Therapy for Asthma

I would like to comment on the interesting report by Emre et al[1] associating *Chlamydia pneumoniae* infection and reactive airway disease in children. They found evidence for *C pneumoniae* infection in 25 (21.2%) of 118 children with acute episodes of wheezing; nine had positive cultures for *C pneumoniae* but did not have diagnostic antibody, 13 had diagnostic antibody but had negative cultures, and three had positive cultures and positive

serologic results. They also report that eradication of the organism after the treatment of wheezing in children with positive cultures was associated with symptomatic and laboratory improvement. They hypothesize that chronic *C pneumoniae* infection can produce chronic airway inflammation and bronchial hyperresponsiveness. Their data also support their statement that use of serologic testing alone would have underestimated the prevalence of *C pneumoniae* infection in children.

An unanswered question raised by their data is: Did some children with negative cultures and diagnostic antibody have *C pneumoniae* lung infection causing wheezing? Indirect evidence might be obtained by evaluating the results of antichlamydial antibiotic treatment in the group of children who had negative *C pneumoniae* cultures but had positive serologic results. For example, I have treated a limited number of adults with positive *C pneumoniae* cultures and chronic asthma symptoms (not experiencing exacerbations) who, like the children described by Emre et al, improved both symptomatically and by laboratory criteria. Adult asthmatics who had negative cultures but had positive serologic results also responded to treatment in an identical fashion.[2] Do the authors have experience with treatment results in children with negative cultures?

It is possible that some of the children with positive cultures described by Emre et al actually had chronic infection. This might explain the nondiagnostic serologic results (which apply to acute infection only) and would be more consistent with their hypothesis concerning infection and inflammation. Adult asthmatics with negative cultures who had low levels of *C pneumoniae* antibody that did not meet criteria for acute infection also have responded to antichlamydial antibiotic treatment.[2] It is possible that culture positivity and serologic positivity are just the tip of the iceberg when it comes to the role of *C pneumoniae* infection in asthma.

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In reply

We appreciate Hahn's taking the time to read and comment on our recent published study in the ARCHIVES[1]*; however, we must take exception with some of those comments. Hahn states that we found evidence of* C pneumoniae *infection in 21 children with reactive airway disease, including nine children who had negative cultures but had "diagnostic" antibody. Unfortunately, diagnostic antibody was also present in 37.5% of the asymptomatic controls with negative cultures, which makes the significance of this antibody questionable. We have found that antibody to* C pneumoniae*, as determined by the microimmunofluorescence test, is frequently not predictive of who is actually infected as determined by culture and/or polymerase chain reaction.*[2] *There are several possible reasons for this. Unlike* Chlamydia trachomatis*, the major outer membrane protein does not appear to be immunodominant in* C pneumoniae *infection. The major outer membrane protein appears to be the primary antigen presented in the microimmunofluorescence test. We performed immunoblotting on serum samples from 21 children with pneumonia who had positive cultures but had negative serologic results; all of them reacted to a number of* C pneumoniae *proteins, but a minority reacted to the major outer membrane protein.*[3] *Thus, failure to detect antibody with the microimmunofluorescence assay may be a problem of the test itself, as we can detect antibody by Western blot. The gene that encodes the major outer membrane protein is highly conserved for both nucleotide and amino acid sequences between the three chlamydial species; thus, cross-reactions can occur. We and others have found that almost 20% of asymptomatic adults will have serologic evidence of acute* C pneumoniae *infection.*[4,5] *These data strongly support our belief that the only accurate way to diagnose* C pneumoniae *infection is by identification of the organism by culture or polymerase chain reaction. We do not use serologic testing to diagnose genital infection* C trachomatis *for similar reasons.*

If one believes the serologic data, as Hahn does, it would imply that we are failing to detect more than 50% of the infections by culture. However, based on a comparison of culture and polymerase chain reaction, we are probably missing less than 5%.[2] *In fact, polymerase chain reaction was only 76.5% sensitive compared with our culture methods. This makes the issue of treating the children who had negative cultures but had positive serologic results moot, as the available data strongly suggest that these children are truly not infected. This raises another point concerning the assessment efficacy of antibiotic treatment in these children. We documented microbiologic eradication in all of the infected children, but not all improved clinically. One child needed three courses of treatment to eradicate the organism, but still did not improve clinically. We did not treat the children who had negative cultures but had positive serologic results because they were not infected by our criteria. Without a specific microbiologic diagnosis, one is left with clinical outcome as an end point, which, unfortunately, is frequently nonspecific.*

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How to Improve Teaching on the Hospital Wards

Bellet's[1] discussion of how to improve teaching on the hospital wards in the June issue of the ARCHIVES was excellent. I would like to comment on a few issues that the author touched on only briefly and offer other suggestions on how to make teaching more effective.

Whereas I agree with Bellet that the ward teaching responsibilities need to be shared by the attending physician and the senior resident, he does not specifically mention how to accomplish this. If the attending and senior resident met to negotiate the division of teaching responsibilities, these would be more clear, as would the expectations of both.[2,3] As an example, the attending could assume the primary responsibility for reviewing every medical student's written history and physical examination of patients, providing each with timely feedback. In addition, many attendings at our institution also conduct student-oriented patient care discussions apart from rounds with the residents. There also needs to be an agreement on what to do regarding a problem with a junior resident, such as not knowing his patients well; ie, who will counsel that individual? These are issues that should be discussed prior to the rotation.

Another important point Bellet mentions is that the attending's teaching sessions should focus on patient problems and should occur at the bedside and/or in the conference room. What these sessions should not be, in my opinion, is a lights-out slide presentation about a topic in general. When residents and students are not actively involved in the session, there is a tendency to "head-nod" and lose interest. These more formal presentations can be reserved for resident core conferences or similar educational meetings. The senior resident and team should be able to identify their learning needs from assessment and management problems on the ward, and the discussion for attending rounds should focus on an aspect of a current patient problem if possible. This does not have to be limited to biomedical issues but can include psychosocial, physical diagnosis, or health matters.

The discussion does not clearly separate work rounds from attending rounds, with the weighting more on the latter. A significant amount of resident time is spent on morning work rounds, and since 1974 our training program has expected that the ward attending physician will make morning work rounds with the residents and students. This is very labor intensive for already stressed attendings, but we strongly believe that this model provides the best care to the patients and the best education to the team. The role of the attending is one of support, ie, a resource person. The senior resident is expected to be in control of rounds and can call on the attending as needed. The latter observes the teaching, presentations, assessments, management plans, and so forth, and is very capable and qualified to evaluate team members at the end of a rotation.

Finally, a major omission from Bellet's discussion is that many of the skills mentioned are learned by attendings through faculty development workshops, and they should be encouraged to attend.[4] The transference of these skills and attitudes from the classroom and from publications such as this takes practice, feedback, and an environment receptive to change.

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In reply

I wish to comment on several issues raised by Dr Greenberg. The roles and responsibilities of the senior resident and attending physician should be based on sound principles that form the foundation of the teaching program. The senior resident should be responsible for so-called work rounds as I outlined in my article. The attending physician should set an example as a clinician and teacher, which is a much more active role than that of a resource person and observer as described by Dr Greenberg. It is crucial that time be set aside specifically for instruction, using the bedside and conference room. These small-group interactive sessions should focus on patients and their problems. I agree that faculty development workshops can be useful in helping attending physicians improve their teaching skills.

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