The Clinician's Management of the Febrile Infant: The Context Is the Key

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The author of the article titled "Fever in Children Younger Than Three Months of Age: A Pooled Analysis,"[1] in this month's issue of The Journal, has performed a valuable service to the readers of this journal and indeed to all physicians who care for children in this age group. The younger than 3-month-old infant who presents with fever is clearly such a clinical dilemma that many investigators have attempted to shed light on defining the optimum approach. Unfortunately, many of the data that have resulted from these various studies have only led to more uncertainty and confusion when they are read individually. The questions asked by the majority of investigators exploring this all too frequently encountered clinical "black box" are often the same:

1. Are there any clinical measures, objectively quantifiable, that can be relied upon to distinguish the bacteremic infant from the nonbacteremic infant?
2. Are there specific laboratory measures or other diagnostic strategies that can be used as discriminating diagnostic screening tools for helping the clinician determine which infant is bacteremic?
3. Is the height of fever any indicator of the severity of infection?
4. Can clinical experience be measured, and is it a factor in helping the clinician to determine the presence of bacteremia?

The present study presents all of the relevant recent research on this subject in a pooled analysis so that readers can have the opportunity to reach several workable conclusions in their future approach to patients with this presenting problem. By combining the patient populations from ten different studies through a statistical technique that, though controversial, appears sound in concept and interpretation, the author has enabled the reader to answer many of the above questions by getting a bird's-eye view of what is the true risk, what are or are not the useful disciminating measures for detecting a bacteremic infant, and what might be a rational approach to take toward such infants in their own clinical settings.

Fever curves, white cell counts, sedimentation rates, house officers' perception of sepsis, or other attempted discriminating markers notwithstanding, however, from my own experience and that of the institutions with which I have had experience, underlying all of these attempts to distinguish the truly sick from the not so sick infant with fever are three crucial factors. These factors must be incorporated into all judgments, and indeed they play such a significant role in determining the disposition of such infants that they should really come first, not last, when considering how to manage such ill infants. The following three factors are the crucial substrate of all physician-patient encounters:

1. The patient population served by the physician
2. The nature of the ambulatory practice setting with specific focus on the ability to have true continuity of care before and after the visit
3. The experience of the clinician examining the infant at the time

I venture to say that with any number of additional studies, when it is all said and done, investigators will still have their own preferred way of dealing with these infants, but their preferences will all be qualified by the contribution of these three factors to the final clinical decision.

PATIENT POPULATION

How reflective of the population as a whole are the patient populations represented by these studies?

All the studies included in this review were based on populations seen in busy ambulatory settings in major urban medical centers. These populations are not nec-

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essarily representative of the overall population, but they represent a large enough constituency that the results must be regarded seriously with respect to patient populations of similar socioeconomic status, environmental exposure, family composition, level of ongoing health care and surveillance, degree of illness in the family, amount of time spent in day care settings, and overall state of health. How representative, however, are the patients in these studies when compared with the population as a whole? Is it appropriate to extrapolate from these infants and their potential problems, many of whom come from high-risk settings, to a more broad-based population? It appears to me not. Until the results of a study of a more broad-based population are available (difficult to orchestrate, I will admit), it is possible to generalize the results from these studies not to the overall population, but only to the type of population from the at-risk background used as subjects in these studies.

A similar inability to generalize from one population to a more broad-based population arose when the subject of otitis media in the neonate was addressed in the 1970s. At that time people drew conclusions for managing this problem from the study of otitis media in the younger than 3-month-old infant by Bland et al.[2] In that study of a relatively small sample (30 neonates) from a selected environment (a neonatal intensive care unit), the investigators found that there was a significant incidence of gram-negative meningitis secondary to otitis media and that one of the neonates died from this infection. For several years afterward, many medical centers became extremely guarded about their management of neonates who carried the diagnosis of otitis media and urged that full sepsis workups be performed on all such infants. Many others even suggested a course of antimeningitic doses of antibiotics until the culture of cerebrospinal fluid proved to be negative. Only after subsequent studies were performed on a more representative population, through a collaborative project including private pediatricians and a busy urban ambulatory center, did a more accurate picture of otitis media in this age group develop. The setting and the type of patients and the ability to follow patients closely gradually allowed careful readers to realize that this diagnosis did not carry the predictions of dire outcome that appeared to be the result of the initial, more narrowly based study. Fortunately, as a result, clinicians in many ambulatory settings developed a less knee-jerk response to neonates with otitis media and broadened their approach to manage them in a manner similar to the management of other infants with that diagnosis.

I believe that the same course should result from future research using a population-based sample that is broader based and more representative. I still do not think physicians have a true perception of the reality of bacteremia in this age group in the population as a whole.

THE CLINICAL SETTING AND THE ABILITY TO HAVE CONTINUITY OF CARE BEFORE AND AFTER THE ACUTE CARE VISIT

All the studies reported in the article by Gehlbach were necessarily based in busy, ambulatory care settings. The clinical encounters were primarily made by house officers, with more experienced attending pediatricians in consultation. These academic ambulatory sites provide not only the highest volume of patients with this potential problem but also the clinical faculty who are interested in the particular problem. There are some significant shortcomings inherent in these settings, however, with respect to the ability to make judgments on how well the child with fever might be. How well known are the family and infant to the caregiver? Usually these encounters are in acute care settings where the child and family are not well known by the physician making the initial assessment. What are the various options for close or frequent contact should there be a decision not to admit the infant to the hospital?

There is all too often limited or no continuity of care either before or after the visit to the walk-in or emergency room facility. Hence, there is a need to be on the safe side by admitting all infants and treating or not treating pending the results of diagnostic studies performed. In my view, the major forces driving the decision to admit is the believed high risk of bacteremia in this age group and the presumptive belief in impending, overwhelming sepsis, combined with the lack of familiarity the physician has with the infant and family. The lack of true and effective continuity of care is a major contributing factor to the dis-ease physicians in these settings experience with these infants. The more familiar the physician is with the parents, and the parents' way of interpreting their baby's behavior, and the greater the physician's ability to have close follow-up of the baby in the ensuing 48 hours, the more likely will the infant be identified who might be potentially truly in trouble from overwhelming infection.

I am often bombarded with comments from pediatricians in private practice who tell me that they have rarely seen infants who are febrile in the first three months develop any serious complications. In addition, they also report that they rarely do extensive diagnostic testing because of limitations in their ability to perform reliable and cost-efficient laboratory diagnostic studies. Much of their decision making is based on their relationships with the parents and being able to appreciate the parents' observations and concern, an invaluable and difficult-to-quantify piece of information. In addition, they depend on their ability to have close follow-up, either through the office or by telephone. Without these two important cornerstones to the practice of clinical medicine, these

physicians' ability to feel secure in their decisions regarding the care of these infants with fever would be severely hampered. With it, and with the incidence of bacteremia being about 3 percent as a mean across all of the studies, these physicians feel comfortable with their ability to detect the seriously ill child who may be at risk for bacteremia.

The importance of continuity of care, therefore, cannot be overemphasized when the physician is faced with this clinical problem. The poorer the ability to know the family before the acute visit, the less reliable will the information be from the history, and the less able will the physician be to interpret the results of the queries. Similarly, the less the physician is able to have close follow-up either in person or by telephone, the less likely will the physician be to send home the infant with fever. Hence, the degree of effective continuity of care is a major determinant of how these infants should be managed.

THE LEVEL OF EXPERIENCE OF THE EXAMINING PHYSICIAN

The third major factor underlying the ability to make proper decisions regarding infants who present with fever is the degree of experience of the examining physician, and therefore the ability of the physician to recognize the infant who "looks sick" in determining who is at risk for dangerous bacteremia. The present review corroborates that several of the individual studies placed a significant degree of faith in the examining physician's ability to make clinical judgments based on "soft" clinical findings such as consolability, irritability, activity, and presumption of sepsis. The ability to detect those bacteremic infants yielded a 92 percent sensitivity, with the examiners being, for the most part, house officers at different levels of training. Individual comments from many of these investigators through personal communication clearly reinforce what many of my colleagues know to be the case; the more experienced the examining physician, the more likely will these "truly bacteremic infants" be detected.

In summary, what are the implications of these thoughts combined with the excellent review by Gehlbach? They are the following:

1. The more experienced the examining physician, the less likely it is that any additional tests, beyond a peripheral white cell count, will be useful or cost effective in managing febrile infants younger than 3 months old.
2. The greater the continuity of the physician's care before and after the acute visit, the better able will the physician be to assess accurately the risk of sepsis in the infant.
3. Fever above 39.0 °C in the infant younger than 1 month old continues to represent a more significant risk; such an infant should be separated out from others who are younger than 3 months of age with lower fevers.
4. Decisions about the proper way to manage such infants must be tailored to the type of facility where they are seen. The less the ability for true continuity and the higher the risk of the population, the more these febrile infants require scrutiny by the most senior and experienced of physicians. This scrutiny can still occur in consultation with more junior trainees (which will actually enhance, not detract from, the education of the trainee), but it must be a required part of any patient encounter in this setting with this problem.
5. There is still a need for additional research with a more broad population base that considers many of the variables outlined above, including level of experience, degree of continuity of care available, and further long-term outcome. This research is most important if physicians are to limit with even more accuracy the degree of concern to the proper group, being sure that the population covers a wider base than those who truly are bacteremic. This capability is probably even more important in light of the recent evidence of the use of the long-acting antibiotics given systemically and their prevention of subsequent bacteremia. It would be a dreaded outcome of the currently available research simply to find security in this particular route. This approach would only lead to further studies, a certain increased morbidity, and probably even more potential iatrogenesis than already exists now.

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LETTERS TO THE EDITOR

The Journal welcomes Letters to the Editor, if found suitable, they will be published as space allows. Letters should be typed double-spaced, should not exceed 400 words, and are subject to abridgment and other editorial changes in accordance with journal style.

OBSTETRICS IN FAMILY PRACTICE

To the Editor:

Regarding the article by Smucker and the guest editorial by Rosenblatt in the February issue of The Journal,[1,2] with all due respect to the concept of natural childbirth and noninterventional obstetrics, and with a hearty seconding of the motion for a critial review of different obstetric approaches, the unpleasant fact remains that obstetric protocols currently are being "assembled from courtroom dockets." In such a practice environment, in which it is stated that a physician is seldom, if ever, sued for doing a cesarean section but often sued for not doing one, an alternative interpretation of the Ohio data emerges. Specifically, with only one out of 282 respondent family physicians currently doing cesarean sections, and only 21 of that total number ever having done cesarean sections, coupled with 47 percent of these respondent physicians not being residency trained, it is entirely possible that inadequate training or at least the perception of inadequate training is a prime factor in forcing these individuals out of obstetric practice. When one couples this with the much-publicized insurance news from Alabama in the summer of 1985, that the Mutual Assurance Society of Alabama would "no longer cover deliveries by family practitioners unless the physician is prepared and willing to perform Cesarean sections" (*Family Practice News,* vol 15, No. 22, 1985), it becomes imperative that, in creating a "new paradigm" of family practice obstetrics, we do not equate adequate family practice residency training in obstetrics with that training provided to nurse midwives. As an individual residency-trained in performing and continuing to perform cesarean sections for a variety of well-accepted indications, and also as one on excellent consultative terms with the two board-certified obstetricians in my community, I can attest that there are alternative definitions of low-risk vs high-risk obstetrics other than simply leaving all interventions to the obstetricians.

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MONOCLONAL ANTIBODY PREGNANCY TEST

To the Editor:

We read Dr. Andolsek's recent article describing presentation of unruptured ectopic pregnancies[1] with interest and enjoyment. In her recommendations Andolsek favors the use of serum beta subunit human chorionic gonadotrophin radioimmunoassays over "less sensitive" urine pregnancy tests. We are curious as to whether the urine test employed in her study was based on monoclonal antibody technology.

Tests of this type (monoclonal antibody) are available for use in ambulatory settings and approach serum

radioimmunoassays in sensitivity. The advertised lower limits of sensitivity for most tests range from 20 to 50 IU/L (20 to 50 mIU/mL) of human chorionic gonadotrophin; actual sensitivity may be even better.[2] Another study suggests that sensitivity may be amplified, when urinary human chorionic gonadotrophin concentrations are very low, by use of 20 drops of urine rather than the usual 5.[3]

We have conducted our own observations to judge the extent to which these reports apply in our setting. Using the Abbott "Testpack" (urine), whose advertised lower limit of sensitivity is 50 IU/L (50 mIU/mL),[4] we measured urinary human chorionic gonadotrophin concentrations that were confirmed by radioimmunoassay. Positive results were obtained from urine samples with concentrations of 48, 35, and 26 IU/L (48, 35, and 26 mIU/mL), while urine samples with concentrations of 8 IU/L (8 mIU/mL) and less than 1 IU/L (1 mIU/mL) tested negative. Use of the 20-drop method did not yield a positive result with urine containing 8 IU/L (8 mIU/mL) that had tested negative with five urine drops.

Based on these results, we conclude the sensitivity of the monoclonal antibody pregnancy test we use approaches reported limits. Hence, we rely on it both for clinical use in detecting early gestations and in diagnosis of ectopic pregnancies and also as a pregnancy outcome measure for research purposes. We are using serum radioimmunoassays only for quantitation and for those few instances when clinical suspicion persists despite a negative urine test. We found the 20-drop method did not amplify sensitivity over the range of concentrations evaluated and, hence, have not adopted it for this purpose, although we did not measure concentrations between 8 and 26 IU/L (8 and 26 mIU/mL).

We welcome any observations from Dr. Andolsek and others regarding their experiences with monoclonal antibody urine pregnancy tests.

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INFLUENZA IMMUNIZATION OF ELDERLY

To the Editor:

I read with a great deal of interest the commentaries on vaccination of persons over 65 years of age for influenza that appeared in the *Journal of Family Practice* (*Is routine influenza immunization indicated for people over 65 years of age? Thompson MD: An affirmative view. Frame PS: An opposing view. J Fam Pract 1988; 26: 211–214*). We have recently published a study[1] that has led me to believe that this should not be a controversy; that it is controversial among primary care physicians probably contributes to the poor vaccine compliance among elderly persons. I am in general agreement with the statement of Thompson; therefore, I would like to direct my comments to Frame.

The first problem that I have with Frame's approach is defining, from the public health standpoint, who is chronically ill. I am concerned that many persons are not aware they have ischemic heart disease or mild chronic obstructive pulmonary disease or both until, perhaps, they have been hospitalized with pneumonia or some other complication during an influenza epidemic. Our estimate of the proportion of elderly persons with high-risk conditions, however, is considerably higher than the 40 percent stated by Frame. Using the National Health Survey data for prevalence of selected chronic conditions, we estimated that at least 54 percent of persons 65 years of age or older have conditions for which the Immunization Practices Advisory Committee now currently recommends influenza vaccination for persons of all ages. Our estimate represents the patient's own perception because it was obtained by household interview. In actuality a higher proportion may have chronic conditions.

Using the National Health Survey rates for the prevalence of the high-risk conditions to estimate denominators, we calculated the rates of hospitalization for acute respiratory disease (usually pneumonia) during influenza epidemics. We found only a small difference in the rate of hospitalization for persons ≥65 years of age with or without an accompanying discharge diagnosis of one or more high-risk conditions. The rate for persons with high-risk conditions—usually cardiac or pulmonary disease—was 47 per 10,000 and the rate for persons without a high-risk diagnosis was 37 per 10,000. In fact, the rate for persons ≥65 years of age without high-risk conditions was twice as high as the rate for persons <65 years of age with high-risk conditions. This finding has brought us to the conclusion that all persons ≥65 years of age, regardless of their condition, should have highest priority for influenza immunization. Our goal should be to keep active elderly persons out of the hospital.

Frame has made some unwarranted assumptions about morbidity associated with influenza infection. We would agree with the assessment

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of Marine[2] that Barker and Mullooly have underestimated the serious morbidity caused by influenza in their studies because they attributed to influenza only the excess of cases that occurred during influenza A (H3N2) epidemic years as compared with influenza B epidemic years. Frame mistakenly assumed that Barker and Mullooly overestimated the risk because public health laboratories report positive cultures from fewer than 25 percent of patients during influenza epidemics. Systematic surveillance by the Influenza Research Center in Houston for 14 years has demonstrated that up to 50 percent of patients presenting for medical care with acute respiratory tract disease during influenza epidemics will have positive cultures under less than optimal conditions for virus recovery.[3,4] Furthermore, other respiratory tract viruses are relatively inactive during the most intense periods of influenza epidemics, leading to the conclusion that most of the acute respiratory illness during epidemics is caused or initiated by influenza virus infections.

Frame's best argument against immunization is the less-than-perfect efficacy of influenza vaccines, especially in the elderly. Several factors contribute to this problem. One is the mutability of the viruses, which results in epidemics caused by variants that have drifted antigenically from the viruses used to make the vaccine. Despite worldwide surveillance by the World Health Organization laboratories to detect antigenic changes at the earliest possible moment, the lag time for producing and distributing vaccine makes it inevitable that this will happen. It does not mean, however, on those occasions when drift occurs that the vaccine is not useful. Some immunity usually results, which, although it may not prevent infection, may be sufficient to prevent serious complications and death.

Another problem is that elderly debilitated persons may not have optimal antibody responses to current vaccines; therefore, other adjunctive measures must be taken to protect these vulnerable persons. Amantadine can be used to reinforce vaccine protection during influenza A epidemics. Healthy contacts should be vaccinated to reduce the likelihood that high-risk persons are exposed to infection. Efforts of this nature are particularly indicated for nursing homes to prevent nosocomial exposures. Better vaccines and strategies are needed to protect the elderly, but we are sure that Frame understands that, under current recommendations, placebo-controlled studies are not ethical. Most evaluations must be performed comparing outcomes in persons who do or do not accept vaccine.

In summary, the best information available indicates that all persons over 65 years of age are at highest risk for influenza and deserve vaccination. New efforts must be put forth to improve vaccine acceptance for this vulnerable age group.

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3. Couch RB, Kasel JA, Glezen WP, et al: Influenza: Its control in persons and populations. J Infect Dis 1987; 153:431–440
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The preceding letter was referred to Dr. Frame, who responds as follows:

The letter by Dr. Paul Glezen certainly demonstrates that indeed in-

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fluenza vaccination of healthy persons over age 65 years is a controversial issue. The articles Glezen references demonstrate that hospitalizations for acute respiratory disease in Houston, Texas, correspond to periods of high influenza activity in the community. This is certainly not a new finding, but it does suggest a causative role for influenza in some of these cases. It is certainly not, however, a sufficient reason to recommend influenza vaccination for all persons aged over 65 years. The studies say nothing about whether these persons had or had not received influenza vaccination and make no attempt to evaluate vaccination effectiveness.

Glezen mentions the calculation that 54 percent of persons over the age of 65 years are high risk. In his paper (reference 1) he presents the finding that 60 percent of persons hospitalized for acute respiratory disease were high risk. In contrast, Barker and Mullooly took their data on the prevalence of risk factors from a defined population of health maintenance organization participants in Portland, Oregon. The vast majority of these persons did not require hospitalization and were ambulatory. Thus, when talking about prevalence of risk factors, we must be certain to know whether we are talking about persons hospitalized for acute respiratory tract disease or about the general population.

I am surprised by Glezen's finding that there were only small differences in the rate of hospitalization between persons with and without risk factors. This is certainly not my experience or that reported by other studies.

My statement that only about 25 percent of persons presenting to physicians with respiratory complaints during an influenza epidemic will have positive influenza cultures comes from work by Sabin published in JAMA in 1975, not from the work of Barker and Mullooly. Glezen (reference 1) reports one epidemic in which 47 percent of persons presenting to sentinel practices with respiratory complaints had positive influenza cultures, but he also presents data from two other epidemics in which the rates were 17 percent and 20 percent. In any case, his data support my statement that the majority of patients presenting to physicians during an influenza epidemic with respiratory complaints will not have culture-provable influenza.

I do not believe that a prospective placebo-controlled study of influenza vaccination in healthy persons would be unethical. After all, less than 25 percent of the population are currently receiving influenza vaccination, and thus there should be no great concern if some people were randomized into a group that did not receive vaccination. I believe such a study would be most useful and should be undertaken. In the absence of a prospective controlled study of influenza vaccination, the restrospective case-control method used by Barker and Mullooly provides the best data and the only controlled data we have. I would reiterate that these data show little benefit for healthy persons of any age from influenza vaccination.

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SCREENING FOR ENDOMETRIAL CANCER

To the Editor:

I was very happy to read Jaber's article on screening for endometrial cancer (*Jaber R: Detection of and screening for endometrial cancer. J Fam Pract 1988; 26:67–72.*). This is certainly one area where family physicians can have a major impact on long-term health of female patients, both those who are postmenopausal and those with dysfunctional bleeding.

While several devices for obtaining endometrial cell samples were mentioned, the "Pipelle endometrial suction curette" was not mentioned. The device is a 24-cm strawlike plastic catheter which includes a piston that allows the creation of negative pressure. The device is introduced through the cervical canal and the

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