Today's Treatment

Use of antibiotics

Treatment of neonatal bacterial infection

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The fetus is unlikely to encounter many bacteria during intra-uterine life, but rupture of the membranes, passage through the birth canal, and first contacts with the outside world change that. Over the first days of life the newly born infant becomes colonised by bacteria at all the usual sites, yet in all but a few instances he manages to live harmoniously enough with his organisms. Bacterial infection accounted for only 2% of stillbirth and first-week deaths in the national survey of births held in Britain during one week of 1970; these deaths were caused equally by pneumonia and extrapulmonary infections. In surviving babies major bacterial infections are also rare, though sometimes the resulting structural damage to an organ may severely limit its potential for normal growth and function.

Diagnosis

The difficulties of diagnosis in the neonatal period are such that brief mention must be made of those at risk, the presenting signs of infection, and the few helpful diagnostic tests. Those most prone to infection are preterm infants; indeed, inflammation of placenta and membranes may be associated with a number of premature labours. Preterm and low-birth-weight infants account for a minority of all births, so that actual numbers of them infected may not be greater than those of similar infants who are well grown and mature. Other infants at risk include those born after prolonged rupture of the membranes, those born to mothers who have had previously unsuccessful pregnancies or who are in poor socioeconomic circumstances, boys, and infants artificially rather than breast-fed. Intrapartum infection often, though not invariably, presents as respiratory distress soon after birth. Periods of apnoea may occur early, and deterioration may be rapid. Early signs of later infection that may start appearing from the middle of the first week onwards are non-specific and will probably be noted by those careful observers—most importantly, mothers, who study infant behaviour minutely. Such signs—often dismissed as trivial by doctors—include low-grade fever, unusual lethargy or irritability, a reluctance to feed eagerly, vomiting, or some looseness of the stools. Severe jaundice, recurrent apnoea, and abdominal distension are most likely in the immature.

Final proof of bacterial infection in newborn babies is little different from that at other ages and largely rests on finding positive cultures from blood, cerebrospinal fluid (CSF), or

urine; on recovering pus from superficial or deep lesions; on radiological findings; and on necropsy evidence. As accurate diagnosis may be essential for successful treatment cultures should be made whenever possible before starting antimicrobial treatment. In many cases, however, serious deterioration or death may occur before the results are available, particularly in infection acquired intra partum, so that rapid accurate diagnostic tests are urgently needed. Yet it is probably true to say there are none at present that can be relied on absolutely. Of those that can be done near the bedside and without elaborate laboratory equipment, probably only urinary microscopy (see urinary tract infection) and the white cell count will be helpful.

WHITE CELL COUNT

During the first 48 hours of life (when babies who have acquired infection during labour and passage through the birth canal become ill) there is normally a sharp rise in the white cell count, followed by a fall to normal of the total count and total neutrophil count. It is a falling count, however, or low numbers during this period ($<6.0 \times 10^9/l$ and $<4.0 \times 10^9/l$ respectively) that are likely to be associated with serious intra-partum infection; and at present, for infants born after prolonged rupture of the membranes or presenting soon after birth with respiratory distress, this seems the most helpful test. In other babies who do not fall into these two groups, and who present with the other signs suggestive of infection mentioned above at any time in the first month, high total neutrophil and non-segmented neutrophil ("band") counts ($>7.5 \times 10^9/l$ and $>1.5 \times 10^9/l$ after the first 24 hours of life respectively), sometimes in conjunction with low platelet counts ($<125.0 \times 10^9/l$), are found significantly more often in infected infants than in those who present with similar signs but are uninfected.

Factors governing treatment

Factors governing treatment include the wide range of infecting organisms likely at this age and the peculiarities of neonatal pharmacology. The group B beta-haemolytic streptococcus, found in the birth canal of fewer than a quarter of pregnant women, is probably the commonest cause of intra-partum infection in Britain at present; *Escherichia coli* follows it closely, while *Proteus* spp, the Klebsiella-Enterobacter-Serratia group, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Campylobacter fetus*, *Listeria monocytogenes*, and anaerobes such as *Bacteroides* spp are among the other organisms occasionally implicated. Later infection may be acquired from the environment, and among low-birth-weight babies at least must include, as well as those already mentioned, lesser known bacteria—some of them, mostly Gram-negative, to be found in the humidification units of apparatus—which rarely compromise the healthy adult host. Staphylococcal illness, foremost among

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later infections in the 1950s, is now much less common in most newborn nurseries, though small outbreaks have been reported again in recent years.

The newborn infant does not metabolise or excrete drugs as efficiently as older children and adults. Enzyme systems responsible for conjugation in the liver and renal tubular and glomerular function are imperfect by adult standards. Other factors, such as differing amounts of extracellular water at differing gestational ages, the unusual permeability of the skin of preterm infants, and the possibility of drug competition with bilirubin at protein-binding sites, have to be considered when prescribing. On the practical side of administration, the small muscle bulk of some very immature infants and the uncertainties of absorption from the gastrointestinal tract in the first days of life may mean that the intravenous route will have to be used. Suitable drug dosage has been established for most of the antimicrobial drugs (see appendix), but individual variation in metabolism and excretion at the lowest gestational ages make it essential that drug concentrations are checked when serious infections occur.

Treatment of suspected major infection

SEPTICAEMIA OR BACTERAEMIA, PNEUMONIA

In the neonatal period infection is usually suspected rather than proved when antimicrobial treatment is started, for serious deterioration or death may occur before the results of culture are available, particularly in intrapartum infection. This inevitably results, in neonatal intensive care units at least, in a worrying overusage of drugs, though knowledge of which infants are at particular risk and of white cell counts may allow some restraint to be practised. Present experience and sensitivity patterns suggest that the combination of benzylpenicillin (most effective of the penicillins against group B beta-haemolytic streptococcus) and an aminoglycoside will be suitable, at least until further information is available from the laboratory. Gentamicin, which has now been widely used, and the newer tobramycin and amikacin have the widest spectrum and cover most eventualities. Kanamycin is also a well-tried aminoglycoside, and satisfactory where *E coli* and certain *Proteus* isolates are sensitive and *Ps aeruginosa* infections unlikely. Infection known to be due to penicillinase-producing staphylococci would be covered by the aminoglycosides, though methicillin or cloxacillin should replace benzylpenicillin.

In hospitals today the combination of ampicillin and cloxacillin is much less useful, particularly for low-birth-weight infants, for *Ps aeruginosa* is not catered for, many *E coli* isolates are now ampicillin-resistant, and staphylococcal infections are unusual. While the duration of treatment should be individually decided, five to seven days may be sufficient for pneumonia, and seven to ten days for bacteraemia, but these are arbitrary recommendations.

URINARY TRACT INFECTION

All available evidence suggests that it is in very early life that urinary tract infections cause kidney damage. It is then that vesicoureteric reflux is relatively common, and scarring of the kidney parenchyma and impaired renal growth may follow. Thus detection and prompt treatment in the neonatal period assume added importance and urgency. Boys are affected more commonly than girls, in contrast to later childhood and adult life, when the converse is true; and blood-borne rather than ascending infections are also not uncommon, and may be associated with parenchymal lesions. *E coli* is responsible for nearly 80% of cases; the remainder are caused by *Klebsiella* spp and a miscellany of other organisms.

The collection of uncontaminated urine specimens from the newborn so necessary for diagnosis requires patience and attention to detail. The perineum should be washed with soap

and water, rinsed, and dried with sterile swabs before a collecting bag is applied, or the infant is held or placed over a sterile collecting dish. A negative culture from bag-urine rules out infection at the time of collection, but positive cultures or the finding of > 10 pus cells/mm³ requires further confirmation, and either a true midstream specimen or urine collected by suprapubic aspiration must be sought. Cultures of 10^5 /ml or more from midstream specimens, preferably on more than one occasion, or any growth from suprapubic aspiration constitute infection. The finding of bacteria on microscopy of freshly collected unstained uncentrifuged or centrifuged urine correlates well with a significant growth on culture, and should be used for rapid diagnosis. Urine specimens should be in the laboratory within an hour of collection or stored in the domestic refrigerator until this is possible if other methods such as the dipslide are not available on the ward.

Initial treatment could be as for suspected major infection, that is, a penicillin and an aminoglycoside, for bacteraemia may accompany the urinary tract infection. Although many isolates of *E coli* may be resistant to ampicillin, when this is not so the combination of ampicillin with gentamicin may allow synergistic action. In relatively asymptomatic non-jaundiced infants presenting later in the neonatal period a sulphonamide or co-trimoxazole will often prove effective. Intravenous urography and micturating cystourethrography should be carried out when the infection has been successfully treated, usually after a seven-day course, and regular urine cultures made during long-term follow-up.

MENINGITIS

E coli and the group B streptococcus are the organisms most often responsible for neonatal meningitis, with the former still predominating in Britain. A wide range of bacteria, however, have been known to cause the disease, the majority Gram-negative. The aminoglycosides would cover all-comers, but when used systemically they do not penetrate the CSF sufficiently to reach inhibitory concentration for many Gram-negative organisms. Clinical and experimental evidence suggests that drugs given by the lumbar intrathecal route will not achieve this either in ventricular fluid, and a persisting ventriculitis is a well-known feature of neonatal meningitis. Thus daily injections into right or left ventricles alternately or the insertion of a catheter at the outset with a reservoir through which injections may be made is necessary if the drugs are to be used most effectively.

Intraventricular treatment is usually continued until four or five negative CSF cultures have been obtained, and systemic treatment is continued for 10-14 days. The combination of ampicillin and gentamicin without intraventricular gentamicin cannot be considered suitable initial treatment, because although ampicillin penetrates the CSF effectively, about one third of *E coli* isolates are resistant to it. The alternative drugs, which may avoid potentially damaging passage of needles or catheter through brain substance, are chloramphenicol and co-trimoxazole or the penicillins for sensitive organisms, for they appear to give adequate CSF concentrations when given systemically only. Chloramphenicol may be the drug of choice at present for initial treatment when the organism is unknown, but resistance of some of the likely offenders is unfortunately possible, and neither it nor the sulphonamides are effective against *Ps aeruginosa*. Here gentamicin could be used as above alone, or systemically with carbenicillin, which would itself penetrate the CSF. Isolates of *Ps aeruginosa*, however, may be carbenicillin-resistant.

GASTROENTERITIS

Shigellae and salmonellae are rare causes of diarrhoea in the neonatal period, and are usually transmitted from the mother. *E coli* mediated diarrhoea, due to enteropathogenic, enterotoxic,

or enteroinvasive strains, may occur more commonly. The detection of enterotoxigenicity or enteroinvasiveness in isolates is still largely a matter for research laboratories, and such outbreaks go undiagnosed in neonatal units which depend only on the routine laboratory. The role of bacteria in rotavirus infections is not precisely known. As in so many other major neonatal infections, a coincident bacteraemia will probably be present at first, and systemic treatment with an aminoglycoside or chloramphenicol is indicated in ill and immature infants as well as intravenous fluid and electrolyte replacement. There is still unresolved controversy surrounding the oral treatment (with aminoglycoside or poorly absorbed sulphonamide) for relatively well infants who continue to excrete a bacterial pathogen. While it seems clear that carrier states may be prolonged by their use, there does seem occasional justification for such treatment if isolation elsewhere is impracticable and a preterm infant has to remain in a neonatal unit.

NECROTISING ENTEROCOLITIS

Antimicrobial treatment seems necessary for necrotising enterocolitis, a disturbing recent feature of neonatal intensive care units, for Gram-negative aerobes, or anaerobes such as clostridia and *Bacteroides* spp, may invade the blood stream. It occurs most often in sick low-birth-weight infants and after exchange transfusion. A combination of benzylpenicillin (or ampicillin) with an aminoglycoside would be suitable initial treatment. Experience with metronidazole in the neonatal period is extremely limited as yet, and it cannot be considered a satisfactory first choice. Conservative treatment—the early institution of gastric suction, withdrawal of oral feeds, and substitution of intravenous fluids—has been most favoured, though occasionally operation to resect necrotic bowel or repair a perforation is necessary.

With this approach, survival rates of over 80% are not uncommon now, in contrast to the high mortality of previous years. Nevertheless, the incidence of this condition has greatly increased, some infants are surviving after varying degrees of small bowel resection, and there is an urgent need for neonatal units to look carefully at their control of infection procedures (see Prevention) if this “epidemic” is to be halted.

OSTEOMYELITIS AND SEPTIC ARTHRITIS

Osteomyelitis and septic arthritis were relatively common when staphylococcal colonisation of infants after birth was the rule rather than the exception. They are now rare among major infections but always to be feared for their possible late effects on normal bone growth. Deep soft tissue swelling is the most consistent early radiological sign. A stained smear of aspirate from direct needle puncture of the affected area may give some guidance as to initial treatment. While staphylococci may still be the causative organism, Gram-negative enteric bacteria, *Neisseria gonorrhoeae*, and group B streptococcus have also been implicated in recent years. Methicillin (or cloxacillin) and gentamicin would probably be the best initial choice of drugs until culture results are available, combined with local surgical measures such as incision and drainage and, if necessary, bone drilling. Established orthopaedic practice favours prolonged (four to six weeks) courses, but alternatives to the potentially ototoxic and nephrotoxic aminoglycosides should be sought whenever possible.

Treatment of less serious infections

While such conditions as purulent conjunctivitis, superficial skin sepsis, and umbilical infection may be considered minor if promptly recognised and treated, their potential for becoming more serious or leading to generalised infection should not be underestimated.

CONJUNCTIVITIS

The most important but still uncommon gonococcal ophthalmia can nearly always be successfully treated with systemic benzylpenicillin, together with either frequent saline irrigation of the eyes or frequent instillation of aqueous penicillin G eye drops containing 10 000 units/ml. Discharge from the eyes usually occurs early in the first week, though it may occasionally be delayed. Penicillin-resistant gonococci are still relatively uncommon in Britain, but paediatricians and practitioners need to be aware of this possibility if rapid improvement does not occur.

Chlamydia trachomatis infections, while not strictly bacterial, are more common and tend to occur a little later in the first week, though there may be overlap or even mixed infections. Special laboratory techniques will be necessary to confirm the diagnosis. Pannus formation and the development of conjunctival scars may occur unless prompt treatment is given: this should consist of chlortetracycline eye ointment (1%) applied four times daily and used for several weeks. Saline irrigation or sulphacetamide eye drops (10%) usually suffice for the “sticky eye” not due to these two organisms.

SKIN SEPSIS

Skin sepsis is usually staphylococcal and has been less common in recent years; it is occasionally streptococcal. Pustules are more common than blistering lesions. Washing the infant's skin with either hexachlorophane or chlorhexidine, used according to the manufacturers' instructions, may prevent the lesions from spreading and is not contraindicated in well-grown mature babies and when there are no large raw areas of skin. Isolated pustules could also be treated with an application of triple dye, and do not warrant systemic treatment in an otherwise well infant. If they are numerous methicillin or cloxacillin would be the drug of choice, at least until laboratory cultures are available.

UMBILICAL INFECTION

Careful attention to the umbilical cord at birth has greatly reduced the incidence of umbilical infection. Again some application to the site such as hexachlorophane dusting powder, triple dye, or an antibiotic spray will considerably lessen the degree of bacterial colonisation there, not only reducing the likelihood of the local infection but of that elsewhere in the skin.

THRUSH AND VAGINAL MONILIASIS

One of the commonest minor infections of the neonatal period, thrush, is non-bacterial but may be briefly mentioned. It is usually secondary to maternal vaginal moniliasis caused by *Candida albicans*. Oral thrush will clear on its own eventually, but 100 000 units of the oral suspension of nystatin given six-hourly for a week may hasten the process. If monilial dermatitis is present in the napkin area nystatin ointment may be used locally as well. Crystal violet, applied as a 1% solution to buccal or perineal lesions, is as effective and cheaper but is disliked by mothers.

Prevention

Gonococcal ophthalmia is one of the few neonatal infections that can be prevented, though treatment has not been given routinely to all infants born in Britain for several years. One drop of 1% silver nitrate solution placed in each eye after birth, and not rinsed out, is almost universally effective. Any mild resulting chemical conjunctivitis does not persist for more than a day or two.

The use of hexachlorophane for bathing infants and for hand washing by people working in nurseries controlled staphylococcal colonisation in maternity units when it was common. The knowledge that this antibacterial substance is absorbed through the skin of the immature, and deposited in brain substance, led to its withdrawal from use in very low birth weight infants. Triple dye, or an antibacterial spray containing drugs not used at all in systemic treatment, applied to the umbilicus is probably an acceptable alternative. The mainstays of prevention, however, whether in hospital or at home must be as scrupulously clean an environment as possible and the full understanding by all concerned with the newborn that their conscientious and effective hand-washing, particularly in hospital, is one of the most important measures in safe neonatal care. The overuse of antibiotics is nowhere to be more deplored than in the newborn nursery, for it leads to colonisation with multiple resistant organisms in the first days of life. Changes in the balance of bowel flora may have played some part in the serious outbreaks of necrotising enterocolitis that have occurred among low-birth-weight infants in newborn units in recent years.

Finally, the successful promotion of breast-feeding goes far towards protecting babies from invasion by bacteria.

Appendix

SUGGESTED DOSAGE FOR NEONATAL BACTERIAL INFECTION

<i>Drug</i>	<i>Single dose</i> (intramuscular or intravenous)
Ampicillin	50 mg/kg
Benzylpenicillin	50 000 U/kg
Carbenicillin	100 mg/kg
Cloxacillin	25 mg/kg
Methicillin	25 mg/kg

<i>Drug</i>	<i>Single dose</i>
Amikacin*	7.5 mg/kg
Gentamicin*	2.5 mg/kg
Kanamycin*	7.5 mg/kg (increase to 10 mg/kg after first 48 hours of life in term infants and after first week in preterm)
Tobramycin*	2.5 mg/kg
Chloramphenicol*	25 mg/kg
Co-trimoxazole	15-20 mg/kg†
sulphamethoxazole	3-4 mg/kg†
trimethoprim	(the intravenous solution should be diluted immediately before use with 7 to 10 volumes of physiological saline and given not more than 12-hourly)

Frequency (except where stated)*

<i>For term infants (>37 weeks' gestation)</i>	<i>For preterm infants (<37 weeks' gestation)</i>
Every 12 hours in first 48 hours of life	Every 12 hours in first weeks of life
Eight-hourly between three days and two weeks	Eight-hourly between one and four weeks
Six-hourly if over two weeks	Six-hourly after four weeks

Intraventricular dosage: gentamicin 1-2 mg, kanamycin 2-3 mg—the smaller doses for preterm infants. If marked hydrocephalus is present, however, much larger doses may be necessary.

*Should not be given more than eight-hourly.

†The smaller dose for preterm infants.

Note: Intramuscular injections should be given into the anterolateral thigh and not buttock muscles. Intravenous injections should be given as a very slow bolus.

Drug concentrations in blood (and CSF where relevant) should be checked whenever possible because of the many variables affecting drug metabolism and excretion in ill newborn infants.

Letter from . . . Chicago

Continuing education

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Two eminent Chicago surgeons looking back on their successful careers in a widely publicised interview last year declared that medicine was not what it used to be—and said that they would not become doctors if they had to live their lives all over again, nor would they advise their children to do so. Complaining in particular about the changing character of medical practice and the erosion of the doctor-patient relationship, they pointed to the growing encroachment of Federal bureaucracy and to the constant disparagement of doctors by consumer groups. "Almost everything written about doctors tends to be negative," said one of the surgeons, "and the few bad apples in the pro-

fession are cited to tar the overwhelming number who are honest, conscientious, and moral." The surgeons blamed the modern teaching hospital for destroying the warmth and trust of the doctor-patient relationship and thought that full-time physicians lacked the patient orientation of the doctors in practice and would not "inspire young men in medical school with the realisation that curing sick people is what medicine is all about."¹

Loss of bedside teaching

Echoing the surgeons' misgivings was Dr William Regelson,² who recently mourned the death of Oslerian tradition with its emphasis on bedside teaching by clinicians with a broad knowledge of medicine in a setting dominated by concern for the patient as an individual and an orientation towards broad-based academic humanism. Today in most schools patient care has become less important as a primary professional responsibility, writes Dr Regelson, and the practising physician is no longer a

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