

# Naming the Problem That Underpins “Rule-out Sepsis”

## The Need for Bayesian Thinking



Joseph Schulman, MD, MS

Director, NIQU Quality Measurement and Improvement

California Children’s Services

Department of Health Care Services

Sacramento, CA

[Joseph.Schulman@dhcs.ca.gov](mailto:Joseph.Schulman@dhcs.ca.gov)

# Many providers appear to consider “Rule-out Sepsis” as a simple categorical matter

- Yes, infection/No – end of investigation.
- If the culture does not grow a pathogen, providers may consider some array of clinical signs and study results nonetheless to indicate “Yes” (“Culture-negative sepsis”) – with little consideration of alternative explanations.
- We generally don’t accept such an approach to diagnostic reasoning for other pathological entities.
- It is crucial to objectively – and when possible, quantitatively – evaluate alternative possible explanations for a particular array of clinical signs and study results.
  - Today, we will examine what we mean by evaluating possible explanations objectively and quantitatively.

# Differential diagnosis underpins reliably accurate diagnostic assignment

- Providers may feel that once they decide to initiate antibiotics for a symptomatic baby, they and the baby are “covered.”
  - Such confidence may be warranted only when bacterial infection is objectively the most likely explanation.
  - Absent confirmatory culture results, providers may not actually determine “the **most likely** explanation” from systematic consideration of alternative explanations.
    - “Most likely” should amount to a comprehensive and quantitative assessment.
  - Other explanations for the clinical presentation may spontaneously resolve without medical intervention, but perhaps sub-optimally.

# Clinical/Lab/Imaging Information From Previous Vignettes

- Maternal temperature 103 F shortly before delivery
- Difficulty with first oral feed
  - ?Aspiration?
- Increasing respiratory distress at about 4 hours after birth
- CXR with areas of consolidation
- Blood culture negative, or organism of unclear pathological role

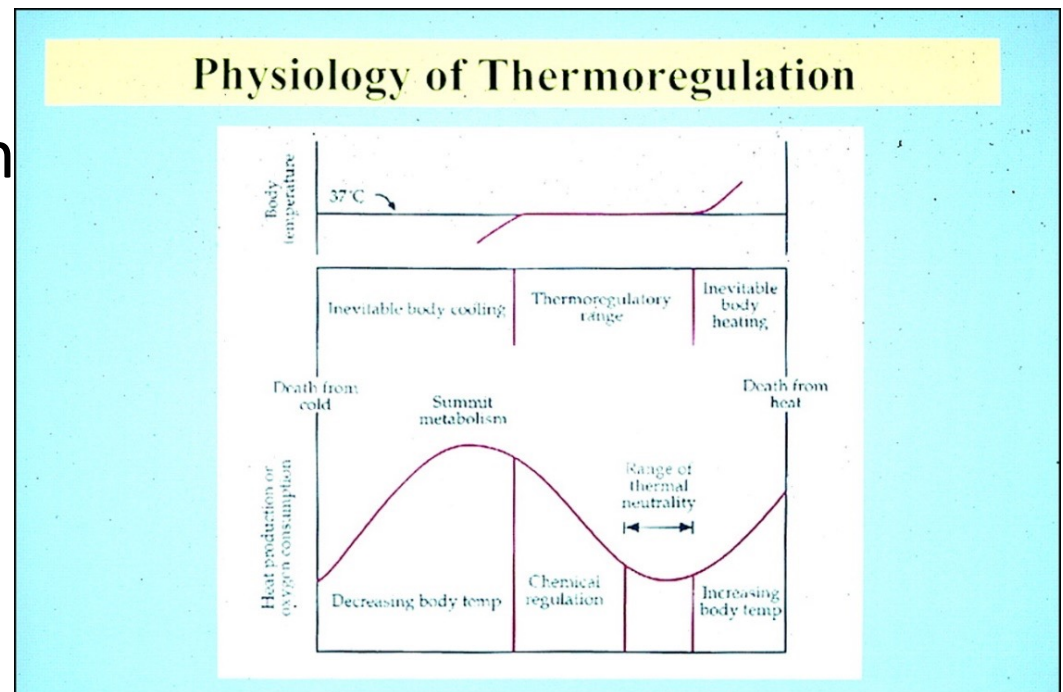
For each information element just presented, what explanation comes to mind as most likely?

How many alternatives explicitly come to mind?

# Here are just a few possibilities

Not listed in rank order (varies with the individual baby's particulars)

- Thermal stress
  - Environmental
  - Maternal temp – either low, or elevated – effect on neonatal metabolic rate vs nutritional supply
- Retained fetal lung fluid
- Delayed perinatal transition
  - Circulatory
  - Unequal distribution of ventilation
- Hypoglycemia
- Aspiration
- Bacterial infection
- Viral infection

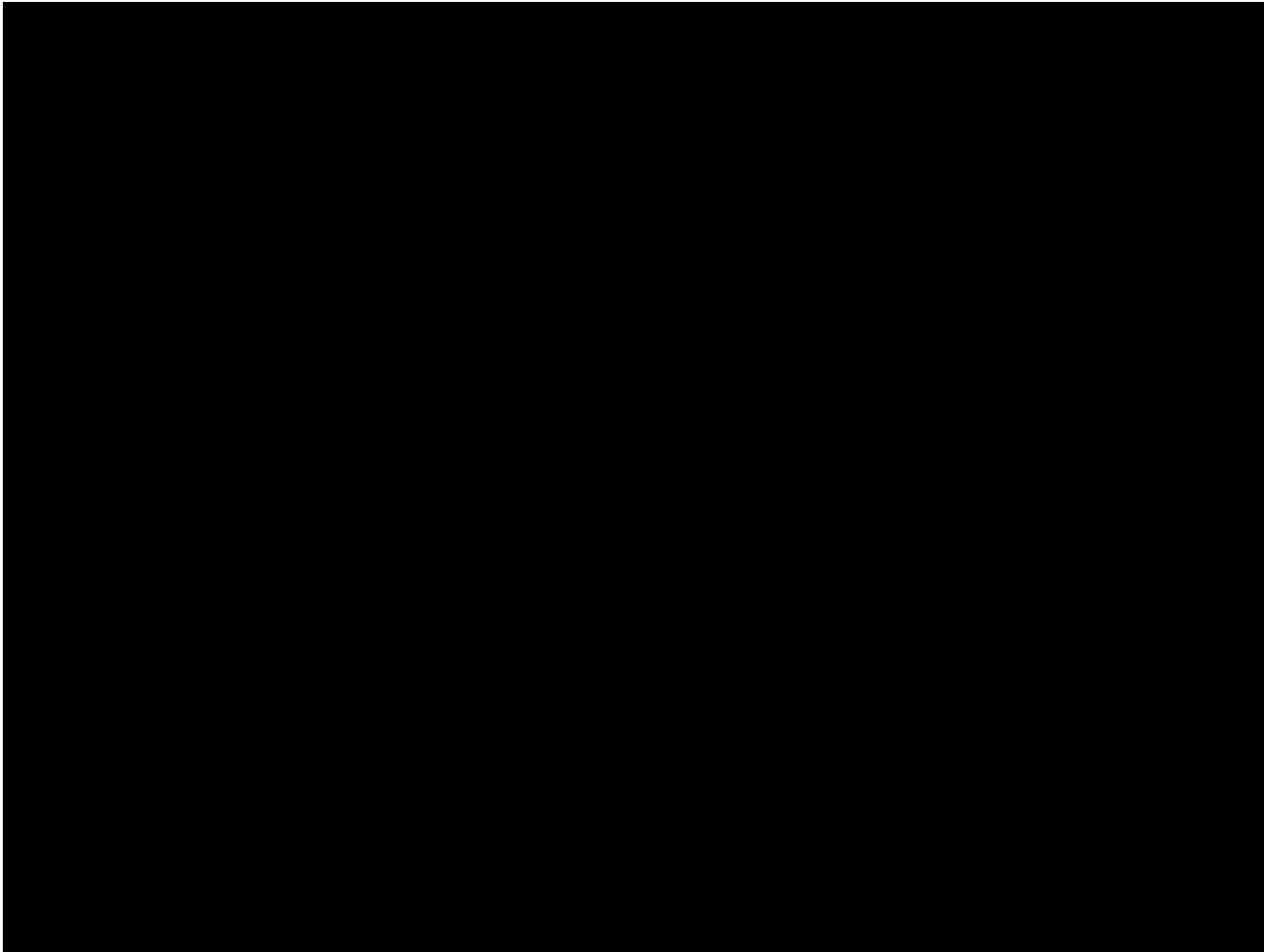


# Here are just a few possibilities

Not listed in rank order, as this varies with the individual baby's particulars

- Thermal stress
    - Environmental
    - Maternal temp – either low, or elevated – effect on neonatal metabolic rate vs nutritional supply
  - Retained fetal lung fluid
  - Delayed perinatal transition
    - Circulatory
  - Hypoglycemia
  - Aspiration
  - Bacterial infection
  - Viral infection
- If Aspiration, or Pneumonia, what evidence is there these can resolve clinically and radiographically in 2-3 days?
- Chemical pneumonia (especially meconium aspiration) typically lasts for weeks. The inflammatory process of bacterial or viral pneumonia plausibly does too (remains radiographically evident), but these questions have not been rigorously studied.

Too often, we only see what we  
look for







It's hard to see the ballerina in this picture if you're used to only looking for flamingos.

---

**AVERY'S  
DISEASES  
OF THE  
NEWBORN**

---

EIGHTH EDITION

**H. William Taeusch, M.D.**

Professor and Vice Chair of Pediatrics  
University of California, San Francisco  
San Francisco General Hospital  
San Francisco, California

**Roberta A. Ballard, M.D.**

Professor of Pediatrics and Obstetrics and Gynecology  
University of Pennsylvania School of Medicine  
The Children's Hospital of Philadelphia  
Hospital of the University of Pennsylvania  
Philadelphia, Pennsylvania

**Christine A. Gleason, M.D.**

W. Alan Hodson Professor of Pediatrics  
Head, Division of Neonatology  
University of Washington  
Children's Hospital and Regional Medical Center  
Seattle, Washington

## Index

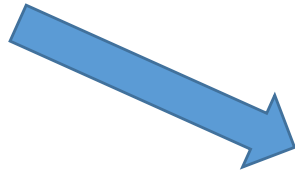
Arrhythmia(s), 873-885  
fetal  
assessment of, 873, 874f  
bradycardia as, 873-876  
heart block and, 874-876  
premature atrial and ventricular atopy and, 873-874  
tachycardia as, 876-879  
supraventricular, 876f, 876-879, 877f  
ventricular, 879  
hydrops fetalis associated with, 64t, 67  
neonatal  
bradycardia as, 879f, 879-880, 880f  
tachycardia as, 880-885  
supraventricular, 880-884, 881f, 882f  
ventricular, 884f, 884-885  
Arterial malformation(s), cutaneous, 1526  
Arterial muscle hyperplasia, diaphragmatic hernia and, 764  
Arterial puncture, pain management for, 443  
Arteriovenous connection(s), placental, in monochorionic twins, 58, 58t  
Arteriovenous malformation(s), pulmonary, 753  
Arthritis, septic, neonatal, 1432-1433  
Arthrogyposis, 315  
Arthrogyposis multiplex congenita, 1000-1001  
neonatal, 1000-1001  
Ascites, neonatal, 1103-1104, 1104f, 1104t  
biliary, 1103  
chylous, 1103, 1104f  
pancreatic, 1104  
renal and urinary tract disorders and, 1270  
urinary, 1103  
with ruptured ovarian cyst, 1104  
Ascorbic acid, route, dose, adverse effects, and cautions regarding, 1558, 1566  
Ash-leaf macules, 1527, 1527f  
Aspergillus infection(s), in neonatal intensive care unit, 509  
Asphyxia, 350-352, 873  
definition of, 350  
physiology of, 350-351, 352f, 352t, 353f  
thrombocytopenia due to, neonatal, 1168-1169  
Asphyxiating thoracic dystrophy, 759-760, 760f  
Asplenia, neonatal, 858-859, 860f  
Asplenia syndrome, 793  
Assist/control mode ventilation (A/CV), 656, 657

Atropine  
for laryngoscopy, 812  
route, dose, adverse effects, and cautions regarding, 1558  
Auditory brainstem responses (ABRs), 324  
Autocrine system, 46  
Autoimmune neonatal thrombocytopenia, maternal idiopathic thrombocytopenic purpura and, 1171-1172  
Autoregulation, cerebral, 904  
Autoregulatory escape, 1077-1078  
in necrotizing enterocolitis, 1123  
Autosomal dominant polycystic kidney disease (ADPKD), 1276-1277, 1277f  
Autosomal recessive polycystic kidney disease (ARPKD), 1275-1276, 1276f  
Avery, Mary Ellen, 670

## B

B lymphocytes, 459f, 459-460  
Baby Doe case, 17  
Bacille Calmette-Guérin (BCG) vaccine, for tuberculosis prevention, 547  
Bacitracin, route, dose, adverse effects, and cautions regarding, 1558  
Back examination of, for dysmorphology, 197  
Bacterial infection(s). *See also specific infections.*  
of central nervous system, congenital, neuroimaging of, 930, 931f  
Bacterial meningitis, neonatal, 569-573  
clinical manifestations of, 569, 570t-571t  
diagnosis of, 569, 571, 572t  
pathology of, 569  
prognosis of, 573  
therapy for, 571, 573  
Bacterial overgrowth, in short bowel syndrome, 1130  
Bacterial peritonitis, neonatal, 1104  
Bacterial sepsis, neonatal, 551-568, 552f  
acute phase reactants and erythrocyte sedimentation rate in, 560-561  
cerebrospinal fluid in, 559  
clinical manifestations of, 557, 557t  
clinical spectrum of, 564

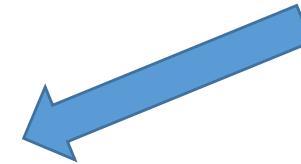
Where is  
"Aspiration"?



Index

- Phototherapy, to reduce serum bilirubin production, 1248-1250
- Physical dependence, on pain medications, 444
- Physical examination of neonate, 306-320, 307f, 308f, 309t
  - for nosocomial infection, 306
  - gestational age assessment and, 309
  - inspection by system in, 310-318
    - of abdomen, 314, 314f, 315t
    - of chest and lungs, 313
    - of cry, 311
    - of ears, 312
    - of eyes, 312, 312f
    - of genital system, 314-315
    - of head, 311, 311t
    - of heart and vascular system, 313-314
    - of mouth and lower face, 312
    - of musculoskeletal system, 315-317, 316f
    - of neck, 312-313
    - of neurologic system, 317f, 317-318, 317b-319t, 318f
    - of nose, 312
    - of skin, 311
    - of skull defects, 311-312
  - laboratory screening in, 319-320
  - overall appearance in, 309-310, 310t
  - ultrasonography in, 318-319
    - of head, 318
    - of heart, 318-319
    - of renal system, 319
  - vital signs in, 307-308
  - weight, length, and head circumference in, 308-309, 309f
- Physical maturity rating form, 1573
- Physiologic anemia of infancy, 1203t, 1203-1204
- Phytonadione, route, dose, adverse effects, and cautions regarding, 1566
- Piebaldism, 1490, 1491f
- Pierre Robin syndrome, 190, 200, 737-738
- Pigmented lesions, 1480
- Pili torti, in inborn errors of metabolism, 223t
- Pilocytic astrocytoma, neonatal, neuroimaging of, 931
- "Ping-pong ball" sign, in rickets, 1360
- Piot, Peter, 473
- Piperacillin, route, dose, adverse effects, and cautions regarding, 1564
- Pitressin, route, dose, adverse effects, and cautions regarding, 1564
- Pituitary deficiency, neonatal hypoglycemia due to, 1416
- Pityrosporum folliculitis, 1477
- Pius XII, Pope, 159
- Placenta
  - anatomy of, 24, 26, 26f, 26t, 27f
  - circumvallate, 26, 27f
  - embryologic development of, 23, 24f, 25f
  - examination of, 27-28, 28t, 29t
  - fetal growth restriction related to, 33-34
  - fixed acid excretion and, 1283
  - gross anatomy of, 28, 28t
- Plasma
  - concentrations in, in neonates, 1147, 1152
  - route, dose, adverse effects, and cautions regarding, 1564
- Plasmin, regulation of, 1150
- Plasminogen, fetal, 1147
- Plastic blankets, for temperature regulation of premature infants, 368
- Plastic hoods, for temperature regulation of premature infants, 367
- Plateau drug concentrations, 434, 434f
- Platelet(s), 1150, 1152
  - activation and secretion of, 1152
  - adhesion of, 1150, 1152
  - aggregation of, 1152
  - disorders of, 1168-1172. *See also specific disorders*
    - qualitative, 1172
    - quantitative, 1168-1172
  - in neonate, 1150, 1152
  - function of, 1150, 1152
- Platelet concentrates, for thrombocytopenia, 1169-1170
- Platelet count(s)
  - developmental changes in, 1141
  - in bacterial sepsis, 560
- Platelet function
  - indomethacin and, 822
  - testing of, 1152
- Platelet replacement, for intraventricular hemorrhage, 1158
- Platelet-derived growth factor (PDGF), fetal, development and, 51t, 56
- Pleconaril, for enterovirus infection, congenital, 1158
- Pleural cavity disorder(s), 761-763. *See also specific disorders*
- Pleural effusion
  - diagnosis of, 761, 762f
  - pathomechanisms of, 761
- Pleural fluid
  - clearance of, decreased, 761
  - filtration of, increased, 761
- Pluripotent stem cells (PPSCs), 1215
  - biology of, 1135-1136
- Pneumocystis carinii* pneumonia (PCP), neonatal, 487-488
  - HIV/AIDS, 487-488
- Pneumomediastinum, with mechanical ventilation, 662-663
  - diagnosis of, 662, 663f
  - epidemiology of, 662
  - natural history of, 662
  - treatment of, 662-663
- Pneumonia, nosocomial, definition of, 579t
- Pneumopericardium, with mechanical ventilation, 663, 663f
- Pneumoperitoneum, with mechanical ventilation, 663
- Pneumothorax, with mechanical ventilation, 662-663
  - diagnosis of, 662, 663f
  - epidemiology of, 662
  - natural history of, 662
  - treatment of, 662-663


Where is a general discussion of "Pneumonia"?



# Common Problems in the Newborn Nursery

An Evidence and Case-based  
Guide

Gilbert I. Martin  
Warren Rosenfeld  
*Editors*

 Springer

2019

## Contents

<b>1 Post-resuscitation Care of the Depressed Newborn</b> . . . . .	1
Stephany M. Guiles and Jay P. Goldsmith	
<b>2 Newborn Birth Injuries</b> . . . . .	13
Smeeta Sardesai	
<b>3 Visual Diagnosis in the Newborn</b> . . . . .	27
David A. Clark	
<b>4 Common Dermatological Conditions</b> . . . . .	39
Mercedes E. Gonzalez	
<b>5 Evaluation and Management of the Late Preterm Infant</b> . . . . .	55
Stephen A. Pearlman and Kaitlin Kenaley	
<b>6 Jaundice in the Newborn</b> . . . . .	61
Warren Rosenfeld	
<b>7 Neonatal Bacterial Infections</b> . . . . .	71
Thomas A. Hooven and Richard A. Polin	
<b>8 Viral Infections in the Nursery</b> . . . . .	81
Asif Noor, Theresa M. Fiorito, and Leonard R. Krilov	
<b>9 Anemia in the Nursery: When to Observe, When to Treat, and When to Refer</b> . . . . .	89
Emily A. Morris and Ann R. Stark	
<b>10 Neonatal Hypoglycemia</b> . . . . .	99
David H. Adamkin	
<b>11 Disorders of Calcium, Phosphorous, and Magnesium in the Newborn</b> . . . . .	109
Arielle L. Olicker, Avroy A. Fanaroff, and Jonathan M. Fanaroff	
<b>12 Nutrition in the Newborn</b> . . . . .	117
Stephanie Tong-Miller and Henry H. Bernstein	
<b>13 Cardiology in the Newborn Nursery</b> . . . . .	131
Bruce D. Sindel and Joseph Ahdoot	

Is this really a  
“common problem  
in the newborn  
nursery?”



Or, do we just  
commonly think  
of it?

Arrhythmia (*cont.*)

## tachyarrhythmias

atrial flutter/fibrillation, 154–155

initial therapy, 153

reentrant supraventricular tachycardia, 155

sinus tachycardia, 154

supraventricular tachycardia, 154

ventricular tachyarrhythmia, 155–156

ventricular preexcitation, 158

Arterial cord acidosis, 3, 4

Arthrography, 199

## Atresia

duodenal (*see* Duodenal atresia)esophageal (*see* Esophageal atresia)

postsurgery care, 168

surgery care, 168

Atrial flutter/fibrillation, 154–155

Atrial septal defects, 164

Atrioventricular block, 152, 153

Autism, 59

Autoimmune illness, 159

Automated auditory brain stem response (AABR),  
228–232

Automatic empiric antibiotic administration, 72

AV node, 151, 152

**B**

Bacterial conjunctivitis, 220–221

## Bacterial infections

ampicillin, 73

B *Streptococcus meningitis*, 73, 74early-onset sepsis (*see* Early-onset sepsis)

gentamicin, 73

*L. monocytogenes* infection, 73

neutrophils, 71

perinatal period, 71

rhinorrhea, 75

Barlow maneuver, 195, 196, 198

Benign asymptomatic rhythm abnormalities, 149

Benign neonatal

pseudoparalys

risk factors, 13

scalp swelling,

skull radiograp

soft tissue inju

subcutaneous f

subgaleal hemo

Birthmarks, 39

Blue TETS, 164

Bohn nodules, 30, 3

Bone marrow failur

Bowel obstruction

diagnosis, 167

differential diagn

surgical interven

treatment, 168

x-ray, 166

Brachial plexus palsy

Brachycephaly, 29, 1

## Bradyarrhythmia

atrioventricular bl

EKG rhythm, 151

initial therapy, 151

management, 151

PAC-induced brad

premature atrial co

sinus arrest, 152

sinus bradycardia,

## Breastfeeding

artificial teats, 122

body positioning, 1

bottle-feeding, 122

breast milk, 120

cluster feeding, 124

colostrum, 122

estrogen-containing

formula, 123, 126

galactosemia, 125

growth, 127

Aspiration is  
not listed

# Pneumonia?

Plagiocephaly, 29  
Plaque neutralization testing (PRNT), 84  
Polyhydramnios, 161, 162, 172, 173  
Polyspemia, 152  
Positive pressure ventilation (PPV), 6, 7, 93  
Prader-Willi syndrome, 178–180  
Preeclampsia, 3, 55, 56, 59, 112, 113, 171, 175  
Premature atrial contraction (PAC)-induced bradycardia, 153  
Primary congenital glaucoma  
  clinical presentation, 223  
  diagnosis of, 223  
  differential diagnosis of, 223  
  etiology of, 222  
  incidence of, 222  
  treatment of, 223  
Prostaglandin E1 (PGE), 138, 139, 145, 159  
Pseudo-esotropia, 224  
Pseudoparalysis, 21–23  
Pulmonary artery pressures, 139, 143, 145  
Pulmonary vascular resistance (PVR), 139  
Pulse oximetry, 136–138, 140–142, 153, 157  
P wave, 151–155

**Q**  
QRS ventricular conduction, 152

**R**  
Ranula, 31, 45  
Recurrent/persistent hypoglycemia, 107  
5- $\alpha$ -Reductase-2 deficiency, 211  
Reentrant supraventricular tachycardia, 153–155  
Respiratory distress syndrome (RDS), 57  
Rhinorrhea, 75, 76  
Rhinovirus, 76, 96, 97  
RSV bronchiolitis, 58

**S**  
Sacrococcygeal teratoma, 36, 37  
Sarnat staging system, 4–6, 10, 184, 186, 187  
Scalp edema/ swelling, 13–15, 29

**SRY gene**, 204, 206, 212  
Stalked (extra) digits on fifth finger, 27, 28  
Standard phototherapy, 67  
Steroid 5- $\alpha$ -reductase-2 deficiency (SRD), 211  
Strabismus, 223–225  
Stuporous newborn, 5  
Subcutaneous fat necrosis (SFN), 24, 25  
Subgaleal hemorrhage (SGH), 15–18, 92  
Sugar Wheel nomogram, 100, 101  
Superficial pustules, 40–43  
Supernumerary nipples, 35  
Synophrys, 30  
System lupus erythematosus (SLE), 135, 137  
Systemic illness, 159, 172, 174

**T**  
Tachyarrhythmias  
  atrial flutter/fibrillation, 154–155  
  initial therapy, 153  
  reentrant supraventricular tachycardia, sinus tachycardia, 154  
  supraventricular tachycardia, 154  
  ventricular tachyarrhythmia, 155–156  
Tachypnea, 165  
Teratologic dislocation of the hip, 193  
Tetralogy of Fallot (TOF), 142, 143, 164  
Thalassemias, 97  
Therapeutic hypothermia (TH), 1, 4–7, 9  
Thyroglossal duct cysts, 32  
Thyroid hyperplasia, 32  
Timolol, 49, 51  
Tongue-tie, 31  
TORCH (toxoplasmosis, rubella, cyton varicella) screening test, 172, 224  
Total anomalous pulmonary venous re, 144, 146  
Transient neonatal pustular melanosis  
  characteristic phases, 40  
  differential diagnosis, 41  
  treatment, 41  
Transposition of the great arteries (T) / Transposition of the great vessels (T)  
Treacher Collins syndrome, 30  
Tricuspid atresia, 142, 144, 146, 147  
Trigonocephaly, 29  
Trisomy 21, 166, 168, 179, 231  
  arteriosus, 132–135, 142, 143, 144, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000

Where are  
Transient  
tachypnea,  
Retained fetal  
lung fluid?



# Are We Locked Into *Unrepresentative* Categories for Thinking?

**TABLE 1** Distribution of EOS and LOS Rates, Percentage of All Live Births Who Received a Newborn Antibiotic Exposure and Sepsis Diagnostic Efficiency

	Hospital-Level Mean (SD)	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile	Lowest	Highest	Statewide
Percentage of births exposed to antibiotics	8.53 (6.27)	3.67	4.69	7.35	9.55	14.14	1.59	42.54	8.43
Diagnostic efficiency, EOS + LOS	66.35 (91.70)	16.54	26.06	41.25	69.50	122.00	7.25	781.00	34.26
<b>EOS</b>									
Rate (cases per 1000 live births)	0.72 (0.69)	0	0	0.53	1.17	1.70	0	2.89	0.75
Diagnostic efficiency	95.08 (71.14)	33.44	46.87	69.52	122.84	178.54	11.45	335.75	88.82
<b>LOS</b>									
Rate (% of admissions with high illness acuity)	3.18 (3.10)	0	0	2.99	4.69	7.25	0	18.75	3.67
Diagnostic efficiency	19.60 (24.02)	3.88	7.09	12.18	22.36	36.96	2.02	164.01	10.35

Few of us are guided by an objective evidence base derived from our own experience.

Schulman J, Benitz WE, Profit J, et al. Newborn Antibiotic Exposures and Association With Proven Bloodstream Infection. *Pediatrics*. 2019;144(5):e20191105

# Basics of Medical Bayesian Logic

**One can't interpret a test result without considering pre-test probability.**

- Most tests are imperfect; they do nothing more than adjust probability – which may or may not “rule in” or “rule out” the disease.
  - Depends on the situation: risk of not treating when you should have; risk of treating when you shouldn't have.

**How often do we actually consider an explicit pre-test probability estimate at the bedside?**

- We tend to charge ahead ordering tests without explicitly considering what the new information may be reasonably expected to contribute.

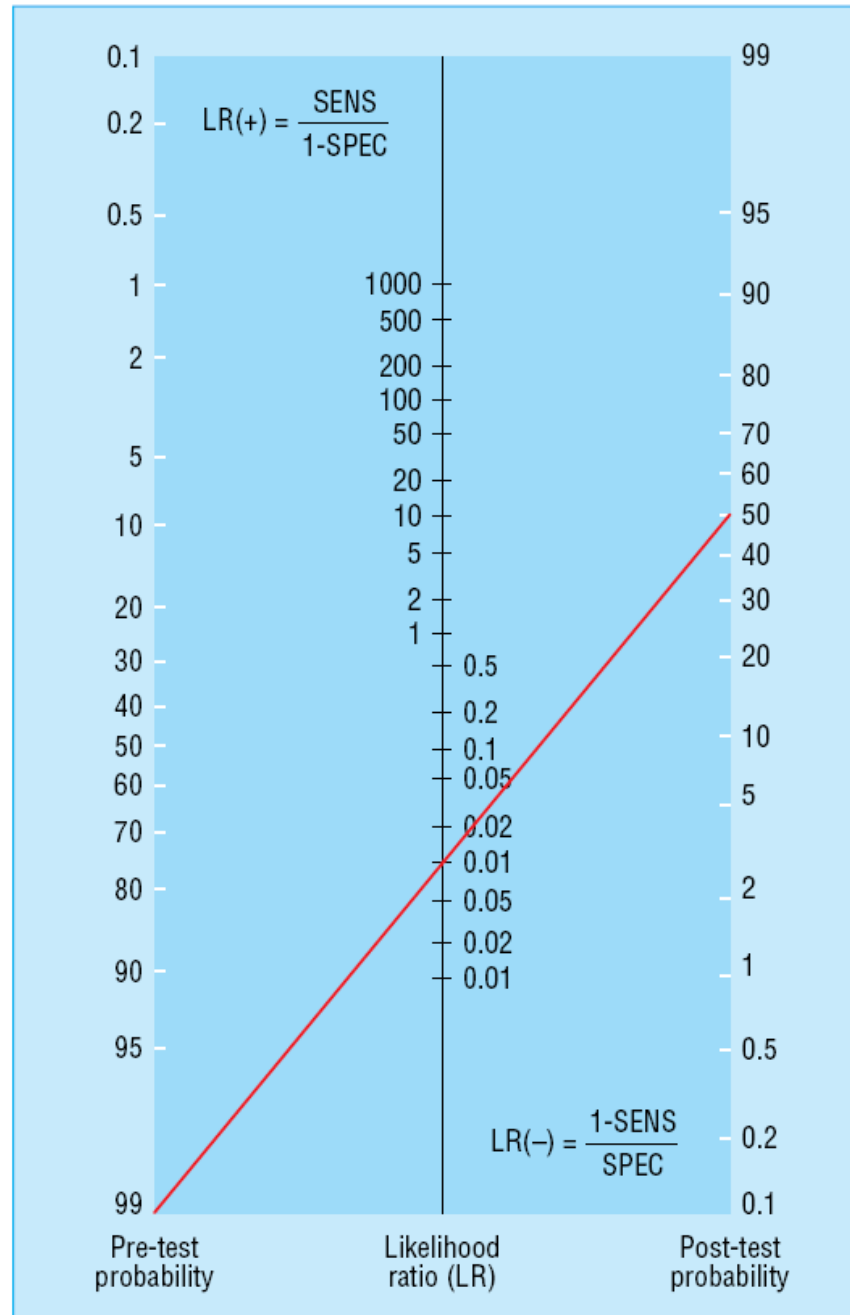
# Likelihood Ratio

- LR tells you how likely it is a patient has a disease or condition.
- The higher the ratio, the more likely a patient has the disease or condition.
- A low ratio means that they very likely do *not*.

$$\text{Likelihood Ratio} = \frac{\text{probability a person with the condition has a certain test result}}{\text{probability a person without the condition has a certain test result}}$$

- **Positive LR:** Tells you how much to increase the probability of having a disease, given a positive test result.
- **Negative LR:** This tells you how much to decrease the probability of having a disease, given a negative test result.

T+ Adjusts probability  
upward **LR(+)**  
a number > 1

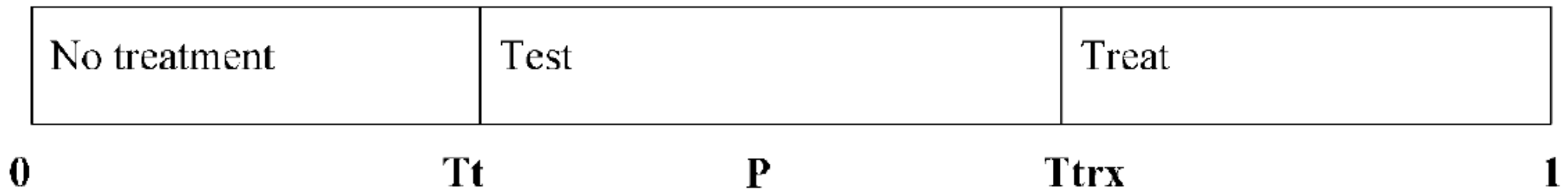


T- adjusts probability  
downward **LR(-)**  
a fraction < 1

**Fig 1** Nomogram (adapted from [www.CEBM.net](http://www.CEBM.net) with permission) to convert pre-test probability to post-test probability using the likelihood ratio. The line refers to a text example

# Test Results Are Useful In Relation to Conceptual Thresholds for Action

- Test-treatment, or treatment threshold
  - P above which dx sufficiently likely to warrant treatment
  - Pre-test  $P >$  treatment threshold
    - Confirmatory test to increase  $P(D)$  ***does not contribute.***
- No test-test, or test threshold
  - P below which dx warrants no further consideration
  - Pre-test  $P <$  test threshold
    - Exclusionary test to further decrease  $P(D)$  ***does not contribute.***



Test may be diagnostically useful when pre-test  $P(D+)$  high enough to test for, not high enough to treat, and if the test can move the  $P(D+)$  across either threshold

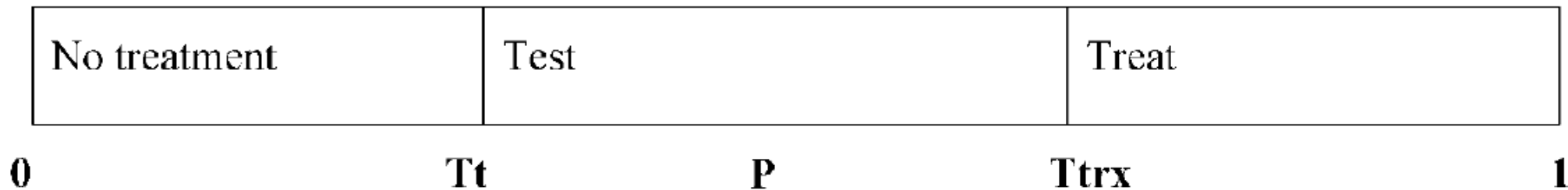
Did you notice, this is the conceptual approach behind the Kaiser sepsis calculator?

**Table 4.** The likelihood ratios of clinical findings for neonatal bacterial infections.

Clinical finding	Likelihood ratio
<b>Common signs</b>	
Pallor	14.4
Poor feeding	8.7
Tachycardia/arrhythmia	5.6
Decreased peripheral perfusion	5.4
Unstable blood pressure	4.0
Abdominal distention	3.5
Apnea	3.1
Lethargy	2.3
Hyperbilirubinemia	2.0
Retractions	1.7
Grunting	1.6
Abnormal tone	1.6
Tachypnea	1.3
Cyanosis	0.3
Temperature instability	0.7
<b>Uncommon signs</b>	
Purpura	47.0
Omphalitis	32.5
Vasomotor instability	8.1
Bleeding	6.5
Pustules	6.1
Bulging fontanel	5.4
Splenomegaly	4.1
Rash	4.0
Diarrhea	3.6
Seizures	2.3

If one is starting with a low probability of bacterial infection, most of these will not substantially change the consideration.





- **The error in post-test  $P$  attributable to a physician's estimate of pre-test  $P$  *might be more important* than the error involved in many medical tests**
- Error or bias in  $P$  estimates could mean many hypotheses cross the test or test-treat threshold, demanding more tests be performed and more patients be treated, some unnecessarily.
- Some say it is unnatural for people to give numerical estimations, and that **using verbal estimations (such as 'pretty sure' or 'unlikely')**, may yield more reliable answers

**(BMJ 2006;333:445)**

If something always happened, what percentage frequency would you assign to that event? Presumably 100%. And if something never happened? Presumably 0%. Well, not everyone shares that opinion... The table shows combined results of seven studies of what people mean (*Drug Safety* 2005;28:851-70)...

For comparison, ...definitions from the *Oxford English Dictionary*. Look, for example, at “occasionally,” “infrequently,” and “seldom”... according to the dictionary they all mean roughly the same thing. ...perhaps when we use words like this we should remember what the German conductor Hans Richter supposedly once said: “Up with your damned nonsense will I put twice, or perhaps once, but sometimes always, by God, never.”

Interpretations of words used to indicate frequencies		
Word	Interpretation (range of mean percentages)	Definition in the <i>Oxford English Dictionary</i>
Invariably/always	91-100	At every time, on every occasion, at all times, on all occasions. Opposed to sometimes, occasionally
Almost always	85-94	—
Normally	71-81	Under normal or ordinary conditions; as a rule, ordinarily
Usually	70-84	In a usual or wonted manner; according to customary, established, or frequent usage; commonly, customarily, ordinarily; as a rule
More often than not	64	—
Common(ly)	56-69	As a usual circumstance; as a general thing; in ordinary cases; usually, ordinarily, generally
Often	42-71	Many times; at many times; on numerous occasions; frequently; for a significant amount or proportion of the time
Frequent(ly)	36-72	At frequent or short intervals, often, repeatedly
Not infrequently	24-35	Rather frequently
Occasionally	17-21	Now and then, at times, sometimes; irregularly and infrequently
On occasion	12	As need or opportunity arises; now and then, occasionally
Infrequently	12-14	Not frequently; somewhat rarely, seldom
Sometimes	11-33	On some occasions; at times; now and then
Seldom	7-8	On few occasions, in few cases or instances, not often; rarely, infrequently
Almost never	2	Scarcely ever
Very rare(ly)	0.8-3	—
Rare(ly)	0.5-9	Seldom, infrequently, in few instances
Exceptionally	0.4-1	Uncommonly, unusually
Never	0-2	At no time or moment; on no occasion; not ever

	<b>BMJ</b>	<b>6W</b>
<b>Invariably/always</b>	<b>91-100</b>	<b>98-100</b>
<b>Almost always</b>	<b>85-94</b>	<b>75-99</b>
<b>Normally</b>	<b>71-81</b>	<b>50-&gt;90</b>
<b>Usually</b>	<b>70-84</b>	<b>50-90</b>
<b>More often than not</b>	<b>64</b>	<b>25-100</b>
<b>Common(ly)</b>	<b>56-69</b>	<b>10-80</b>
<b>Often</b>	<b>42-71</b>	<b>50-80</b>
<b>Frequent(ly)</b>	<b>36-72</b>	<b>50-80</b>
<b>Not infrequently</b>	<b>24-35</b>	<b>33-85</b>
<b>Occasionally</b>	<b>17-21</b>	<b>10-40</b>
<b>On occasion</b>	<b>12</b>	<b>10-30</b>
<b>Infrequently</b>	<b>12-14</b>	<b>5-20</b>
<b>Sometimes</b>	<b>11-33</b>	<b>4-40</b>
<b>Seldom</b>	<b>7-8</b>	<b>&lt;2-20</b>
<b>Almost never</b>	<b>2</b>	<b>1-10</b>
<b>Very rare(ly)</b>	<b>.8-3</b>	<b>.5-20</b>
<b>Rare(ly)</b>	<b>.5-9</b>	<b>.1-20</b>
<b>Exceptionally</b>	<b>.4-1</b>	<b>.01-10</b>
<b>Never</b>	<b>0-2</b>	<b>0</b>

# Neonatal MRI to Predict Neurodevelopmental Outcomes in Preterm Infants

Woodward, Anderson, Austin, Howard, and Inder  
N Engl J Med 2006;355:685-94

## **Methods**

We studied 167 very preterm infants (gestational age at birth, 30 weeks or less) to assess the associations between qualitatively defined white-matter and gray-matter abnormalities on MRI at term equivalent (gestational age of 40 weeks) and the risks of severe cognitive delay, severe psychomotor delay, cerebral palsy, and neurosensory (hearing or visual) impairment at 2 years of age (corrected for prematurity)...

## **Conclusions**

Abnormal findings on MRI at term equivalent in very preterm infants strongly predict adverse neurodevelopmental outcomes at two years of age. These findings suggest a role for MRI at term equivalent in risk stratification for these infants.

## Conclusions

Abnormal findings on MRI at term equivalent in very preterm infants ***strongly*** predict adverse neurodevelopmental outcomes at two years of age...

What do they mean by “strongly”? “Almost always”; “often”; “sometimes”? Does it depend on whether you’re speaking to someone at your own NICU or in Boston?

- Using incidence data provided in the article for
  - i. severe cognitive delay
  - ii. severe motor delay
  - iii. CP
  - iv. neurosensory impariment

and based on the test characteristics in the following Table, how much does the post-test probability of certain outcomes change?

**Table 5. Sensitivity and Specificity of Findings on MRI and Cranial Ultrasonography in Predicting Severe Neurodevelopmental Impairment at a Corrected Age of Two Years.\***

Outcome	Moderate-to-Severe White-Matter Abnormalities (N=35)		Any White-Matter Abnormalities (N=120)		Abnormalities on Cranial Ultrasonography† (N=13)	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
<i>percent</i>						
Severe cognitive delay						
Value	41	84	89	31	15	95
95% CI	23–61	76–89	70–97	23–39	4–35	89–98
Severe motor delay						
Value	65	85	88	30	18	95
95% CI	39–85	78–90	62–98	22–38	5–44	89–97
Cerebral palsy						
Value	65	84	94	31	18	95
95% CI	39–85	76–89	69–100	24–39	5–44	89–97
Neurosensory impairment						
Value	82	82	89	30	16	95
95% CI	48–97	75–88	65–98	23–38	4–40	89–97
Any neurodevelopmental impairment						
Value	38	89	84	34	11	95
95% CI	25–51	80–94	71–92	25–44	4–23	89–98

\* CI denotes confidence interval.

† Abnormalities on cranial ultrasonography were defined as grade III or IV intraventricular hemorrhage or periventricular leukomalacia.

### Neonatal MRI to Predict Neurodevelopmental Outcomes in Preterm Infants

Lianne J. Woodward, Ph.D., Peter J. Anderson, Ph.D., Nicola C. Austin, M.D., et al NEJM 2006;355:685-94

# Likelihood Ratios

	Moderate to Severe White Matter Abn		Any Abnormality		Abnormality on Cranial Ultrasound	
	LR +	LR -	LR +	LR -	LR +	LR -
Severe Cognitive Delay	2.56	0.70	1.29	0.36	3	0.89
Severe Motor Delay	4.33	0.412	1.26	0.4	3.6	0.863
Cerebral Palsy	4.06	0.417	1.36	0.19	3.6	0.86
Neurosensory Impairment	4.56	0.22	1.27	0.37	3.2	0.88
Any Neurodevelop Impairment	3.45	0.7	1.27	0.47	2.2	0.94

Remember,

**Positive LR:** Tells you how much to increase the probability of having a disease, given a positive test result.

**Negative LR:** This tells you how much to decrease the probability of having a disease, given a negative test result.

	Moderate – Severe White Matter Abnormalities	Any White Matter Abnormalities		Grade III or IV IVH or PVL on HUS		
	LR+ Sens/1-Spec	LR- 1-Sens/Spec	LR+	LR-	LR+	LR-
Severe cognitive delay Pre-test <i>P</i> 17%	2.56	0.7	1.29	0.35	3	0.89
Post-test <i>P</i>	~30%	~10%	~21%	~6%	~30%	~13%
Severe motor delay Pre-test <i>P</i> 10%	4.33	0.41	1.26	0.4	3.6	0.86
Post-test <i>P</i>	~28%	~4%	~12%	~4%	~25%	~7%
CP Pre-test <i>P</i> 10%	4.06	0.42	1.36	0.19	3.6	0.86
Post-test <i>P</i>	~32%	~4%	~12%	~2%	~24%	~8%
Neurosensory (hearing/vision impaired) Pre-test <i>P</i> 11%	4.56	0.22	1.27	0.32	3.2	0.88
Post-test <i>P</i>	~31%	~2%	~13%	~3%	~27%	~10%



# Let's Name The Problem

- Too often, we appear to be locked into ***unrepresentative*** categories for thinking.
- Most of the babies we treat with antibiotics represent indistinct diagnostic categories, for which our evidence base is insufficient to objectively assign probability of disease.
- We often devote insufficient effort exploring differential diagnoses because the underlying pathophysiology resolves spontaneously – so, “it doesn’t seem to matter” that diagnosis is less than definitive.
  - If we *rule-out* sepsis, we should *rule-in* the condition that explains the baby’s problem.

# Let's Name The Problem

- Our EMRs must help us compute the unintuitive, quantitative aspects of our decision making for possible bacterial infection and related differential diagnoses.
- We must move beyond vague, undefined thresholds for action when “ruling out sepsis.”
  - At what estimated **probability** value that a patient has a bacterial infection do we **test**, do we **treat**?

